CHAPTER 53 – Postmarketing Surveillance and Epidemiology:
Human Drug and Therapeutic Biological Products

SUBJECT:	IMPLEMENTATION DATE:
POSTMARKETING ADVERSE DRUG EXPERIENCE (PADE) INSPECTIONS COMPLIANCE PROGRAM FOR HUMAN DRUG AND THERAPEUTIC BIOLOGICAL PRODUCTS	10/18/2022

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
eNSpect does not require product codes for Postmarketing Adverse Drug Experience (PADE) reporting inspections	53001A Adv Drug Experience Rptg Regs Center Initiated

FIELD REPORTING REQUIREMENTS:

Consult the CDER Pharmacovigilance Compliance (PVC) Team at CDER-OSI-ADE@fda.hhs.gov, or the PVC Team Consumer Safety Officer (CSO) point of contact (POC) listed in the assignment memorandum, at least two weeks before initiating the inspection.

Consult your Supervisory Consumer Safety Officer, CDER PVC Team at CDER-OSI-ADE@fda.hhs.gov, or PVC Team CSO POC listed in the assignment memorandum, if there are questions or concerns prior to documenting any observations on a Form FDA 483.

Complete all establishment inspection reports (EIRs) in accordance with FMD #86, "Establishment Inspection Report (EIR) Conclusions and Decisions."

Send a copy of the Form FDA 483, "Inspectional Observations" (483), if issued, to the PVC Team at CDER-OSI-ADE@fda.hhs.gov and to the PVC Team CSO POC via email within three business days of inspection closeout.

All EIRs, complete with attachments and exhibits, are to be submitted promptly via eNSpect to the center POC. Once the EIR has been uploaded and endorsed in eNSpect, please notify the PVC Team at CDER-OSI-ADE@fda.hhs.gov.

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PART I – BACKGROUND

Postmarketing safety data collection and adverse event reporting is a critical element of the Food and Drug Administration's (FDA's, the Agency's) postmarketing safety surveillance program for FDA-regulated drug and therapeutic biologic products. While many common and preventable risks are identified and evaluated before a product is marketed, some risks become evident only after a product is marketed and real-world experience with the product is documented. Postmarketing safety data collection encourages informed decision-making that maximizes benefits and minimizes risks to patients. The Agency's existing postmarketing safety requirements for human drugs and therapeutic biological products can be found in the tables below. Biological products subject to the Public Health Service Act (PHS Act) also meet the definition of drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Prescription Drugs for Human Use

FD&C Act, subchapter V, part A, section 505 (21 U.S.C. 355)	New Drugs
21 CFR 310.305	New Drugs: Records and reports concerning adverse drug experiences (ADEs) for marketed prescription drugs for human use without an approved new drug application
21 CFR 314.80	New drug applications: Postmarketing reporting of ADEs
21 CFR 314.81(b)(2)	New drug applications: Annual reports
21 CFR 314.90	New drug applications: Waivers
21 CFR 314.98	Abbreviated applications: Postmarketing reports
21 CFR 314.540	Accelerated approval of new drugs for serious or life-threatening illnesses: Postmarketing safety reporting
21 CFR 314.630	Approval of new drugs when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR part 4, subpart B	Postmarketing safety reporting for combination products

Licensed Biological Products

PHS Act, subchapter II, part F, subpart 1 (21 U.S.C. 262)	Regulation of biological products. Biological products subject to the PHS Act also meet the definition of drugs under the FD&C Act.
21 CFR 600.80	Biological products: Postmarketing reporting of adverse experiences
21 CFR 601.28	Biologics licensing: Annual reports of postmarketing pediatric studies
21 CFR 601.44	Accelerated approval of biological products for serious or life-threatening illnesses: Postmarketing safety reporting
21 CFR 601.70	Postmarketing studies: Annual progress reports of postmarketing studies
21 CFR 601.93	Approval of biological products when human efficacy studies are not ethical or feasible: Postmarketing safety reporting
21 CFR part 4, subpart B	Postmarketing safety reporting for combination products

Nonprescription (Over-the-Counter (OTC)) Monograph Drugs

FD&C Act, subchapter VII, part H, section 760 (21 U.S.C. 379aa)	Serious adverse event reporting for nonprescription monograph drugs
21 CFR 329.100	Postmarketing reporting of ADEs under section 760 of the FD&C Act

Combination Products

21 CFR part 4, subpart B	Postmarketing safety reporting for combination products

FDA's postmarketing safety surveillance programs rely on Individual Case Safety Reports (ICSRs), as well as periodic reports [for example, Periodic Adverse Drug Experience Reports (PADERs), Periodic Adverse Experience Reports (PAERs), Periodic Safety Reports (PSRs), and Periodic Benefit-Risk Evaluation Reports (PBRERs)], and Annual Reports (ARs) for each approved new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA), including combination products. FDA expects these reports to be complete, accurate, and timely. An ICSR describes one or more adverse experiences related to an

individual patient or subject. Periodic and Annual Reports, on the other hand, are composed of aggregated data received by an application holder during a specified time period.

