



Ready for Pharmacovigilance Inspection – USFDA

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Accepted on: 18-10-2015; Finalized on: 31-10-2015.

ABSTRACT

Every Pharmacovigilance (PVG) function at one time or another, undergo governmental or health authority inspections as well as audits by license partners, internal auditors and others. Postmarketing safety data collection and adverse event reporting is a critical element of the Agency's Postmarketing safety surveillance program for United States Food and Drug Administration (USFDA) regulated drug products. The USFDA has several obligations for Pharmaceutical companies to ensure that patient safety is considered as priority along with Good Pharmacovigilance Practices. There is a consistent increase in efforts from USFDA inspectors to ensure that companies comply with all regulations, which is most important in terms of human interest. In cases of non-compliance, various enforcement actions can be considered by USFDA which can result in withdrawal of marketing authorization of products or other serious outcomes. An audit is necessary before an inspection, as it provides an overview of PVG activities required for identification of gaps with respect to present regulations, which is very crucial in terms of brand value.

Keywords: Pharmacovigilance inspection, Drug Safety Audit, Good Pharmacovigilance practice, Periodic adverse drug experience report.

INTRODUCTION

The safety of medicines is of utmost importance in reference to patients and healthcare professionals.

The pharmaceutical companies have ethical responsibility to ensure that their marketed products will have appropriate safety and efficacy. In addition, there are enormous repercussions for patients and healthcare professionals pertaining to a new drug with potential adverse drug reaction (ADR) profile.

The United States Food and Drug Administration (USFDA) was highly criticized after public health disaster of Rofecoxib (Vioxx) at the beginning of this century. Thereafter, to oversee the management of drug safety issues, an independent Drug Safety Oversight Board was established in 2005 by USFDA. The Postmarketing Adverse Drug Experience (PADE) and safety reporting regulations in USFDA are set forth in Title 21 of the Code of Federal Regulations (21 CFR) Sections - 310.305, 314.80, 314.81(b)(2), 314.98, 314.540, 314.630, 600.80, 601.28, 601.44, 601.70, and 601.93, and in the Federal Food, Drug, and Cosmetic Act (FD&C Act) Chapter VII, Subchapter H, Section 760. A guidance for industry on Good Pharmacovigilance Practices (GVP) and Pharmacoepidemiologic assessment (March 2005) was also issued by USFDA.

Currently, there has been significant increase in Pharmacovigilance (PVG) inspections by USFDA to ensure that industry is complying with its responsibilities to safeguard human interest.

USFDA Obligations for Drug Safety Monitoring

The major PVG activities in US include compliance with

post-market requirements under the Federal Food, Drug, and Cosmetic Act and USFDA implementing regulations pertaining to post-marketing surveillance and risk assessment. The PVG plan includes various procedures apart from routine post-marketing ADR reporting and is aimed to enhance the sponsor's acquisition of safety data.

Under USFDA, following three parts include guidance to cover the different phases of the risk assessment and risk management for sponsors.¹

Premarketing risk assessment

The marketing authorization holder (MAH) is responsible for reviewing the safety data information obtained or otherwise received by the MAH from any clinical study or epidemiological investigation.

Post-marketing Pharmacovigilance and Pharmacoepidemiologic Assessments

Under USFDA, all the scientific and data gathering activities related to detection, assessment and evaluation of safety signals as depicted in Figure 1, includes signal identification, interpretation followed by a PVG plan.

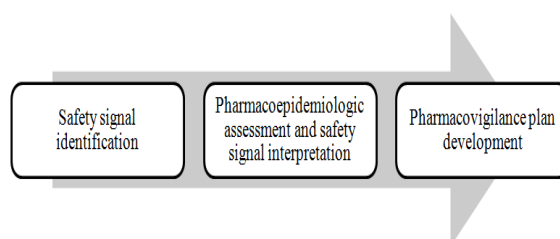


Figure 1: Signal Evaluation



Risk Evaluation and Mitigation Strategies

The USFDA has an obligation for MAH to generate special risk management programs, known as Risk Evaluation and Mitigation Strategies (REMS). The MAH with approved application for new drug or abbreviated new drug or biological medicinal product needs to submit REMS, in case the benefit of drug outweighs the risks.^{2,3}

In US, under Title 21 of Code of Federal Regulation (CFR) §§ 314.80, 314.98, 600.80, Periodic adverse drug experience reports (PADERS) includes all serious expected and non-serious adverse events (AEs), which are not reported through “15-day Alert reports” or their follow-up reports. In addition, the PADERS are also endowed with narrative summary of information in the safety report and an analysis of “15-day Alert reports” submitted during the routine PVG activities.

