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PHARMACOVIGILANCE OPERATIONAL EXCELLENCE: A CASE STUDY

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This article describes a case study on how the principal elements of operational excellence were put to task by a dynamic, self-directed pharmacovigilance team to better ensure patient safety.

Patient-safety regulations, particularly in Europe, are evolving in complexity and robustness, consequently challenging marketing authorization holders (MAH) and their service providers to rapidly redesign their own drug-safety processes in order to maintain compliance. Even though the desired outcome is to possess better defined and robust pharmacovigilance (PV) processes, the actual challenge lies in designing and implementing the transformation when so many processes may require simultaneous modifications in a short period of time.

One established framework to achieve measurable long-term improvement, operational excellence (OE), can enable the MAH to transform their PV processes by rigorously aligning strategic objectives with the operational actions and vice versa. OE is increasingly being leveraged in transactional processes as compared to its familiar setting of manufacturing, so it is an ideal improvement framework for PV processes.

This article describes a particular case study on how the principal elements of OE were put to task by a self-directed PV team of a global pharmaceutical organization. The perception of the new European PV regulations being the most stringent, combined with an increased percentage of the organization's products being distributed and sold in a number of European countries, motivated the PV compliance objectives toward alignment with these specific regulations. The case study describes how the organization's strategy was tightly linked to PV operations through the plan-do-check-act (PDCA) cycle and also presents how much-needed metrics were established to enhance performance monitoring of each PV process.

What Is PV OE?

Dissimilar industries, and even diverse companies within the same industry, perceive OE differently. The pharmaceutical industry is no exception. In spite of this, one clear fact is that OE matters to these industries because it provides tangible results sustained over time and contributes to overall competitiveness.[1]

There are four critical themes common to the genetic makeup of successful companies leveraging OE:

1. Efforts are driven from an overall business strategy.
2. Use metrics to tie efforts to the strategy and track progress.
3. Structure the program so that people at all levels have a meaningful role.
4. Understand and use the right approach to address unique goals and challenges.

Successful companies have broad knowledge and ability to apply the right tool or approach based on the problem being solved. They combine Six Sigma, lean, theory of constraints, and other approaches into an overall program for improvement. And they don't usually employ a large staff whose sole responsibility is continuous improvement.[1]

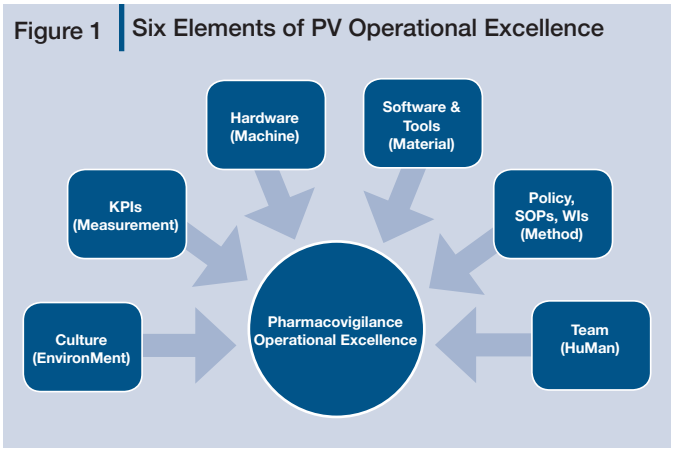
Since each organization is unique, there is no set road map to follow on the OE journey. Moreover, the challenge is to address the existing processes, the network of existing service providers, and products already on the market. Such a transformation may require varying degrees of culture change since fundamentally important to OE is the mindset of continuous improvement, collaboration, and open communication.[2–3]

There are also numerous definitions for OE, but, for simplicity's sake, we use the following:

Operational excellence is an element of organizational leadership that stresses the application of a variety of principles, systems, and tools toward the sustainable improvement of key performance metrics.[4]

According to the World Health Organization (WHO), pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.[5]

Figure 1 Six Elements of PV Operational Excellence



In distilling the two definitions, PV OE is positioned as "measurable drug-safety processes with a goal of continuous improvement."

Figure 1 shows the six elements that drive PV OE: culture; key performance indicators (KPIs); team; hardware; software and tools; policy, standard operating procedures (SOPs), and work instructions (WIs). Each is directly related to the "six Ms" of Six Sigma: Environ**M**ent, **M**easurement, **M**achine, **M**aterial, Hu**M**an, and **M**ethod, respectively. The six elements are commonly known as the probable roots for issue investigations, where one or more often contribute to potential variations of a process. In this context, the issues are typically analyzed to determine what kind of correction, corrective, and/or preventive action should be taken in the short and long term. Conversely, and often overlooked, these elements are the root causes for opportunities in implementing the continuous improvement of a process. In this positive light, they offer a constructive framework from which each element of a process can be evaluated and improved in the short and long term.

The PDCA Cycle

In the presented case study, as part of the outcome of its annual strategic review in Q4 2011, a global MAH decided to align its PV processes with the European Medicines Agency (EMA) good pharmacovigilance practices (GVPs) prior to these guidelines (listed in Table A) becoming effective. At the time, the GVPs were a relatively new layer of PV guidelines designed to increase patient safety and help foster improvement of PV at the operational level in the member states of the European Union (EU). Since the MAH was increasing the number of marketed medicinal products in the EU, it was a logical choice to ensure compliance to this level. In contrast, the US Food and Drug Administration (FDA) PV guidance documents (listed in Table B) were perceived as describing the FDA's current thinking on the specific subject but not necessarily required, while the EU modules, which are referred to as guidelines, were considered mandatory.