Under this compliance program, FDA inspects entities involved in the mandatory reporting of postmarketing safety information for approved and unapproved prescription and nonprescription drugs, as well as therapeutic biologics regulated by the Center for Drug Evaluation and Research (CDER). Postmarketing safety reporting requirements for combination products assigned to CDER, or combination products for which CDER is the lead center, are also subject to inspection under this program. The regulatory responsibilities for inspected entities vary based on their roles and the types of products involved.

All ICSRs received by applicants of approved NDA, ANDA, and therapeutic BLA products must be evaluated as:

- Spontaneous or solicited, depending on the source of the information. Solicited adverse events are adverse events that are not spontaneously reported.
- Serious or nonserious, depending on the outcome of the event
- Expected or unexpected, depending on the current U.S. label

Solicited adverse events must receive an additional evaluation for causality.

Nonapplicant manufacturers, packers, or distributors named on the label of an approved prescription drug marketed for human use must evaluate all incoming safety information to comply with the requirements of 21 CFR 314.80(c)(1)(iii). For biological products, any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing must evaluate all incoming safety information to comply with the requirements of 21 CFR 600.80(c)(1)(iii).

All evaluations are significant and will be subject to review during inspection because they impact how information is reported to FDA. To further ensure complete, accurate, and timely reporting, FDA requires application holders, holders of biologic licenses, and nonapplicants named on a product label as a manufacturer, packer, or distributor, to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse experiences to FDA.

Some or all required postmarketing safety obligations may be contracted to other entities, but the application holder, holder of a biologic license, or nonapplicant named on a product label retains the statutory obligation to ensure compliance with the applicable regulations pertaining to postmarketing safety.

Postmarketing safety reporting requirements for over-the-counter (OTC) monograph drugs marketed in the U.S. are governed by Public Law 109-462, the Dietary Supplement and Nonprescription Drug Consumer Protection Act, which was signed into law on December 22,

2006. Prior to the enactment of Public Law 109-462, only OTC drugs marketed with an approved application were subject to mandatory postmarketing safety reporting requirements. However, under the Dietary Supplement and Nonprescription Drug Consumer Protection Act, the manufacturer, packer, or distributor whose name appears on the label of a monograph drug marketed in the U.S. must submit any domestic report received of serious adverse events associated with such a drug to the Agency within fifteen (15) business days.

Citations for postmarketing safety requirements can be found in eNSpect.

Questions concerning postmarketing safety reporting requirements should be addressed to CDER's Office of Compliance, Office of Scientific Investigations, Pharmacovigilance Compliance (PVC) Team, at CDER-OSI-ADE@FDA.HHS.gov.

PART II - IMPLEMENTATION

1. Objective

The objective of the Postmarketing Adverse Drug Experience (PADE) Compliance Program is to monitor industry compliance with postmarketing safety laws and regulations for human drugs and therapeutic biologics, and to ensure that accurate, reliable, and timely safety data are submitted correctly to FDA. The objectives of the PADE Compliance Program will be met by:

- Assessing compliance with postmarketing safety laws and regulations for human drugs and therapeutic biologics
- Providing information to responsible parties during inspections to encourage voluntary compliance with PADE requirements

2. Program Management Instructions

A. Coverage

The purpose of this compliance program is to provide instructions to field and center personnel for conducting inspections of applicants, nonapplicants, holders of biologic licenses, and contractors working on their behalf, and recommending associated advisory and enforcement actions, as appropriate.

B. Inspection Assignments

The CDER Office of Compliance (OC), Office of Scientific Investigations (OSI), PVC Team uses a risk-based approach to select firms for inspection each year.

(1) The PVC Team issues PADE Compliance Program inspection assignments to the Office of Regulatory Affairs headquarters (ORAHQ) bioresearch monitoring (BIMO) Inspection POC through the appropriate information systems. There are no ad hoc or field-initiated PADE Compliance Program inspections.

(a) The inspection assignment lists the firm name, the inspection goal date, and the PVC Team CSO POC responsible for the inspection assignment. The inspection assignment memorandum may contain specific concerns to be addressed during the inspection.