PVG Audit before an Authority Inspection

PVG audit may be defined as a critical review and analysis of the compliance [with global and local legislation, internal Standard Operating Procedures (SOPs), Working Instructions (WIs), contracts/agreements] of the systems supporting the monitoring of AEs and detection of signals.

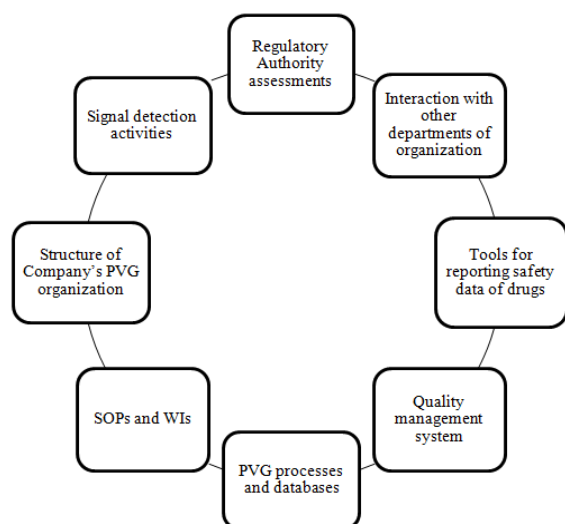


Figure 2: Basic Elements of PVG System

Its purpose is to provide assurance that the internal PVG (and related) systems are robust, in order to assure the protection of public health.⁴ The audit can be done internally by respective department of MAH or it can be outsourced to third party. An audit is very crucial to keep the drug safety operations ready for an authority inspection. Following are the objectives of a PVG audit or inspection:

- To assure availability of safe and effective drugs to people
- To monitor the quality of post-marketing safety data submitted to Regulatory authorities (RA)
- To help officers within RA by ensuring the receipt of effective safety data for proper evaluation of product safety

- To evaluate industry's compliance with respect to PADE reporting requirements

Further, there are some basic elements of PVG system as depicted in Figure 2, which are assessed in audit/inspection.⁴⁻⁷

USFDA PVG Inspection in detail

The USFDA is increasing its demands on industry for robust safety monitoring systems. Those responsible for reporting PADE to USFDA are referred to as “Responsible Firms”. The risk-based approach followed by agency for inspection includes factors like date of firm's last PADE inspection, past compliance history, identified deficiencies, acquisition of new drug approvals (NDAs) or abbreviated new drug approvals (ANDAs).

The firm shall be notified regarding statutory inspections in advance or otherwise there shall be no notification, if there is a genuine reason for a triggered inspection. The inspection will review global activities and processes that involve products with a pending or approved marketing authorization of products. The following information shall be examined during a drug safety inspection by USFDA.⁴⁻¹¹

Documented Procedures, SOPs and WIs

The responsible firms should ensure that the SOPs/WIs should meet the requirements for content, quality, and completeness of drug safety information. Further, it must be ensured that the relevant personnel are well trained and these procedures are adequately followed.

The firms are also required to have various documented procedures (guidance documents/annexes) for the receipt, assessment and reporting of PADE reports to USFDA. The various requirements pertaining to PADE written documents are included in 21 CFR 310.305 and 314.80.

- USFDA can evaluate the firm's documented procedures for receipt, assessment, and submission of AE data and it can be evaluated whether these procedures are adequate for effective and quality PADE reporting.
- These procedures must be easily available and all employees involved in PVG system should be well trained on the same.
- The firm's procedures should also address the handling of safety data received during non-working hours through electronic means, like e-mail.