With so many existing process improvement methodologies such as organizational portfolio management maturity model (OPM3), lean management, Six Sigma, total quality management (Tqm), and quality by design, there is no single way to embark on the journey of PV OE. Conversely, these process improvement methodologies share many similarities, and, likewise, it appears that Six Sigma combined with lean management offer a superior approach with numerous tools to support their journey.[6] The PDCA cycle provides businesses, and their departments such as PV, with a cyclic methodology for continuous improvement toward OE.

In the presented case study, the established OE framework is depicted as two PDCA cycling gears propelling the MAH PV processes into increased efficiency and quality over time, as shown in Figure 2. The number of gears shown represent the number of critical monitoring cycles when applying PDCA at both strategic (larger gear) and operational (smaller gear) levels.

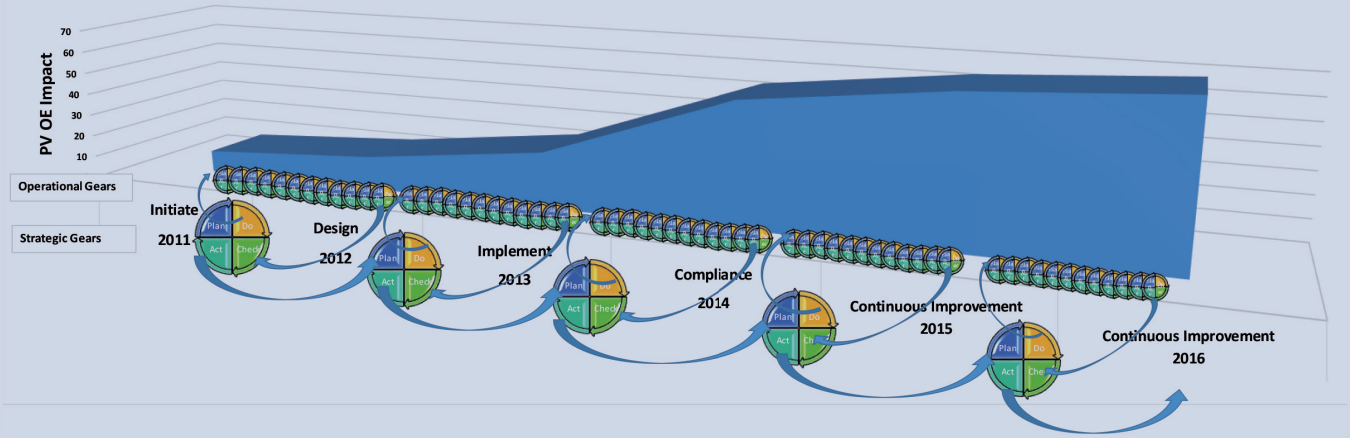
For example, the larger strategic PDCA gear rotates through a cycle over a longer period, annually, for example, to determine what strategic objectives must be completed, adapted, abandoned, or created across the different departments to successfully achieve the business mission.

Once the annual objectives are defined (PLAN phase) and communicated (DO phase), the objectives are converted into the operational tactics—i.e., the PLAN phase of the operational gear. The multiple smaller gears represent the recurring operational PDCA cycles to keep improving the various processes simultaneously.

At the end of the year, the overall operational progress and lessons learned are communicated back to the strategic team, rotating to the strategic gear to the CHECK phase, where the results of these multiple executions are verified against the initial objectives and amalgamated lessons are openly shared, leading to adjustments in the future strategy (ACT phase). These modifications are then used to realign the PLAN phase for following year's strategic objectives. Together, the dual PDCA cycles repeat themselves, adjusting to the strategic forces (environmental, internal, supplier, client, and competition) acting upon and within the organization.

For 2012, the MAH's strategic focus of the PLAN phase was the design of both required changes to the existing PV processes, such as auditing, individual case safety reporting, and literature surveillance, and any needed new processes, such as the post-authorization safety studies. In 2013, the strategy progressed to the implementation of the intended changes, while 2014 concentrated on measuring the actual compliance of the retrofitted processes. Finally, as of 2015, the focus is continuous improvement of each individual process.

Figure 2 PDCA Strategic and Operational Cycles along Operational Excellence Journey



Strategic and Operational PDCA Cycles

PLAN: Setting the Annual Strategic Objectives

To estimate the magnitude of the design improvement activities, a number of gap assessments were completed comparing expected activities identified in each of the 16 EMA GVP modules (listed in Table A) with the MAH's PV Standard Operating Procedures (SOPs), associated Work Instructions (WI), and other supporting tools. Each recognized gap was noted, along with the potential improvement actions to enhance the PV operational and quality processes. As process gap areas were reviewed and deliberated, opportunities regarding automation, the number and type of human resources, and the current technology were also considered.

The rollout of the effective GVP modules was forecasted by the EMA to occur during the period of 2012 to 2015; consequently, not all process gap assessments could be performed from the beginning of the realignment. Hence, the scope of the total effort was expected to increase as more of the EMA GVP requirements became available. To initiate the realignment, a charter was prepared identifying the various internal (project specific and departmental) and external stakeholders. An order of magnitude cost estimate to secure the required funding was prepared, and approved by the Chief Medical Officer, the project sponsor.

Once the funding was approved, a formal project implementation plan, including definite cost and time estimates for the known recommended realignment actions, was prepared. Communication requirements were clearly documented and validated by the director of PV, the appointed champion, who socialized the approach with the various department heads to secure buy-in. Each of the required future PV processes was assessed using the key elements of OE for compliance with the forthcoming regulatory guidelines. The critical PV OE design considerations are listed and categorized in Table C.

A risk register was created in order to identify, review, monitor, mitigate, and record risk-management activities. Some of the key risks identified and monitored included the potential for increased scope due to evolving regulatory requirements, insufficient internal resources to support the efforts, and PV service providers not complying with the regulations in the required time and/or to the appropriate level.