(b) The PVC Team CSO completes the inspection assignment memorandum, which is sent to the ORAHQ BIMO Inspection POC before the inspection.

(c) The ORA investigator should review the inspection assignment memorandum and should contact the PVC Team CSO POC and the PVC Team mailbox (CDER-OSI-ADE@fda.hhs.gov) at least two weeks before the initiation of each inspection to

discuss any updated information for the inspection and any specific concerns identified in the assignment memorandum.

(d) For inspection assignments that identify a PVC Team CSO requesting to participate as a Subject Matter Expert (SME) in the inspection, the ORA investigator, as well as the SME, should follow IOM 5.1.2.5 "Team Inspections." The SME should follow established OBIMO procedures for requesting to participate in an inspection and for obtaining credentials.

(e) The ORA investigator should allot adequate time to complete the Postmarketing Adverse Event Compliance Program inspection as detailed in the inspection assignment instructions, especially in the case when the inspection is conducted in conjunction with another assignment, such as REMS.

(2) For any inspection that cannot be completed by its due date, the ORA Supervisory Consumer Safety Officer should notify the PVC Team mailbox at CDER-OSI-ADE@FDA.HHS.gov in advance of the due date and should include a justification for the delay in completing the assignment.

C. ORA Investigator Responsibilities

(1) Establish initial contact with the PVC Team CSO POC identified in the Postmarketing Adverse Event Compliance Program inspection assignment memorandum at least two weeks before the PADE inspection start date for any updates to the assignment.

(2) Coordinate the inspection timing for inspections that identify a PVC Team CSO requesting to participate as a Subject Matter Expert (SME) in the PADE inspection.

(3) Schedule and conduct the PADE Compliance Program inspection.

(4) Contact the PVC Team CSO POC for clarification during the PADE inspection, if needed.

(5) Discuss findings and any potential observations with your Supervisory Consumer Safety Officer, and consult the CDER PVC Team at CDER-OSI-ADE@fda.hhs.gov, or the PVC Team CSO POC listed in the assignment memorandum, as needed, if there are questions or concerns prior to writing and issuing the Form FDA 483.

(6) Forward as soon as possible to the PVC Team CSO POC a copy of any written response to the Form FDA 483 by the inspected party. The ORA investigator should provide the PVC Team correspondence address [CDER-OSI-ADE@FDA.HHS.gov] to the firm so that their response to the Form FDA 483 can be sent directly to the Center for review, as well as to the OBIMO correspondence box.

(7) Enter the initial PADE inspection classification into the appropriate information technology system. All members of the inspection team, if applicable, should write the EIR.

D. PVC Team CSO Responsibilities

(1) Conduct a risk-based assessment of responsible entities to select sites for PADE inspection. This assessment may include input from other FDA offices.

(2) Draft and issue the PADE inspection assignment memorandum.

(3) Provide the completed inspection assignment memorandum for distribution to ORA, using the appropriate information systems.

(4) Provide expert technical guidance, information, and support to the ORA investigator before, during, and after the inspection.

(5) Review the EIR and supporting documents to determine the final classification of the PADE inspection.

(6) The PVC Team CSO POC will forward to the OBIMO correspondence box for the respective division, a copy of any response to a Form FDA 483 that does not appear to have been shared with the inspecting OBIMO division.

(7) Enter the final PADE inspection classification into the appropriate information technology systems.

(8) Review any response to the FDA Form 483 provided by the firm to determine the appropriate post-inspection correspondence.

(9) Issue post-inspection correspondence to the OBIMO correspondence mailbox for the respective division and the inspected firm.

(10) For inspected entities with one or more approved applications, upload a copy of the post-inspection correspondence into the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).

(11) For foreign inspections, complete and issue the Field Management Directive (FMD)-145 - Release of the Establishment Inspection Report (EIR) after the inspection is closed.

E. ORA Supervisory CSO Responsibilities

(1) Assign the PADE inspection assignment to an investigator.

(2) Review and endorse the EIR.

(3) Notify the PVC Team of the availability of the completed EIR using the appropriate information technology system.

As required, notify the PVC Team mailbox at CDER-OSI-ADE@FDA.HHS.gov of any due date extensions for inspection assignments and the justification for the delay.

PART III - INSPECTIONAL

1. Operations

Inspections under this program will be preannounced unless otherwise instructed in the inspection assignment or a determination is made not to preannounce by ORA.