Products covered during inspection

The various products endowed with greatest potential or actual impact on patient safety, including products with:

- more than average potential safety impact (products with a narrow therapeutic index or indicated for special population)

- incomplete safety profile (with limited presence in market or approved within last three years)
- have emerging safety issue (products with post-marketing requirements, post-marketing safety studies)

Processing and submission of Individual Case Safety Reports including sampling of cases

The firm's procedures can be evaluated for determining the method of extraction of information from source documents for incorporation in 15-Day Alert reports. The USFDA can determine if these procedures are appropriate to ensure that the respective information is adequately included in these reports. The firm should also have appropriate documented procedures for management of spontaneous and study reports of adverse events.

The clear definition of initial date is necessary in both expedited and periodic reports. The same is very crucial in terms of initial notification and any further follow-up communication. The receipt date should be the date that MAH or contractors receives the information, irrespective of their qualification to identify a reportable Individual Case Safety Reports (ICSRs).

The inspector can perform sampling of cases, for e.g. few numbers of cases can be selected and comparison can be done between data in ICSR and data in the source documents to ensure completeness and accuracy. In addition, following aspects shall also be determined:

- Labeling

Labeling of a reported AE, i.e. if it is considered labeled or unlabeled as per the Reference Safety Information (RSI).

- Seriousness

Criteria on which an adverse event is considered serious

- Event Coding

The firm should have written procedures in place for appropriate coding of ADR data, for e.g., MedDRA coding.

- Reporting

Non-submission or late reporting of any ADR data

- 15-Day Alerts

During an inspection, firm can be requested to provide a listing of all 15-Day Alert reports which were submitted late to the Agency. Further, justification and an appropriate corrective action may be required for every late report.

- Foreign PADE Reporting

- The Foreign (outside US) reports of serious, unexpected adverse experiences must be submitted to agency as 15-day Alert reports.
- Other Foreign reports, like serious/expected, non-serious expected/unexpected adverse experiences

are exempted for submission, but are only incorporated in periodic reports.

- Follow-up information

There should be well documented procedures for the collection of four basic elements of a valid ICSR (i.e., identifiable patient, reporter, suspect drug, and adverse drug experience) and appropriate reporter contact details to allow the feasibility of a follow up request in future.

Periodic reports

The responsible firm must submit quarterly and annual Periodic Reports as required by 21 CFR 314.80(c)(2) and 600.80(c)(2) to USFDA, within the required time period, for its approved products. The following information can be evaluated pertaining to these reports:

- The Periodic Reports must include the elements in accordance with 21 CFR 314.80(c)(2)(ii) and 600.80(c)(2)(ii), including a history of actions taken, changes in product label or studies initiated, since the last report because of adverse drug experiences.
- The PADER must contain the elements identified in ICH for USFDA Guidance for industry on E2C (R1) reporting.
- ICSR submitted to authority as part of a Periodic Report should be submitted electronically in XML format through the Electronic Submissions Gateway or on paper to the Central Document Room.

Signal Detection and Management

The Post-marketing PVG and Pharmacoepidemiologic Assessments in US are concerned with identification and interpretation of signals. After identifying a safety signal, USFDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also:

- employ data mining techniques
- calculate reporting rates for comparison to background rates

Based on these findings and other available data (e.g. from preclinical or other sources), USFDA shall suggest the sponsor to consider further study (e.g. observational studies) and establish the existence of a potential safety risk. During an inspection, the firm's process can be reviewed to ensure that the signaling and risk assessment activities are conducted appropriately and outcome of results is adequately shared with agency.

Risk Management / Pharmacovigilance Planning

The USFDA can require a REMS if the agency determines that safety measures are needed beyond the professional labeling to ensure that a drug's benefits outweigh its risks. The authority can review the firm's procedure of developing REMS as depicted in Figure 3, including reasonable steps taken to monitor and evaluate those in



the healthcare system that are responsible for implementing Elements to Assure Safe Use (ETASU) measures.

