



Audits in Pharmacovigilance: A commitment to Safety

In the realm of healthcare, ensuring patient safety is the most important aspect. That's where pharmacovigilance plays a role in safeguarding lives by monitoring the safety of medicinal products. But how do license holders ensure that these systems are working perfectly well? The answer lies in audits. Audits are the safety checkpoints in the lifecycle of a drug. Audits serve as a critical process to assess, verify, and enhance the compliance and effectiveness of the pharmacovigilance processes, and that's why they matter:

What are the common 483 Observations in recent USFDA inspections:

A fundamental issue in pharmacovigilance is that many cases concern suspected adverse drug reactions. In real-life situations, a very limited number of adverse reactions qualify as 'certain' or 'unlikely'; most are usually in between, i.e., either 'possible' or 'probable'. To address this issue, many methods have been developed to harmonize causality assessment. However, causality assessment has become a common routine activity in pharmacovigilance.

The advantages of causality assessment includes the following:

- ✿ Written procedures have not been developed for the surveillance, receipt, evaluation and reporting to FDA of post marketing adverse drug experiences.
- ✿ A postmarketing 15-day Alert report based upon scientific literature was not accompanied by a copy of the published article.
- ✿ 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.
- ✿ Periodic reports of non-alert adverse drug experiences have not been submitted.
- ✿ An NDA-Field Alert Report was not submitted within three working days of receipt of information.

What to expect from a PADE Inspection:

- ✿ Compliance with postmarketing safety laws and regulations for human drugs and therapeutic biologics.
- ✿ Ensure that accurate, reliable, and timely safety data are submitted correctly to FDA.

Who are the responsible firms and what are the applicable regulations:

- ✿ 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).
- ✿ Nonapplicant manufacturers, packers, or distributors named on the label of approved drug products (21 CFR 314.80, 314.98, 314.540, and 314.630).
- ✿ Any person holding a biologics license (21 CFR 600.80, 601.44, 601.93, 601.28, and 601.70).

What NDA/ANDA/BLA Holders shall do to be compliant:

1. Written Procedures

Develop written procedures for postmarketing safety information, including procedures for managing safety information with contractors and business partners, as applicable. Written Procedures Must Address the following:

 Surveillance	 Receipt	 Evaluation	 Reporting
Account for all sources • Spontaneous • Solicited • Internet sources (firm-sponsored) • Literature • Other	ADE info • Initial • Follow-up Receipt from any source	• Seriousness • Expectedness • Relatedness • ADEs from any source • Follow-up procedures	• 15-day Alert Reports • Non-expedited individual case safety reports (ICSRs) • Aggregate Reports

2. Individual Case Safety Reports (ICSRs)

- Applicable Regulations: 21 CFR 314.80 (f), 21 CFR 314.600(f).
- Cases from all Sources (including business partners, social media etc.
- Timely submission of complete ICSR data.
- Follow-up procedure for missing information.

3. Scientific Literature Reports

- Applicable Regulations: 21 CFR 314.80(b), (c)(2), (d), and (f); 21 CFR 600.80(b), (c)(2), (d), and (f).
- Reviews scientific literature at a determined frequency.
- Submit a copy of the published article as an ICSR attachment for each expedited ICSR.

4. Aggregate Safety Reports

- Applicable Regulations: 21 CFR 314.80(c)(2) or 21 CFR 600.80(c)(2), 21 CFR 314.81.
- Contains all the required content and
- PADER, annual reports submitted quarterly/annually in electronic format as per the regulations.

5. Contractor Oversight

- Written procedures for obtaining and processing safety information from the contractors.
- Contractors develop written procedures for the outsourced services and activities.
- Day 0, as soon as the minimum information for a valid ICSR is received by the contractor or its representatives.

How does FDA classify its Inspection:

- 🌀 **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.

References:

- 1. PostmarketingAdverseDrugExperience(PADE)InspectionsComplianceProgramforHumanDrugandTherapeuticBiological Products; 10/18/2022
- 2. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspectional-observations-and-citations>

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Parul is an M.D. in Pharmacology with over 15 years of experience in pharmacovigilance and clinical research. He has managed the expectations of multiple clients on quality and compliance for complex analytical work in medical safety such as signal management, risk management, aggregate report preparation, and on the immediate impact case management functions. He has participated in over 10 regulatory inspections with successful outcomes. Parul has experience across pre and post-marketing pharmacovigilance including signal management, aggregate report, ICSR case processing, SAE/ SUSAR processing and reporting, analysis of similar events, safety management plans, SAE reconciliation plan, etc. In his previous role, he headed the pharmacovigilance department of a global pharmaceutical company where he successfully accomplished global harmonization of the pharmacovigilance function to create a Centre of Excellence.

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We support companies from the initial development stage of a drug/vaccine to the approval and ultimate marketing of the therapy, supporting ongoing operations and regulatory commitments globally.

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