Before beginning a PADE inspection, determine if the firm to be inspected is an applicant, a nonapplicant, or a contractor. A firm may have more than one role. If assistance is needed in determining a firm's role, consult the PVC Compliance Team. Tables of regulations applicable to applicants, nonapplicants, manufacturers, packers, or distributors of approved and unapproved prescription or OTC monograph products appear in Part I above. Apply the Agency's existing postmarketing safety requirements, based on the firm's roles and products.

Firms responsible for reporting postmarketing adverse experiences to the Agency are referred to as "responsible firms." Responsible firms may perform some or all of the postmarketing adverse drug experience (PADE) reporting functions or may contract with other firms to perform some or all of their PADE reporting functions. However, responsible firms retain the regulatory obligation to ensure that all PADE reporting activities are performed in accordance with the applicable FDA laws and regulations, and remain responsible for complete, accurate, and timely reporting of safety data to FDA. Responsible firms include:

1. Holders of approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs) (21 CFR 314.80, 314.81(b)(2), 314.98, 314.540, and 314.630)

2. Nonapplicant manufacturers, packers, or distributors named on the label of approved drug products (21 CFR 314.80, 314.98, 314.540, and 314.630)

3. Persons named as the manufacturer, packer, or distributor on the label of nonapplication prescription drugs (21 CFR 310.305)

4. Persons named as the manufacturer, packer, or distributor on the label of nonapplication nonprescription drugs (FD&C Act, chapter VII, subchapter H, section 760)

5. Any person holding a biologics license (21 CFR 600.80, 601.44, 601.93, 601.28, and 601.70)

The Public Health Service Act (PHS Act) (42 U.S.C. 262) governs the regulation of biologics. Biological products subject to the PHS Act also meet the definition of *drugs* under the FD&C Act. For biological products, any person whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing, must comply with the evaluation and reporting requirements in 21 CFR 600.80(c)(1)(iii).

A. Inspections of Application Holders of Approved Prescription or Nonprescription Products for Human Use, and Nonapplicants Marketing Prescription Products with or without an Approval.

(1) Written Procedures

(a) Applicants and nonapplicants must develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing safety information, including procedures for managing safety information with contractors and business partners, as applicable. Written procedures should be maintained and followed.

i. Surveillance

- Determine if the firm is monitoring potential sources of adverse event information including, but not limited to, commercial marketing experience, postmarketing clinical investigations, reports in the scientific literature, medical information requests, patient assistance and support programs, business partners, firm-sponsored websites, firm-sponsored social media, legal cases, and product complaint files.
- Determine if the firm is surveilling both foreign and domestic sources.
- Determine if the firm is promptly reviewing all postmarketing safety information received from any source.

ii. Receipt

- The timeline for submission of adverse experiences to FDA begins the day that the applicant, nonapplicant, or its contractors or business partners, obtain the minimum data set for a valid adverse event report. The minimum dataset required to consider information reportable is (1) an identifiable patient, (2) an identifiable reporter, (3) a suspect product and (4) an event.
- The date of receipt must be accurately determined and documented for the receipt of initial and follow-up information received by any method (for example, by phone, electronic mail, postal mail, fax, literature, websites, or employees).

iii. Evaluation

- Determine how safety information from any source is evaluated to determine if an adverse experience is present.
- Determine how adverse experience reports are evaluated to establish if each report is spontaneous or solicited.

- Determine how all adverse experiences, both spontaneous and solicited, are evaluated for seriousness and expectedness.
- For adverse experiences originating from solicited sources, determine how the causal relationship between the product and the adverse experience is assessed.
- Determine if adverse experiences that are both serious and unexpected are promptly investigated and if all attempts to obtain additional information are documented.

iv. Reporting

- Determine if spontaneous adverse experiences, foreign or domestic, that have been evaluated as both serious and unexpected are submitted to FDA no later than 15 calendar days from the initial receipt of the information.
- For solicited adverse experiences, foreign or domestic, determine if all adverse experiences that have been evaluated as serious, unexpected, and possibly related to the suspect product are submitted to FDA no later than 15 calendar days from initial receipt of the information.
- Review 15-day Alert reports submitted late to the Agency. For each late report, the firm should provide justification for why the reports were late and appropriate corrective actions, if applicable.
- Determine if domestic spontaneously reported non-expedited ICSRs are being submitted to FDA with or before the Periodic Report.
- Determine if the firm is in possession of any adverse event data that were not reported to the Agency as required. If relevant information was omitted from or misrepresented in a report submitted to the Agency, obtain copies of the source documents and the submitted report, then notify the PVC Compliance Team.

(b) Determine if written procedures provide for complete, accurate, and timely reporting of safety data to FDA.