Perceived as the most substantial gap was the lack of a formal performance measurement system to monitor and control both individual and overall PV process performance, as well as how to address deviations from performance limits. For that reason, this element became the focal point of development for the PV team. Research on recent trends in metric systems was performed to understand the current thinking in the industry.

Noteworthy is ISPE's Quality Metrics program, which is aimed at assisting the industry in considering metrics aligned with the FDA six-system inspection, the product, the quality system, the process capability, and the culture. In addition to helping fulfill one OE's above-mentioned themes, its initial objective is to provide real-world experience with metrics definitions, data collection, and reporting burden for the benefit of both the industry and regulators.[7]

In spite of the EMA providing a robust foundation for PV processes, they have not yet recommended any related performance metrics. Consequently, the PV project team planned their own quality and timeliness metrics for each process primarily based on historical performance and other recommendations from the literature or subject-matter experts.

DO: Converting Strategic Objectives to Operational Actions
To convert the PV strategy to execution, actions with planned completion dates were established based on the perceived individual process risk to the business and the availability of regulatory guidelines.

An agile form of project management, as illustrated in the swimlane diagram in Figure 3, was the chosen operational delivery method, whereby the process owner was accountable for driving the required improvements. If there were issues impeding delivery, then the process owners were to report back to the operational team for further assistance. Hence, a "no news-good news" approach was instituted to minimize distractions and over-reporting.

The process owners and support members met biweekly to review progress and discuss any other process issues, risks, and changes. The qualified person for pharmacovigilance (QPPV) was ultimately responsible for ensuring the compliance of each PV process with the evolving regulatory requirements. Thus, the QPPV would share any newly released information from the EMA and other impacting regulatory agencies. All progress and future action items were recorded in the biweekly tracking report by the project manager and distributed to the operational team. The biweekly meetings served as an appropriate checkpoint for a transformation that was initially estimated to last approximately 2 years. It allowed the team to view the overall health of their project and identify where any additional support was required.

CHECK & ACT: Operational Monitoring and Controlling
To further communicate, monitor, and control the PV OE progress, a monthly update of the PV-related process work was prepared and distributed to the required stakeholders. The "PV Status Update" communication package included a summary of the process development progress to provide a clear snapshot of the entire program, as shown in Figure 4. Additional presentation slides provided supplementary details regarding the actual progress per PV process. Above all, at the executive level, the pragmatic summary slide provided the suitable visibility of scope, cost, and time variations as well as upcoming risks and changes in the team members. This monitoring step also allowed the project team to formally step back to CHECK and determine if they needed to ACT on future tactics.

CHECK & ACT: Strategic monitoring and controlling
In Q4 2012 and Q4 2013, a change request was prepared identifying any deviations and changes to the implementation plan needed for the upcoming year. For consistency, the change request was approved by the same people who had approved the initial implementation plan.

Similarly in Q4 2014, a closeout report identified the completed activities along with outstanding items that had been transferred to the operational team. This marked the turnover to PV operations to sustain continuous improvement efforts through the established feedback channels of the PDCA cycles.

Figure 3 Operational Execution

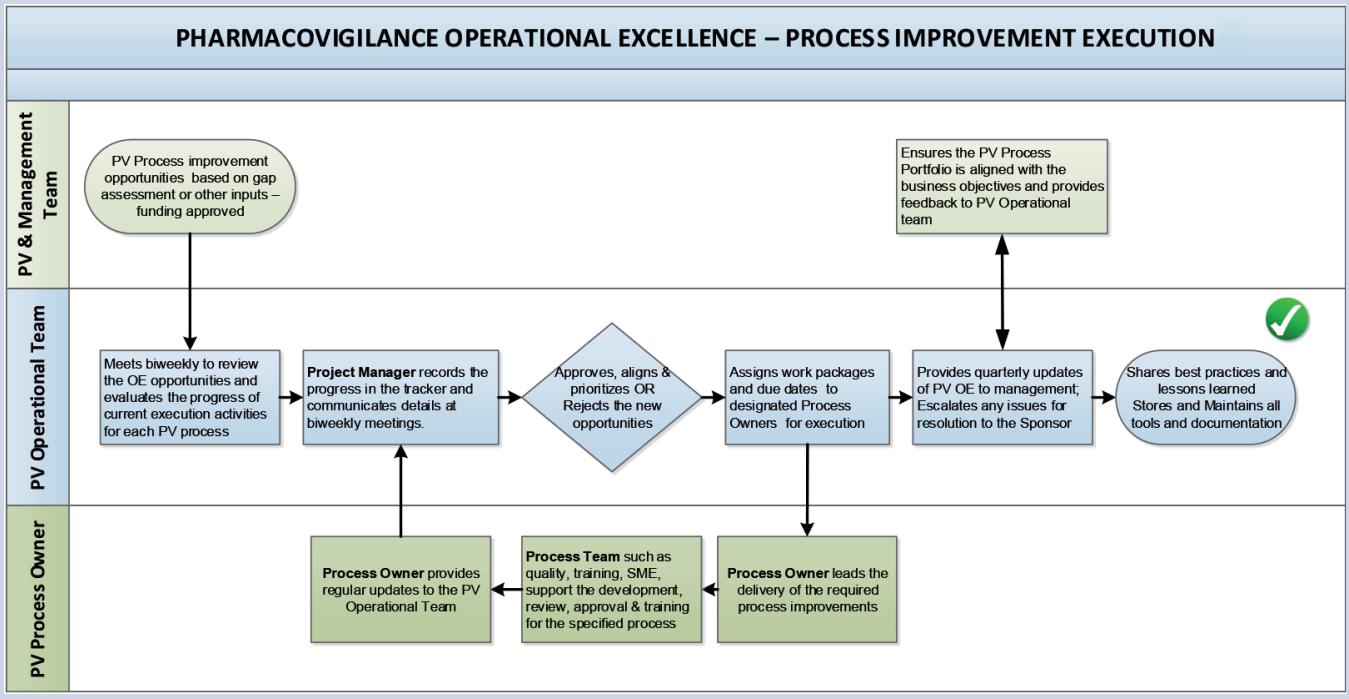


Figure 4 PV Operational Excellence Program Monthly Summary Example

Overall Program Status: Green

Stakeholder Representatives

Sponsor business unit:	Pharmacovigilance
Project Sponsor:	CMO
Project Owner:	Director

