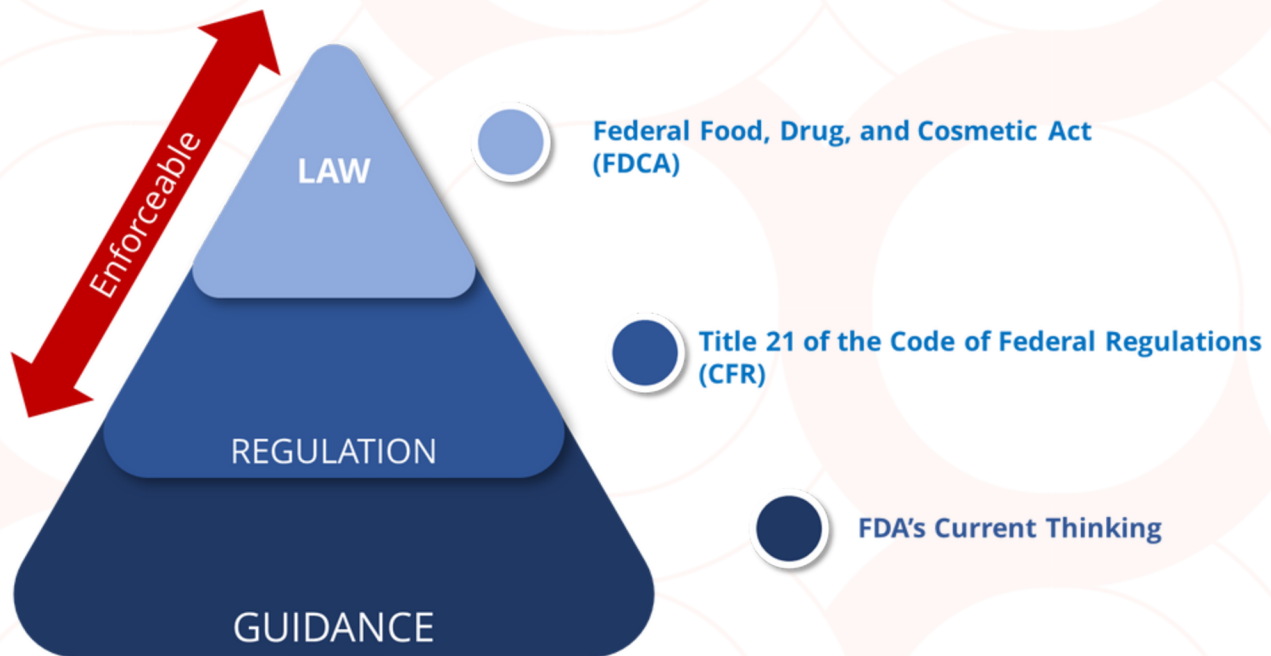


Postmarketing Adverse Drug Experience (PADE) Inspections - Part II

Dr. Sumit Verma MD, DNB - Director and President,
Operations Management, CSPV



Legal Framework of PADE Inspections



Inspectional Observations: USFDA 2023

21 CFR 314.80(b)	Failure to develop written procedures	<ul style="list-style-type: none"> Written procedures have not been developed for the [surveillance] [receipt] [evaluation] [reporting to FDA] of post marketing adverse drug experiences.
21 CFR 314.81(b)(1)(ii)	Failure to meet specifications	<ul style="list-style-type: none"> An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