(c) The Nonprescription Drug Consumer Protection Act does not specifically require written procedures for PADE reporting for OTC monograph drugs. PADE reporting for monograph drugs is discussed in Section B below.

(d) Regulations pertaining to the requirements for written procedures can be found at 21 CFR 310.305(a), 21 CFR 314.80(b), and 21 CFR 600.80(b).

(2) Individual Case Safety Reports (ICSRs)

ICSRs describe one or more adverse experiences related to an individual patient or subject. A valid ICSR contains a suspect drug, an adverse experience, an identifiable patient, and an identifiable reporter.

(a) Determine if ICSRs contain all the required elements and if missing information needed to complete all required elements was sought. Efforts to obtain missing information must be documented.

(b) Review a sample of the source documents to ensure that ICSRs submitted to FDA are accurate and complete.

(c) For marketed prescription drug products without an approved application, determine whether a copy of the current U.S. label was included as an attachment to the ICSR submission or was previously filed with FDA.

(d) Determine if the applicant conducted prompt and adequate follow-up investigation of previously submitted expedited ICSR.

(e) Determine if the firm uses a standardized medical dictionary.

(f) Regulations pertaining to ICSRs can be found at

- 21 CFR 310.305(d) (for prescription drugs marketed without an approval),
- 21 CFR 314.80 (f) (for prescription drugs marketed with an approval),
- 21 CFR 314.600(f) (for nonvaccine biologics), and
- 21 CFR 329.100(b) (for monograph drugs subject to section 760 of the FD&C Act).

(3) Scientific Literature Reports

(a) Determine if the firm reviews scientific literature and the frequency of the review.

(b) Determine if the applicant or nonapplicant is submitting expedited ICSRs for adverse experiences obtained from the published scientific and medical literature that are both serious and unexpected.

(c) Determine if the applicant or nonapplicant is submitting a copy of the published article as an ICSR attachment for each expedited ICSR of an adverse experience obtained from the published scientific and medical literature. Foreign language articles should be accompanied by an English translation of the abstract.

(d) Regulations pertaining to adverse event reporting from scientific literature can be found at

- 21 CFR 310.305(d);
- 21 CFR 314.80(b), (c)(2), (d), and (f);

- 21 CFR 600.80(b), (c)(2), (d), and (f).

(4) Foreign Postmarketing Adverse Experience Reporting

(a) Determine if written procedures address the surveillance, receipt, evaluation, and reporting of adverse experiences from affiliates, subsidiaries, contractors, and business partners outside the United States.

(b) Determine if serious and unlabeled (i.e., unexpected) adverse experiences from foreign sources have been submitted to FDA within 15 calendar days.

(c) Regulations pertaining to adverse event reporting from foreign sources can be found at

- 21 CFR 314.80(b), (c)(1), and (c)(2), and
- 21 CFR 600.80(b), (c)(1), and (c)(2).

(5) Solicited Safety Data

Solicited safety data arises from organized data collection systems, which may include patient assistance programs, patient support programs, physician engagement programs, or any active solicitation of information from patients or providers, when contact between the firm and the patient or provider is predictable in the context of a specific program.

(a) Determine how the firm identifies and monitors all sources of solicited safety information including, but not limited to, postmarketing studies, nonapplicant-sponsored clinical data obtained by the firm, and patient engagement programs, to ensure that the firm's pharmacovigilance personnel receive all potential adverse experiences. The identification and monitoring of solicited safety data should be addressed in the firm's written procedures.

(b) Determine if the firm is monitoring its firm-sponsored internet and social media sites, and the frequency of the monitoring.

(c) Determine if solicited safety data has been assessed for seriousness, unexpectedness, and causality.

(d) Determine if solicited safety data that has been assessed as serious, unexpected, and possibly related to the suspect product has been submitted to FDA within 15 days of receipt of the information.

(e) During inspection, select several Annual Reports and confirm that the status of the firm's postmarketing studies is included in the reports.

(f) Regulations pertaining to safety data that are not spontaneous can be found at

- 21 CFR 310.305(c)(1) and (d)(5)(iii);
- 21 CFR 314.80(b), (c)(2)(ii)(*3*), (e), and (f)(5)(iii); and

- 21 CFR 600.80(b), (c)(2)(ii)(*3*), (e), and (f).

(6) Aggregate Safety Reports

For each approved application or biologics license, FDA requires the submission of Periodic Reports, which describe safety information obtained during the reporting interval. The reporting interval is quarterly for the first three years following the approval of the application or license, and annually thereafter, unless FDA instructs the firm otherwise.