Current Project Team

QPPV, project manager, IT specialists, case reviewers, safety physicians, SDEA manager, quality director, director regulatory affairs, director (chair)

Objective

- Implement a compliant, effective and efficient pharmacovigilance system to align to the new EU legislation.
- Ensure partners and vendors are adapting to meet the changes in legislation so the compliance risk is level is mitigated across all organizational and geographic pharmacovigilance activities.
- Ensure current systems i.e. document management, training, CAPA and resources are sufficient in quality and quantity to manage the future pharmacovigilance system.

Benefit

- Maintain and alignment of regulatory compliance for global pharmacovigilance activities.
- Additional efficiencies and increased quality in current processes.

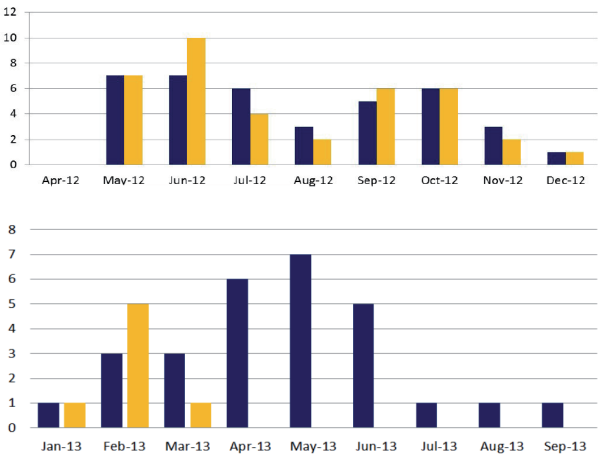
Key Monthly Accomplishments

Progress continued on the following activities:

- ✓ Plan for recruitment effort is still ongoing for compliance manager while the safety physician has been identified and secured
- ✓ The bulk variation submission process is defined and a plan has been prepared and approved
- ✓ PSMF is in place with required documents and the SOP is in review/approve stages
- ✓ CAPA work has impacted quality incident process so the process is being redefined and the work duration will be most likely extended.
- ✓ PASS framework has been established and is under review

Overall project progress since beginning: **67 %**
On track with forecasted completion

Plan vs. Actual Completed Deliverables



Past Key Issues/Risks

- Internal staff was over allocated and caused regular slippage of certain activities.
- New GVP modules increased scope and date of completion of project.
- Partners and/or vendors' lag in maintaining compliance may increase risk.

Changes

- No major scope changes but some activities' delivery dates were adjusted and the details are documented in the biweekly report.

Cost Plan vs. Actual

Met monthly forecast

Hence, the focus shifted from implementation to assessing how well the PV team could perform with their implemented processes and, equally important, how well the measurement system had been established. Another strategic review (CHECK & ACT cycle) will follow at the end of 2015, in order to determine what adjustments may be necessary for continuous improvement.

As part of the 2014 handoff, a more formal lessons-learned session, presented in Table D, was held by the operational team to candidly discuss and record the successes and improvement opportunities of previous years.

PV Measurement System Design and Build

In this section, the overall implementation of the measurement system for identifying, collecting, processing, presenting, and acting on PV process data is discussed. The PV audit process is framed as an example to demonstrate the similar design steps undertaken for each process.

PLAN: Measuring Performance

In the past, PV process reviews were performed on available metrics that had grown organically and so were not deliberate process indicators. A PV performance measurement system was considered a critical element for long-term improvement, not only because it was a stated quality-system requirement in the EMA's Module I, but because visibility would enable faster corrective responses to improve the multiple PV processes.

In establishing the design requirements for the measurement system, the PV team identified and selected 11 significant PV processes aligned with the key the EMA guideline modules.

An SOP was prepared distinguishing these 11 processes along with the metric expectations of timeliness and quality. A KPI dashboard, as shown in Figure 5, aimed to condense and communicate the health of each PV process. Each PV process was designed to have a number of indicators or metrics associated with its performance. In the case of the audit process, the individual metrics identified included percentage of late audits, number of critical findings, number of major findings, percentage of late reports, and percentage of late responses from auditees.

These metrics were summarized by an analytic value (e.g., "A1 PV Audit process") with a possible value of "on-target" or "warning." The direction of the trends of the analytics would be reviewed to diagnose the direction of process variability. Analytics would be monitored monthly, quarterly, or annually depending on the metrics that rolled into their total status. Any negative change in the analytics' trends would act as a signal to the reviewers to drill down to the metrics' level to understand the specifics of the process performance change.

Finally, since certain process KPIs were still in the development phase, these analytics were highlighted in gray to show that the process improvements were not yet effective.