21 CFR 314.80(c)(1)(i)	Late submission of 15-day report.	<ul style="list-style-type: none"> Not all adverse drug experiences that are both serious and unexpected have been reported to FDA within 15 calendar days of initial receipt of the information.
21 CFR 314.80(c)(1)(ii)	Failure to investigate serious, unexpected events	<ul style="list-style-type: none"> Adverse drug experiences that were the subject of post marketing 15-day reports were not [promptly] investigated.
21 CFR 314.80(c)(2)	Late submission of annual safety reports	<ul style="list-style-type: none"> Not all annual periodic adverse drug experience reports have been submitted within 60 days of the anniversary date of the approval of the application.
21 CFR 314.80(c)(2)(ii)(A)	Incomplete periodic safety report	<ul style="list-style-type: none"> Failed to submit a periodic report containing <ul style="list-style-type: none"> [a narrative summary and analysis of the ADE information for the reporting interval in the report.] [an analysis of the post marketing 15-day Alert reports submitted during the reporting interval.] [a history of actions taken since the last report because of adverse drug experiences.] [an index with a line listing of your patient identification code and adverse reaction term(s) for all ICSRs you submitted for the reporting interval.]
21 CFR 314.80(d)	Failure to submit scientific article	<ul style="list-style-type: none"> A postmarketing 15-day Alert report based upon scientific literature was not accompanied by a copy of the published article.
21 CFR 314.80(j)	Failure to maintain records	<ul style="list-style-type: none"> Failed to maintain for a period of 10 years records of all adverse drug experiences known to you, including raw data and any correspondence.
21 CFR 314.81(b)(2)	Timely submission	<ul style="list-style-type: none"> An annual report was not submitted [each year] [within 60 days of the anniversary date of U.S. approval of the application] to the FDA division responsible for reviewing the application.

Written Procedures Must Address

Surveillance

- Account for all sources
- Spontaneous
- Solicited
- Internet sources (firm sponsored)
- Literature
- ...and more!

Receipt

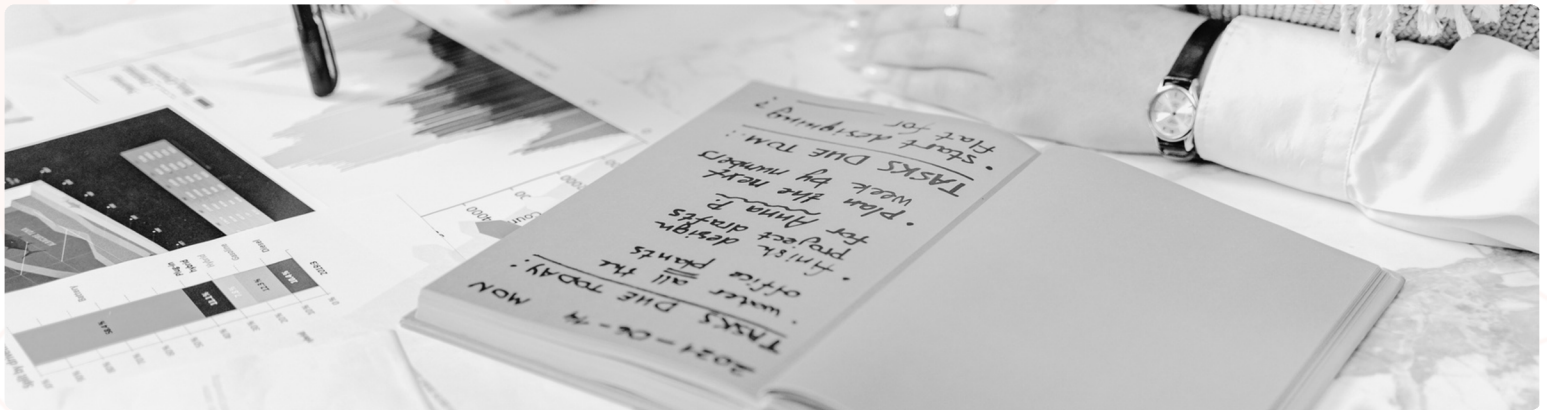
- ADE info
- Initial
- Follow-up
- Receipt from any source

Evaluation

- Seriousness
- Expectedness
- Relatedness
- ADEs from any source
- Follow-up procedures

Reporting

- 15-day Alert Reports
- Non-expedited individual case safety reports (ICSRs)
- Aggregate Reports
- All info must be submitted electronically