(a) Determine if the PADER or PAER contains all the required content as described in 21 CFR 314.80(c)(2) or 21 CFR 600.80(c)(2), respectively.

(b) Determine if the PADER or PAER has been submitted within the required regulatory timelines.

(c) Select several Annual Reports and confirm that the status of the firm's postmarketing studies is included in the reports, as required by 21 CFR 314.81.

(d) All reports must be submitted in electronic format, as described in 21 CFR 314.80(g) and 21 CFR 600.80(h).

(e) Periodic safety reporting does not apply to marketed prescription drug products without an approved application, as stated in 21 CFR 310.305.

(f) Periodic safety reporting does not apply to OTC monograph drugs. Refer to Section B. below.

(7) Contractor Oversight

(a) Oversight of outsourced services may include a broad range of activities to ensure that all outsourced services and activities associated with postmarketing safety are performed according to applicable FDA regulations.

(b) Identify the name, business location, and contact information for any contractor involved in the surveillance, receipt, evaluation, or reporting of adverse experiences to FDA, including all domestic and foreign locations where safety information is processed.

(c) Determine if the applicant or nonapplicant has written procedures for obtaining and processing safety information from its contractors. Assess how the applicant or nonapplicant ensures that its contractors develop written procedures.

(d) Determine the contractor's specific responsibilities. Determine how the applicant or nonapplicant ensures that its contractors fulfill their responsibilities. Applicants or nonapplicants may outsource some or all of their postmarketing safety obligations, but remain responsible for complete, accurate, and timely reporting to FDA.

(e) Determine how the contractor documents its receipt date for obtaining the minimum dataset for a valid ICSR and how it communicates this information to the applicant or nonapplicant. The clock for expedited reporting starts as soon as the minimum information for a valid ICSR has been received by the contractor or its representatives.

(8) Electronic Submissions

(a) Determine if safety report submissions are in an electronic format that FDA can process, review, and archive, as required.

(b) Review system-generated delivery confirmation notices from either the Electronic Submission Gateway (ESG) or the Safety Reporting Portal (SRP) and determine if the firm has a procedure for correcting and resubmitting any submission for which the message delivery notice (MDN) indicated that the submission was not accepted.

(c) Determine if the firm has a corrective action for each late submission to the Agency, according to the MDN.

(d) Determine if MDNs are being retained.

(e) Regulations pertaining to electronic submissions can be found at

- 21 CFR 310.305(c) and (e);
- 21 CFR 314.80(c) and (g)(1); and
- 21 CFR 600.80(c) and (h).

(9) Waivers

(a) If an applicant, nonapplicant, or contractor claims to have a waiver for any regulatory requirement pertaining to postmarketing safety, request a copy of the waiver and determine compliance with the terms of the waiver.

(b) Regulations pertaining to waivers can be found at

- 21 CFR 310.305(e)(2),
- 21 CFR 314.80(g)(2),
- 21 CFR 314.90,
- 21 CFR 600.80(h)(2), and
- 21 CFR 600.90.

(10) Recordkeeping

(a) For approved drugs or biologics, determine if all records containing information relating postmarketing safety reports (whether or not submitted to FDA) have been maintained for a period of 10 years, or for combination products, the longest retention period applicable.

(b) Anyone marketing a prescription drug for human use without an approved new drug application or abbreviated new drug application must comply with the recordkeeping and reporting requirements of 21 CFR 310.305.

(c) Record maintenance requirements for monograph drugs are discussed in Section B. below, "Inspections of Firms Subject to the Reporting Requirements of the Dietary Supplement & Nonprescription Drug Consumer Protection Act."

(d) Regulations pertaining to recordkeeping can be found at

- 21 CFR 310.305(g);
- 21 CFR 314.80(c) and (j);
- 21 CFR 600.80(c) and (k); and
- 21 CFR 600.80(k) and (l).

(11) Inspecting Combination Product Applicants & Constituent Part Applicants

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. A "combination product applicant" is an entity holding the approved or cleared application(s) for a combination product. A "constituent part applicant" is an entity holding an approved or cleared application to market a drug, device, or biological product as a constituent part of a combination product (rather than holding the application for the entire combination product or applications for each constituent part).