According to Module IV in the EMA GVPs, PV audits include both PV system audits and audits of the quality system for PV activities. The overall description and objectives of PV systems and quality systems for PV activities are referred to in Module I, while the specific PV processes are described in each respective module. Module IV, Section IV.B, describes the general structures and processes that should be followed to identify the most appropriate PV audit engagements and the steps that can be

Figure 5 Dashboard of 11 PV Processes with Rolled-Up Analytic Indicators

KPI ID	Collect & Protect Data	Q1	Jan-14	Feb-14	Trend
A3	Literature Surveillance	Monthly	On-Target	On-Target	Same
A4	Individual Case Safety Reports	Monthly	Warning	On-Target	Up
A10	Product Information Maintenance & Safety Variation Submissions	Annually	Annually	Annually	NA
A11	Post-Authorization Safety Studies				

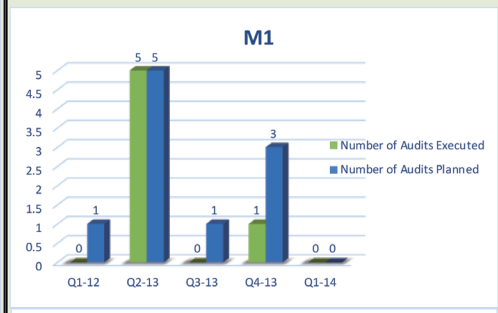
KPI ID	Manage & Minimize Safety Risk	Q1	Jan-14	Feb-14	Trend
A6	Signals	On-Target	Quarterly	Quarterly	NA
A8	Risk Management Plans (RMP) or Risk Evaluation and Mitigation Strategy (REMS)	Annually	Annually	Annually	NA

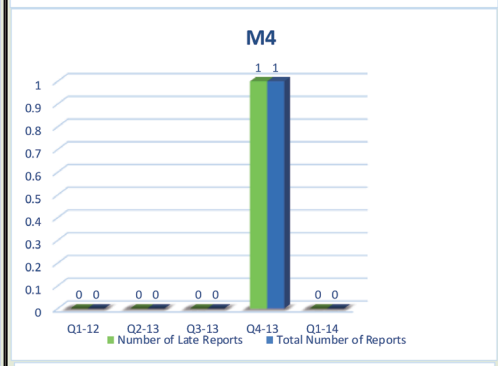
KPI ID	Communicate	Q1	Jan-14	Feb-14	Trend
A5	Safety Data Exchange Agreement	On-Target	Quarterly	Quarterly	NA
A7	Communications to agency and other stakeholders	Annually	Annually	Annually	NA
A9	Aggregate Safety Reports	Monthly	On-Target	On-Target	Same

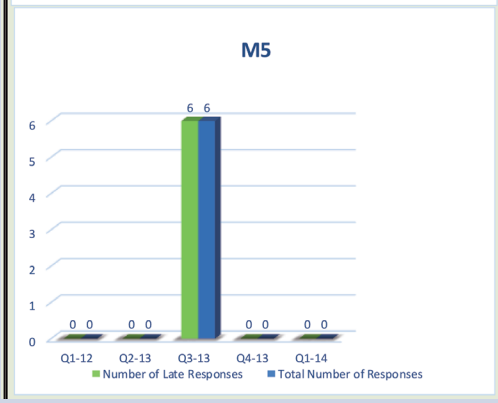
KPI ID	Ensure Compliance	Q1	Jan-14	Feb-14	Trend
A1	Pharmacovigilance Audits	On-Target	Quarterly	Quarterly	NA
A2	Corrective and Preventive Action				

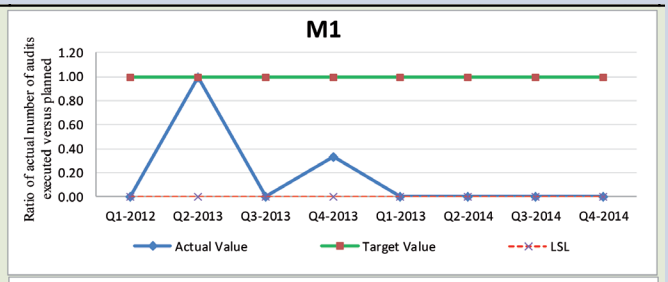
Figure 6 Dashboard of Key Performance Indicators for PV Audit Process

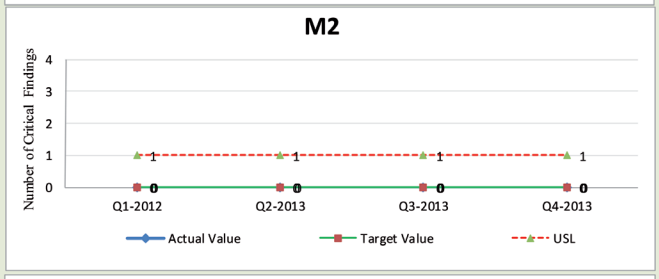
M1	Ratio of actual number of audits executed versus planned	On-Target
M2	Number of critical findings	On-Target
M3	Number of major findings	On-Target
M4	Ratio of actual number of late reports as per the defined time in SOP compared to the total number of reports	On-Target
M5	Ratio of actual number of late responses from auditee as per the defined time in SOP compared to the total number of responses	On-Target
A1	Audit Analytic	On-Target