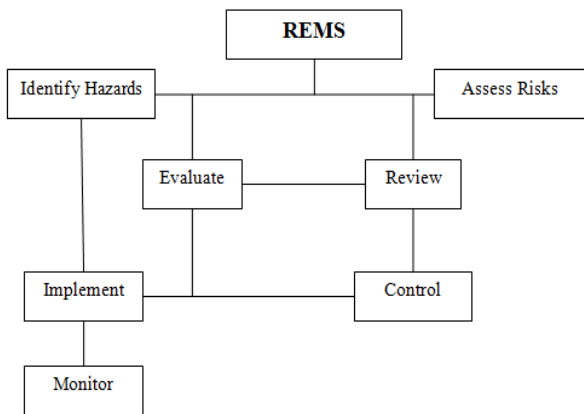


Figure 3: REMS Implementation System

In addition, USFDA believes that for most of the products, routine spontaneous reporting will be sufficient for post-marketing surveillance. However, PVG plans may be appropriate for products for which:

- serious safety risks have been identified pre- or post-approval
- risk populations have not been adequately studied

The USFDA can review firm’s process of evaluation of the safety risk linked with effectiveness of PVG plan.

Quality Management Systems including Key performance metrics

The firm should have a Quality Management Systems (QMS) including a mission statement of the goals and scope of the program as well as applicable laws, regulations and best practices. The firm must monitor and track Key performance metrics (KPIs) to ensure smooth functioning of processes. In case of issues, a root cause analysis should be performed and followed by corrective actions and preventive action plans (CAPAs). The following KPIs should be tracked by PVG department:

- Reporting of ICSRs
- Workflow steps in safety database, e.g., triaging, case closure, coding, medical review
- Late Reports to business partners
- E2B reporting failures
- Submission of aggregate reports
- Generation of CAPAs or file notes
- Personnel training
- Updation or creation of new SOPs

Further, the following information shall also be examined by authority during an inspection, which is presented in Table 1.⁴⁻¹¹

Table 1: Information to be examined during Inspection

Topics	USFDA requirements
Organization charts	Organogram from top level management to the lower one involved in PVG system. In other words, relationship between all the employees is to be depicted in organization chart/organogram.
Process/Workflow diagrams	These diagrams should include various processes followed for receipt, assessment, compilation and reporting of safety data.
Internal and external audit program	The inspector may check the audit schedule and findings from previous PVG audits. The reports from previous inspection/audit reports shall also be reviewed including those from license partners or contractors.
Training program including curriculum vitae (CV), job description (JD) and certificates	There should be an easy access for inspectors to training records, CVs and JDs, which are required to provide evidence of the experience, responsibilities and training of personnel involved in safety data monitoring.
Details for Qualified Person for Pharmacovigilance (QPPV) for Europe and local Qualified Person	The QPPV must be very clear on roles & responsibilities, and the same should also be documented in written procedures: <ul style="list-style-type: none"> - Contact details of QPPV - Documentation regarding QPPV's access to all significant PVG information and notification of details of the QPPV to all relevant competent authorities (CAs) - Documentation for delegation of tasks - In order to ensure compliance in PVG system, verification that the QPPV has sufficient authority within the firm to make necessary amendments - Details of deputy QPPV and other local qualified person (outside EU)
Literature Screening	The authority can evaluate the firm process of scientific literature review for PADE reporting and whether the same has been conducted and reviewed appropriately. The serious and unexpected PADEs from literature search should be reported to the agency within fifteen calendar days, accompanied by a copy of the source article, as required by 21 CFR 314.80(d). In addition, specific literature cases can also be examined after retrieval from the safety database.
Interaction between Drug Safety and	The firm should have a process in place to detect AEs from medical information