(a) Determine if the combination product applicant and the constituent part applicant are complying with postmarketing safety reporting requirements corresponding to the type of application under which they received marketing authorization.

i. Combination product applicants and constituent part applicants must comply with the postmarketing safety reporting requirements under 21 CFR parts 803 and 806 if their product is marketed under a device application.

ii. Combination product applicants and constituent part applicants must comply with the postmarketing safety reporting requirements under 21 CFR 314 if their product is marketed under a drug application.

iii. Combination product applicants and constituent part applicants must comply with the postmarketing safety reporting requirements under 21 CFR 600 and 606 if their product is marketed under a BLA.

iv. All combination product applicants and constituent part applicants must comply with 21 CFR 4.102 to 4.105.

(b) In addition to complying with postmarketing safety reporting requirements corresponding to the type of application under which the marketing authorization

was granted, determine if the combination product applicant is submitting required reports based on the product's constituent parts.

(c) Determine if the constituent part applicant is sharing information received regarding events that involve a death or serious injury within the meaning of 21 CFR 803.3, or an adverse experience within the meaning of 21 CFR 314.80 or 21 CFR 600.80, with the combination product's other constituent part applicants, within five days.

(d) Determine if the applicant is retaining records related to the sharing of information, including the identity of the parties with whom the information was shared and the date shared.

(e) Determine if records are being retained for the longest retention period that applies.

B. Inspections of Firms Subject to the Reporting Requirements of the Dietary Supplement & Nonprescription Drug Consumer Protection Act

The Dietary Supplement & Nonprescription Drug Consumer Protection Act, which was signed into law in 2006, amended section 760 of the FD&C Act and required safety reporting for OTC nonprescription monograph drugs.

(a) Determine if the firm is a manufacturer, packer, or distributor whose name appears on the label of an OTC monograph drug marketed in the United States. If so, determine if the manufacturer, packer, or distributor is submitting all serious adverse events received through the address or telephone number described on the product label, and associated with such drug when used in the United States, to FDA within 15 business days of receipt of the information, along with a copy of the product's label.

(b) If serious adverse event reports for OTC monograph drugs marketed in the U.S. were not submitted to FDA within 15 business days, document whether the report was received through the address or telephone number described on the product label.

(c) Determine whether follow-up information, if any, received within one year was forwarded to the Agency no later than 15 business days after receipt of the new information.

(d) Determine if the firm is complying with 21 CFR 329.100(a) and (c), which require that reports submitted to FDA under section 760 of the FD&C Act be submitted in an electronic format that FDA can process, review, and archive.

(e) Determine if records related to a report of an adverse event are maintained for a period of six years, as required.

(f) When inspecting a retailer, determine if the retailer directs serious adverse event reports to the manufacturer or packer. When inspecting a manufacturer or packer, determine if serious adverse event reports from its retailers are sent to FDA in an electronic format that the Agency can process, review, and archive.

C. Sample Collections

There are no sample collections planned under this program.

2. **Reporting**

A. Form FDA 483, Inspectional Observations

Document observations on the Form FDA 483, "Inspectional Observations." See eNSpect for a list of possible PADE citations.

If there are questions or concerns before documenting any observations on a Form FDA 483, contact the Supervisory Consumer Safety Officer, and consult the CDER PVC Team at CDER-OSI-ADE@fda.hhs.gov, or the PVC Team CSO POC listed in the assignment memorandum.

B. Establishment Inspection Report (EIR)

The ORA investigator should refer to the Investigations Operations Manual (IOM) for guidance on reporting inspection findings.

C. Post-Inspection Communications

The Office of Bioresearch Monitoring Operations (OBIMO) Division should notify the PVC Team mailbox (CDER-OSI-ADE@fda.hhs.gov) and the PVC Team CSO POC of any post-inspection communications with the inspected entity.

PART IV - ANALYTICAL

There are no analytical activities planned under this program.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

The following guidance is to be used in conjunction with the instructions in FMD-86 for initial OBIMO Division and Center classification of EIRs generated under this Compliance Program. Refer to Center (RTC) should not be used where the Center has final classification authority. Possible PADE observations and citations can be found in eNSpect.

No Action Indicated (NAI) - No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action).

Voluntary Action Indicated (VAI) - Objectionable conditions or practices were found, but do not rise to the level warranting OAI classification.

Official Action Indicated (OAI) - Objectionable conditions or practices were found, whose scope, severity, or pattern warrants the recommendation for a regulatory action.

Once an OAI decision is reached, additional information (for example, previous inspection findings, correspondence, or other information) may assist the Center in determining which type of post-inspection activity is appropriate.

Inspection findings documenting that a firm is not meeting its PADE compliance requirements may be used as evidence for taking regulatory or judicial actions. The CDER PVC Team and OSI management will be responsible for drafting, developing, and issuing all Untitled Letters and Warning Letters. The CDER PVC Team will be responsible for the final classification of inspections. The OBIMO Division should consult with the PVC Team when a regulatory action recommendation is considered to allow for discussion of the recommendation.