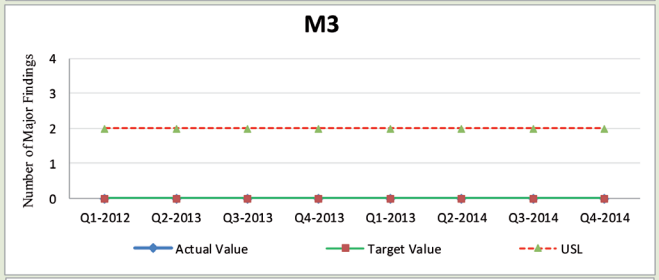


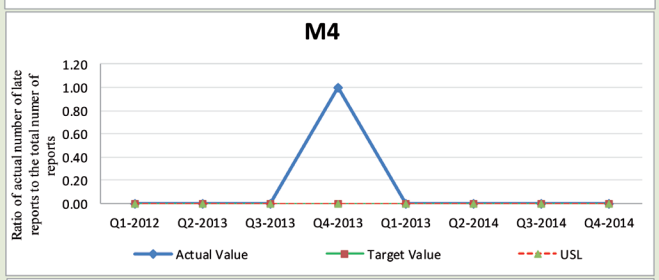


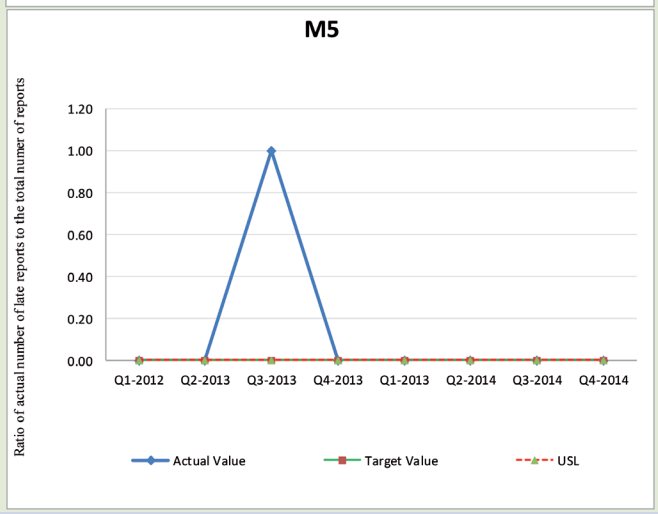












Compliance Status
M1 – For last 3 months planned 1 Audit and executed 0 M2 and M3 – no findings M4 – No reports M5 - No reports
Action Items
1. Confirm location and source to be used to count number of critical/major findings. 2. Discuss at OPS meeting when the planned audit will actually take place

undertaken by MAHs, competent authorities in member states, and the EMA to plan, conduct, and report upon an individual PV audit engagement. This section also provides an outline of the general quality-system and record-management practices for PV audit processes.[8]

In order to assess the compliance of the current PV audit process, the main steps in the audit SOP were evaluated directly through observation and also through the use of a suppliers, inputs, process, outputs, and customers (SIPOC) diagram, as shown in Table E. Any process steps requiring adjustments were revised until the process was endorsed by the PV team. Multiple operational working sessions served as not only an improvement discussion platform but also an excellent training forum and further challenged the understanding of the existing methods and tools.

Next, the team defined the voice of the customer (VOC)—i.e., exactly what they perceived as significant to the process based on EMA guidelines and historical performance. For example, as shown in Table F, PV audit-report approvals were perceived as often taking longer than required, so having a metric for the timeline for approval was "heard" as part of the VOC sessions. Then, these VOC requirements were translated into measurable targets or ratios; for example, 0 was initially targeted for the number of late reports compared to the total number of reports. This was a measurable audit process requirement identified as critical for PV, because the operational team chose to establish a strict target of no late reports. For certain processes, metrics were planned to be categorized further, with weights if perceived as necessary. In general, however, the identified metrics were presented as comparable in importance because it was not perceived as value added to define with further granularity and in the interest of saving time. The idea was to later use the annual review meeting and adjust the measurement system where deemed appropriate.

At this point, the upper and lower specification limits of process performance were also determined, including the expected follow-up actions such as escalation to management or investigations when the limits were exceeded.

Table A	EMA Good Pharmacovigilance Practices (GVP)—Modules		
Module No.	**Guideline Focus**	**Module No.**	**Guideline Focus**
Module I	Pharmacovigilance Systems and their Quality Systems	Module IX	Signal Management
Module II	Pharmacovigilance System Master File	Module X	Additional Monitoring
Module III	Pharmacovigilance Inspections	Module XI	Public Participation in Pharmacovigilance
Module IV	Pharmacovigilance Audits	Module XII	Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication
Module V	Risk Management Systems	Module XIII	Incident Management (this module was later integrated into module XII)
Module VI	Management and Reporting of Adverse Reactions to Medicinal Products	Module XIV	International Cooperation
Module VII	Periodic Safety Update Reports (PSURs)	Module XV	Safety Communication
Module VIII	Post-Authorization Safety Studies (PASS)	Module XVI	Risk Minimization measures – selection of tools and effectiveness indicators

Finally, the anticipated collection and review frequency was scheduled in order to avoid a knee-jerk reaction to an insufficient set of data points. Monthly, quarterly, and annual collection periods were identified for different metrics of the PV processes. For example, the PV audit-process metrics would be collected, evaluated, and reported quarterly, since monthly was perceived as too frequent (i.e., there would be insufficient data) and annually was perceived as not having sufficient time to react to flagged issues.

As the entire measurement system was developed, it became apparent that many desired data points were either not captured by the PV operations team or were recorded in multiple redundant documents. Hence, part of the data-collection requirements involved identifying what the data source would be and where the electronic or paper source data file would be physically located. If source data was not available, then operational tools were prepared to collect the required data. In other instances, redundant data sources were amalgamated into one central location.

DO: Executing the Process

Once all the improvement components of the targeted PV audit process were in place, the retrofitted process was made effective and formal performance monitoring began in late 2013. Similarly, each process was activated when the required elements were endorsed by the PV team.