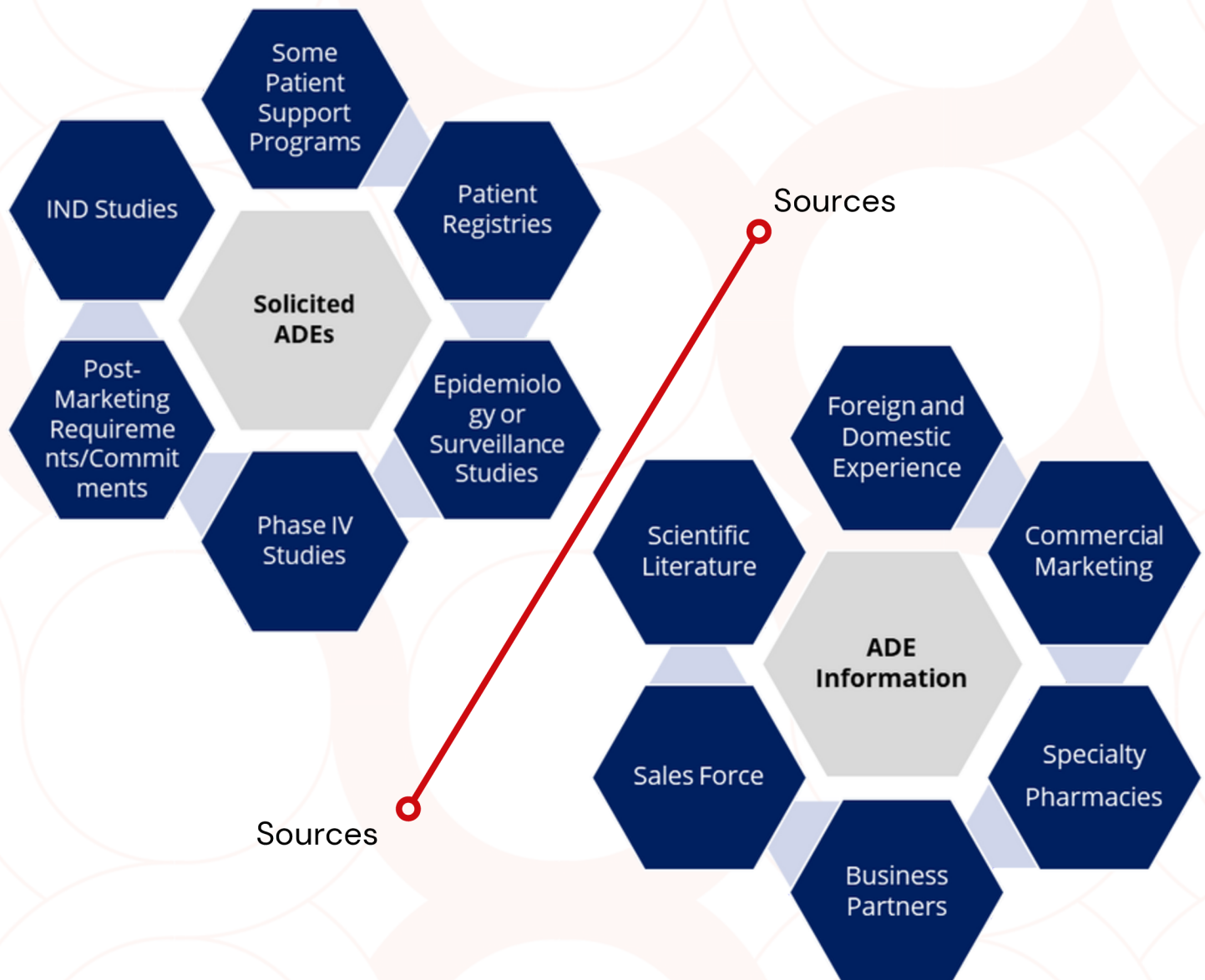


Written Procedures

- ❖ 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.
- ❖ Determine if written procedures provide for complete, accurate, and timely reporting of safety data to FDA.
- ❖ Regulations pertaining to the requirements for written procedures: 21 CFR 310.305(a), 21 CFR 314.80(b), and 21 CFR 600.80(b).