the Medical Information Organization	queries/requests.
Interaction between Drug Safety and Technical Quality Assurance Organization	The process of handling quality defects/complaints shall be reviewed and also the existing links to establish whether there are quality defects that may result in AEs. In addition, there can be a quality defect reported that could be the cause of actual or potential AEs and vice versa.
Electronic Submissions and Compliance	The firm's post-marketing regulatory submissions via electronic format should be in accordance with USFDA's program. <ul style="list-style-type: none"> – Reports which are submitted electronically have the same reporting deadlines as paper reports and the standards must comply with 21 CFR Part 11 standards. – All electronic systems for collection, processing, review or submission of adverse event data should be in line with federal standards for data management under 21 CFR Part 11. – The PADE data should be endowed with electronic records, open and closed systems, digital and electronic signatures.
Responses to USFDA enquiries about drug safety	The firm should have timely submission of responses to USFDA regarding issues related to safety profile of drugs. There should be proper archival of the documents pertaining to liaison with authority.
Out-of-working hours	There must be an appropriate procedure to receive spontaneous reports of products during out-of-working hours (email-id or provision of a phone number with voice message facility).
Safety Data Exchange Agreements (SDEAs)	If the firm shares any PADE reporting responsibilities with contractors in reference to co-marketing or co-licensing of products, then USFDA can review SDEAs. <ul style="list-style-type: none"> – There can be a review of agreements between the firm and any other affiliates, parent companies, licensees or contract research organizations (CROs) to evaluate if the PVG and regulatory activities are in alignment with the SDEAs. – It can also be determined how the firm confirms that other affiliate parties processing adverse event data on its behalf are in compliance with PADE reporting regulation.
Post-marketing studies	As per USFDA, post-marketing study information is related to adverse experiences obtained from patient registries, pregnancy registries, company sponsored patient support programs or disease management programs: <ul style="list-style-type: none"> – Applicants are not obliged to submit ICSRs from post-marketing studies unless the adverse event is serious and unexpected and whether a possible relationship exists between drug and adverse event. – The firm's procedure can be examined regarding identification and monitoring of its post-marketing studies, including the non-applicant-sponsored clinical data, to ensure that all potential PADEs are received to the firm's PVG department.
Corporate transitions	In case of corporate transitions, like corporate mergers, transfer of drug approvals, written procedures can be evaluated to ensure that the firm is in a state of compliance for reporting of safety information.
Product Litigation	In case of any product litigation, firm's written procedures shall be reviewed for forwarding safety information received by company's legal department to its PVG department for reporting to agency as per 21 CFR 314.80(b): <ul style="list-style-type: none"> – The clock-start date is the date on which the legal department receives the PADE information. – An Agency waiver is required in advance, if the firm wants to consider the clock-start date as the date on which the PVG department receives PADE information from its legal department.
Annual Reports	The firms are obliged to submit Annual Reports to authority within 60 days of the anniversary date of approval of the application. <ul style="list-style-type: none"> – The firm should submit Annual Reports with all sections in timely manner for each of its products with an approved NDA or ANDA as required by 21 CFR 314.81(b)(2). – Sometimes, authority can request firm to submit these reports at different time intervals.
Complaint Files	The firm can be requested to provide a list of open or pending complaint files. The authority can select a specific number of complaints and evaluate how the firm addresses the complaints to determine if a PADE report is required for submission to authority.
Waivers	The firm can be issued waivers to submit PSURs instead of PADERS, or exemption for submission of individual reports for non-serious labeled events. The firm should archive or retain the copy of waivers from authority.
Data Security, Back-up, Disaster Recovery and Business Continuity Plan (BCP)	There should be provisions for data security policy, back-up and disaster recovery. The BCPs should also be available to avoid any non-compliance and PVG documents should be kept in water or fire proof cabinets.
Outsourcing to third parties	The third party agreements can be reviewed along with the process workflow for oversight of the party's operations and methods to ensure quality reporting of safety information.

Documentation of Inspection Findings

The documentation of various Inspectional findings during inspection related to deviations in domestic or foreign firm's PADE reporting shall be used as evidence for further appropriate actions.

Establishment Inspection Report

The Establishment Inspection Report (EIR) includes all findings that can significantly impact the decision-making process and include sufficient information to support the recommended classification for inspectional findings.^{6,12}

- The authority shall proceed for subsequent actions after inspection on the basis of findings documented in EIR. The information included in the EIR may be used as a support for an administrative or regulatory action.
- For recommendation of regulatory action, the EIR must include the following information for each product as implicated in the recommended action:
 - Label (including package inserts) in use at the time of report for the product inspected.
 - Product's brand/generic name and its NDA or ANDA number along with approval date.
 - Date used by firm for determining reporting cycles pertaining to periodic reporting requirements. A copy of authority approval is mandatory if this date is different with NDA or ANDA approval date.
 - The effective date(s) and conditions of waivers provided to the firm by authority.
 - The time periods during which the PADE reports scrutinized during inspection were received by the firm, and the dates these reports were submitted to agency.
- An endorsement to the EIR should provide:
 - summary of the major deficiencies observed during inspection
 - implication of corrective actions by the firm
 - district's classification of the inspection

Form FDA-483

- The respective non-compliance and deviations in the firm's process shall be incorporated in Form FDA 483 as per CFR 314.80, 314.98, 310.305, and Section 760.¹³
- There shall be a discussion with the firm regarding queries pertaining to firm's drug labeling, compliance with FDA guidance documents or medical assessment of PADE reports. These discussion points shall not be incorporated in FDA 483 but the same will only be included in EIR.