CHECK & ACT: Monitoring and Controlling the Process

As part of the design, a process-specific KPI dashboard had been prepared, such as the example for the PV audit process shown in Figure 6. The PV KPI dashboard was linked directly to the collected data and fulfilled multiple monitoring needs, such as:

- A quick view via the summary status of each KPI (on target or in warning) as shown in the top left-hand side.
- Current visibility through control charts of each actual KPI with their target and limits. In addition, statistical process control and trending was possible since the data was also presented over a specific time scale.
- Additional graphical information when a ratio was used as a metric, in order to ensure visibility of the magnitude of the numerator and denominator data.
- Descriptive data regarding the current compliance status along with the associated action items to help record and track what the outcome of each analysis required.

This information assisted the PV department to not only “check and act” on planning for the next quarterly cycle, but also helped determine which processes required further strategic improvement. This related operational opportunities back to the strategy with open communication and an “improvement” attitude.

Conclusion

The OE-minded PV team designed its PV process-improvement objectives over 2012 and implemented the majority of them in 2013. The project end date was regularly reassessed as more information became available on the actual requirements of the newly approved EMA modules.

In 2014, performance visibility of both transformed and new processes became possible via a new measurement system, which also provided monitoring and controlling capability of trends and nonconformances. During this period, the required adjustments to the PV processes were discussed, designed, and executed. In some cases, the metrics thresholds were changed and the frequency of data collection was questioned and adapted, if needed. The transformation was considered completed.

Table B	FDA PV Guidance Documents
	FDA Guidance Document
1.	Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection, January 2009
2.	FDA Guidance for Industry and Investigators: Enforcement of safety reporting requirements for INDs and BA/BE studies, April 2011
3.	FDA Reviewer Guidance for a Clinical Safety Review of a New Product Application and Preparing a Report on a Review, February 2005
4.	FDA Guidance for Industry: Pre-marketing Risk Assessment, March 2005
5.	FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005
6.	FDA Guidance for Industry: Development and Use of Risk Minimization Action Plans, March 2005
7.	FDA Guidance for Industry "Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report", August 1997
8.	Draft FDA Guidance for Industry: Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report), April 2013
9.	Draft FDA Guidance for Industry: Determining the extent of safety data collection needed in late stage premarket and post-approval clinical investigations, February 2012
10.	Draft FDA Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications, September 2009

Over 2015 and 2016 an emphasis on continuous improvement is anticipated as the processes appear to be aligned with current external and internal forces.

In this case study, the four themes of the PV OE journey were undoubtedly present, although not necessarily with the same degree of influence. The EMA alignment efforts deposited a catalyst for OE and allowed the PV team to better understand, further develop, and refine their own departmental processes. Since the PV team was already self-driven, collaborative, and transparent in their communications, it was a natural part of their culture to adapt and fuel the required changes to occur and continue the pursuit toward PV OE. The PDCA cycles of strategy and operations worked in conjunction to formally support the collaborative communications for OE.

Indeed, the six elements of PV OE were the levers of change impacting each PV process. Even though the level of pressure applied to each lever is unique for each organization, the elements are the root causes associated with opportunity actions to propel an organization toward OE. Therefore, identifying these accurately should bring about the expected outcomes.

Table C	PV Operational Excellence—Design Considerations
PV OE Element	**Pharmacovigilance Operational Excellence Design Considerations**
Key Performance Indicators	What kind of official performance measurement system should be implemented since no measurement system had ever formally been designed and what measurements should be taken and from which data sources?
Team	What degree of outsourcing versus internal execution of PV related activities should be established to optimize cost and quality? Does the PV department have all the right people (Medical Physicians, Case analysts, Medical writers, administrative support, etc.) on the right seats of the PV bus? Will additional internal and/or external resources be needed to manage the forecasted improved processes t i.e. to set up and retrofit the processes and to run the corresponding operational activities?
Hardware	What kind of new hardware is needed and how should outsourcing data management be leveraged for compliance and efficiency?
Software & Tools	The current PV software tools are becoming obsolete, and significantly newer technology improvements are available to help support the PV processes. Is there an opportunity to procure new systems or upgrades to a more current infrastructure?
Standard Operating Procedures	How should the existing quality management system be leveraged or must new pharmacovigilance quality processes be implemented that address the quality specifics regarding patient and/or drug safety? Many PV procedures, work instructions and tools will need to be adapted, hence, how best to manage the review and approval cycle?
Culture	How can PV achieve a higher level of engagement from other departments such as regulatory affairs, medical affairs, labelling etc. since this appears to be a more visible requirement in the EMA PV Modules? How will shortfalls in resources be dealt with in terms of delays to project and securing other support? How long will it take to realistically achieve such an undertaking since PV still must continue to address its regular operational activities and now, must decide on how to evolve to an improved base line for operations?

Table D	Lessons Learned
Successes	**Improvement Opportunities**
1. Pro-active high performing PV team which went beyond their day to day to complete the activities. 2. Achieved global visibility and support as updates were communicated outside PV team on a regular basis. 3. Project Manager in place helped structure projects and monitor progress. 4. Helped the operational team to focus on PV objectives and increase their own understanding of PV processes. 5. Enabled the operational team to digest and establish the appropriate interpretation of the regulations. 6. Subject Matter Expert facilitated the accelerated development of SOPs and minimized rework. 7. Compliance was monitored continually by having SMEs and Quality personnel as members of project team. 8. Proactive leadership by the PV Director to ensure an appropriate operational balance between the day to day work and the alignment project activities.	1. The project took longer than expected due to the review and approval cycles involving a limited number of personnel, who were expected to maintain normal operations during the project implementation. It would not really have been possible to increase the review/approval resources, which are defined by job function. The aim was to maintain overall compliance of PV activities while completing the project deliverables, albeit, it took longer than initially planned. The operational team did increase the durations and communicate their forecasted dates as constraints were identified. In hindsight, since the project did extend longer than planned, it may have been possible to supplement with other support resources to keep the time variance to a minimum. 2. It was perceived that sometimes too many persons were present at the biweekly meetings. However, the meetings served to ensure alignment amongst the team and to support a common understanding of the process expectations by the EMA. Therefore the meetings also served as training for the entire team. Perhaps, the frequency could have been moved to monthly for certain team members. 3. It was unclear whether or not all the right stakeholders were receiving the right information at the right time. A communication plan had been developed from the start and targeted stakeholders were engaged and informed at the documented frequency and with the desired level of content. It may have been beneficial to share the communication plan further and perhaps consider other context or venues to distribute the project information.