Surveillance

- Determine if the firm is monitoring potential sources of adverse event information
- 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



Many other sources such as firm-sponsored websites, firm-sponsored social media, legal cases, product complaint files etc.

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).



Evaluation

Determine how:

- Safety information from any source is evaluated to determine if an adverse experience is present.
- Adverse experience reports are evaluated to establish if each report is spontaneous or solicited.
- 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.
- If adverse experiences that are both serious and unexpected are promptly investigated and if all attempts to obtain additional information are documented.

Reporting

- ❖ 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
- ❖ Domestic spontaneously reported non-expedited ICSRs are being submitted to FDA with or before the Periodic Report.
- ❖ The firm is in possession of any adverse event data that were not reported to the Agency as required.

Stay tuned for Part III, where we will explore the safety reports.



Selected References

1. <https://www.fda.gov/>
2. Number of 483 issued from the System* Inspections ending between 10/1/2022 and 9/30/2023 <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations>
3. Postmarketing Drug Safety Compliance: 2019 Inspection Findings April 29, 2020 (Live Webinar) Center for Drug Evaluation and Research – Small Business and Industry Assistance, Center for Drug Evaluation and Research, US Food and Drug Administration
4. Postmarketing Drug Safety and Inspection Readiness June 19, 2018 Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Webinar
5. Postmarketing Drug Safety and Inspection Readiness June 19, 2018 Center for Drug Evaluation and Research (CDER) Small Business and Industry Assistance (SBIA) Webinar
6. CHAPTER 53 – Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products, [fda.gov](https://www.fda.gov)

Author



Dr. Sumit Verma

Director and President,
Operations Management, CSPV
Soterius, Inc.

Dr. Sumit Verma is a medical graduate with specialization in anesthesiology and has more than 15 years of experience in the pharmaceutical industry, clinical medicine, clinical research, and pharmacovigilance. He has built teams that have consistently delivered and exceeded customer expectations across pharmacovigilance domains such as case processing, signal management, risk management, aggregate reports, and clinical safety. He has co-authored two books – one on pharmacovigilance and another on pharmacology.

Like This Blog?

[Share on LinkedIn](#)[Share on Facebook](#)[Share on Twitter/X](#)[Share on Email](#)

Disclaimer

The scenario described in this post is entirely hypothetical. It is not based on real-world patient data or individual case safety reports. All pharmacological mechanisms and regulatory references are cited to support discussion only. This post is intended to facilitate dialogue on signal detection and does not imply new safety findings, labeling recommendations, clinical guidance or clinical relevance.

Soterius logo are trademarks or registered trademarks of Soterius in all jurisdictions. Other marks may be trademarks or registered trademarks of their respective owners. The information you see, hear or read on the pages within this presentation, as well as the presentation's form and substance, are subject to copyright protection. In no event, may you use, distribute, copy, reproduce, modify, distort, or transmit the information or any of its elements, such as text, images or concepts, without the prior written permission of Soterius. No license or right pertaining to any of these trademarks shall be granted without the written permission of Soterius (and any of its global offices and/or affiliates). Soterius reserves the right to legally enforce any infringement of its intellectual property, copyright and trademark rights.

Any content presented herewith should only be considered for general informational purposes and should not be considered as specific to the requirements of any particular organisation or for any specific purpose. Soterius, including its authors, presenters, and any affiliated individuals, does not make any representations or warranties about the completeness, reliability, appropriateness, relevance, or accuracy of the content presented here.

Please consult your physician/Health Care Provider for any matters related to health. No one should act on this information without specific professional advise.

connect@soterius.comwww.soterius.com