A. Warning Letters

The issuance of a Warning Letter (WL) may be warranted when the inspection uncovers significant objectionable conditions related to noncompliance with PADE requirements. The CDER PVC Team and OSI management will evaluate all inspections classified as OAI by OBIMO on a case-by-case basis.

B. Untitled Letters

An Untitled Letter (UL) may be warranted when the deficiencies found at the firm are severe enough to justify a formal letter to the firm, but do not meet the threshold of regulatory significance for a WL.

Factors that influence the issuance of a WL or UL include the nature and extent of the violations (for example, if they are repeated or deliberate), the compliance history of the inspected firm, and the corrective actions implemented by the firm.

C. Enforcement Actions

Generally, FDA may take the following enforcement actions if the firm does not implement adequate corrective actions and continues to violate PADE regulations or the FD&C Act following the issuance of a WL or UL.

1. Injunction:

Injunction should be considered when follow-up inspection(s) show that the firm has a continuing pattern of significant and substantial deviations, despite previous attempts by FDA to obtain compliance.

2. Seizure:

Seizure for failure to comply with postmarketing adverse drug experience reporting regulations would be possible only if the approval of the application for the product has first been withdrawn (FD&C Act, section 304(a)(1)). Seizure would then be based on distribution of an unapproved drug product.

3. Prosecution:

Evidence that a firm is submitting false information, not submitting required reports for serious postmarketing adverse events, or withholding important information, the submission of which may have resulted in the Agency requiring labeling changes or withdrawing an application, should be referred to the Office of Criminal Investigations (OCI) for consideration of prosecution.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

A. Introduction of FDA's PADE Compliance Program (YouTube): https://www.youtube.com/watch?v=RX-UGsVlCrM&feature=youtu.be
B. Deeper Dive Webinar: Postmarketing Drug Safety and Inspection Readiness: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/deeper-dive-webinar-postmarketing-drug-safety-and-inspection-readiness-june-19-2018
C. Warning Letters: https://www.fda.gov/drugs/enforcement-activities-fda/warning-letters-and-notice-violation-letters-pharmaceutical-companies
D. Drug Recalls: http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm
E. Recalls, Market Withdrawals, & Safety Alerts: http://www.fda.gov/Safety/Recalls/default.htm
F. Guidance for Industry - Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm092257.pdf
G. Guidance for Industry - Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm171672.pdf
H. Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff: https://www.fda.gov/media/111788/download
I. Providing Submissions in Electronic Format – Postmarketing Safety Reports: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369.pdf
J. Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362174.pdf
K. Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346564.pdf

L. Drug Compliance Program Guidance Manuals: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs
M. Postmarket Requirements and Commitments: https://www.accessdata.fda.gov/Scripts/cder/pmc/index.cfm
N. Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/
O. Investigations Operations Manual: https://www.fda.gov/ICECI/Inspections/IOM/ucm2005387.htm
P. PADE resource page link (FDA Staff only): https://fda.sharepoint.com/:w:/r/sites/insideFDA-CDER-OC/_layouts/15/Doc.aspx?sourcedoc=%7BB03AE29B-C4FB-41BC-87D6-EEBA37BE4C1E%7D&file=2021%2010-08%20Pharmacovigilance%20Compliance%20Team%20Resources%20Updated.doc&action=default&mobileredirect=true
Q. Requirements on the Content and Format of Labeling for Human Prescription Drug and Biological Products – Final Rule: https://www.federalregister.gov/documents/2006/01/24/06-545/requirements-on-content-and-format-of-labeling-for-human-prescription-drug-and-biological-products
R. FDA Safety Reporting Portal: https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=fda16b52-0490-4afe-bcda-76fcbc63e8c1

2. **Program Contacts**

A. PADE

Questions about the PADE compliance program can be addressed to any of the following:

- The PVC Team mailbox at CDER-OSI-ADE@fda.hhs.gov
- The PVC Team CSO POC identified in the inspection assignment
- By mail:
  Pharmacovigilance Compliance Team
  Office of Scientific Investigations
  Office of Compliance, CDER
  Food and Drug Administration
  10903 New Hampshire Avenue
  WO 51, room 5356
  Silver Spring, MD 20993-0002

B. Operational

For operational questions:

- Office of Regulatory Affairs (ORA), Office of Medical Products and Tobacco Operations (OMPTO), Office of Bioresearch Monitoring Operations (OBIMO)
- ORABIMOInspectionPOC@fda.hhs.gov