Table E	Audit Process SIPOC			
Suppliers	**Inputs**	**Process**	**Outputs**	**Customers**
QA/PV	List of different types of audits	Define the types of audits	New List of types of audits	QA/PV
QA/PV	Defined types of audits and criteria for scheduling the audits	Determine the frequency of audits	Determined frequency of different types of audits	QA/Dir. PV/QPPV
QA/Dir. PV/QPPV	Determined frequency of different types of audits	Create a Schedule of the audit plan	Audit Plan Schedule	QA
QA	Audit Plan Schedule	Review and approve the scheduled audit plan	Audit Plan approved	QPPV
QPPV	Audit Plan approved	Maintain the list of scheduled and completed audits in PSMF	Updated List of scheduled and completed audits in PSMF	Admin
Admin	Updated List of scheduled and completed audits in PSMF	Conduct the audit	Audit conducted	QA/designee
QA/designee	Audit conducted	Draft the audit report	Drafted audit report	QA/designee
QA/designee	Drafted audit report	Review and approve the audit report	Audit r eport approved	QA/designee
QA/designee	Audit Report approved	Distribute audit report to auditee, Director PV, QPPV, deputy QPPV, Pharmacist and CMO	Distributed audit report to auditee, Director PV, QPPV, deputy QPPV, Pharmacist and CMO	QA/designee

References

1. Mendelbaum, G., and D. Wireman. "Elements of Success with Operational Excellence Programs." *Supply & Demand Chain*, 11 June 11 2007. http://www.sdcexec.com/article/10289739/elements-of-success-with-operational-excellence-programs.
2. Littlefield, M. "Every Company's Operational Excellence Journey Is Similar—But Different." *GE Intelligent Platforms*, 17 December 2013. http://www.geautomation.com/blog/every-companys-operational-excellence-journey-similar-different.
3. Bigelow, M. "How to Achieve Operational Excellence," *Quality Progress* 35, no. 10 (October 2002): 70–75. http://asq.org/qic/display-item/?item=18448.
4. Wikipedia. "Operational Excellence." https://en.wikipedia.org/wiki/Operational_excellence.
5. European Medicines Agency and Heads of Medicines Agencies. "Guideline on Good Pharmacovigilance Practices (GVP): Annex I—Definitions (Rev3)." 15 April 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf.
6. Gershon, M. "Choosing Which Process Improvement Methodology to Implement." *Journal of Applied Business & Economics* 10, no. 5 (2010): 61–68.
7. International Society for Pharmaceutical Engineering. *ISPE Quality Metrics Initiative. ISPE Proposals for FDA Quality Metrics Program—Whitepaper*. December 2013. www.ispe.org/quality-metrics-initiative/quality-metrics-proposal.pdf.
8. European Medicines Agency and Heads of Medicines Agencies. "Guideline on Good Pharmacovigilance Practices (GVP): Module IV—Pharmacovigilance Audits." 12 December 2012. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136233.pdf.

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Table F	PV Audit Process Key Performance Indicator Requirements					
Critical to quality—KPI / **Voice of customer**	**Importance**	**Ratio of actual number of audits executed vs. planned (M1)**	**Number of critical findings (M2)**	**Number of major findings (M3)**	**Ratio of actual number of late reports compared to the total number of reports (M4)**	**Ratio of actual number of late responses from auditee compared to the total number of responses (M5)**
Ensure PV audits are completed in terms frequency per SOP	5	X				
Number of audit findings (critical and major)	5		X	X		
Appropriate time to achieve an audit report approval	5				X	
Final audit response time from the auditee	5					X
Frequency of data collection/reporting		Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly	Quarterly/quarterly
Target		1	0	0	0	0
Lower specification limit		0	N/A	N/A	N/A	N/A
Action on LSL		If actual ratio = 0 for **one quarter**, then discuss with QA. If actual ratio = 0 for **one year**, then escalate to management and discuss appropriate actions.	N/A	N/A	N/A	N/A
Upper specification limit		N/A	1	2	> 0	> 0
Action on USL		N/A	If actual number of findings ≥ 1, escalate to management	If actual number of findings ≥ 2, discuss at OPS meeting	If the number of late reports > 0, discuss at OPS meeting	If the number of late reports > 0, discuss at OPS meeting
Data type 1		Number of audits executed	Number of critical findings	Number of major findings	Audit report late	Final total audit response
Data type 1—source documents		PSMF_S	Audit reports	Audit reports	PSMF_Audit	PSMF_Audit
Data type 1—location of source document		PSMF—Section 8.3	PSMF— Section 8	PSMF—Section 8	PSMF—Section 8.3	PSMF—Section 8.3
Data type 2		Number of audits planned	N/A	N/A	Total number of reports	Total number of responses
Data type 2—source documents		PSMF_S	N/A	N/A	PSMF	PSMF
Data type 2—location of source document		PSMF—Documents	N/A	N/A	PSMF—Documents	PSMF—Documents