Warning letters

The Warning Letter (WL) is the agency's principal means of notifying regulated industry of violations and achieving prompt voluntary correction. It may be warranted when the firm's PVG inspection is endowed with below mentioned findings.^{6,14}

- Lack of documented procedures (SOPs, WIs) for reporting of PADE information
- No submission of PADE reports for serious and unexpected adverse drug experience events
- No submission of periodic reports or NDA annual reports of approved drugs
- Incomplete and/or inaccurate periodic reports or NDA annual reports submitted to authority
- Serious, unlabeled events of approved drug products submitted in periodic reports instead of 15-day alert reports
- Inaccurate and/or incomplete 15-day alert reports and follow-up reports submitted to authority
- 15-day initial and follow-up reports not timely submitted
- Failure in submission of 15-day reports from post-marketing study, in which there is a possibility that the suspect drug resulted in ADR
- Failure to conduct adequate follow-up investigations of PADE reports that are the subject of post-marketing 15-day alert reports
- Non-compliance in maintenance of records for quality complaints and PADE records

Untitled letter

- An Untitled Letter (UL) shall be warranted in case the deviations at the firm are not subject to issue of WL, but are enough for a notification of formal letter.^{6,14}
- The WL or UL are issued based on the following factors:
 - extent and type of deviations
 - history of compliance of the inspected firm
 - implementation of corrective actions by the firm

Corrective & Preventive Actions

After the issue of inspection report, the firm has to provide responses to identified deviations and share an appropriate CAPA plan with agency. There shall be a specific deadline for firm for provision of responses. The District Office of USFDA is responsible for evaluation of responses to WLs, CAPA plans and their implementation.^{6,15}

- Follow-up measures will be performed by District Office in case of inappropriate response and



correction actions or failure to submit any response to inspection findings.

- In case of adequate responses from firm, District Office shall perform verification of commitments and corrections achieved.
- Follow-up inspections can be conducted by agency after the respective date of completion of corrective actions as promised by the firm.
- The Districts may go ahead with a regulatory meeting with firm, in case of inadequate corrections by the firm following UL and WL or existing deviations are not severe enough for an enforcement action.

Enforcement Actions

In case of incomplete corrections by the firm after a UL/WL or existing violations as described below, the agency may consider the following measures for enforcement.^{6,16}

- Injunction: Injunction shall be considered, if the firm continues with violations in PADE reporting despite earlier attempts of USFDA to obtain compliance.
- Seizure: It will be followed, if the firm fails in compliance with PADE reporting regulations following earlier withdrawal of product approval applications.
- Prosecution: Prosecution shall be considered if the firm submits false information, fails to submit serious PADE reports or withholds significant product safety information and the result of these activities lead to inappropriate label changes/application withdrawals.

CONCLUSION

In order to ensure compliance, firms should align with best practices in industry. It includes timely awareness of all appropriate regulatory obligations to identify any gaps and risk in routine PVG activities. The concept of timely internal audits or mock inspections can play a vital role in understanding of current position in comparison to best practices. The firms should also provide complete and accurate responses within specified time to queries from authorities or findings in audits/inspections.

The non-compliance in PADE reporting requirements can have a severe impact on the firm. After inspection, the USFDA shall perform verification of corrections from firm's end and there can be follow-up inspections to ensure compliance is achieved. However, in cases of non-compliance, there can be big penalties or suspension of license for marketing of drugs, which can seriously affect company's revenue and brand value.

The foremost aim of USFDA and other health authorities is to ensure patient safety by evaluating the activities of responsible firms, whether these are compliant to PVG obligations. Therefore, a well effective PVG system is a condition for firm to maintain the marketing

authorisation of product and it is also very essential for safety of people worldwide.

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Source of Support: Nil, **Conflict of Interest:** None.

