



SAFETY & REGULATORY SOLUTIONS FOR SMALL- AND MEDIUM-SIZED LIFE SCIENCE ORGANIZATIONS

A key issue for small- and medium-sized enterprises is the optimal utilization of their limited resources for moving their product pipeline through clinical development, and launching and marketing their approved product(s). This is further heightened as both clinical trials and post-marketing activities continue to grow in complexity and scope due to stringent regulatory pressures, patient involvement and globalization. Yet companies face overwhelming pressure to get their product to market as quickly as possible.

Clinical trials are typically outsourced end-to-end to full-service clinical research organizations (CROs). SMEs may select CROs for their niche patient recruitment capabilities in certain geographies and therapeutic areas/indications. As a result, some CROs may not always have the required level of expertise and experience in other aspects of clinical trials, such as data management, statistical design and analysis, medical writing and regulatory submissions.

Another challenge is that trials may be outsourced to several different CROs, meaning that safety and pharmacovigilance (PV) activities, along with the technology infrastructure that supports it, are thus housed in different locations. This often leads to safety data being reviewed and reported for each clinical trial rather than being reviewed and analyzed at the aggregate (product) level, causing challenges in integrating the data, with little or no control over data standardization. This puts organizations at risk at the time of filing of a new drug application to obtain marketing authorization, when it's important to review and analyze consolidated data, define the initial product label and proactively identify and manage safety concerns.

In both pre- and post-marketing phases, many small to medium companies find that it is not practical to have an internal resource-heavy, end-to-end safety and risk management system as it diverts extensive time, effort and financial spend away from a company's core activities of product development and marketing. Oftentimes, such organizations do not have an established safety group and either the clinical development or regulatory groups are responsible for safety activities, leading to lack of focus on critical PV activities. Clinical and regulatory activities in the post-approval phase for registration in different markets and evaluation of safety, efficacy and effectiveness for patient sub-groups and other indications can also be resource-intensive.

EMBRACING NEWER STRATEGIES

Within the clinical trial environment, a comprehensive understanding of the safety profile of a product often requires evaluation of safety data across all completed and ongoing clinical trials, as well as of any other drugs in the same class. Multiple key safety surveillance activities play a critical role in enabling a comprehensive evaluation of the evolving safety profile of innovator molecules and biologics that are still in clinical development. These include deployment of a relevant safety surveillance plan (SSP), evaluation of individual study data by an external Data Monitoring Committee (DMC), review of aggregate safety data by an internal Safety Assessment Committee (SAC) and performing Analysis of Similar Events (AoSE) for individual expeditable cases.

In accordance with the FDA guidance for industry regarding safety assessment for IND safety reporting (Dec 2015) and the subsequent revisions in 2017, the sponsor is expected to follow a systematic approach to safety surveillance using an SSP and conducting regular SAC meetings to review ongoing data. A properly constituted SAC is multidisciplinary in its composition and would typically meet more frequently than a DMC. The SAC periodically reviews specific accumulating aggregate safety data collected across multiple studies (completed and ongoing) and any other sources, analyze the data and after unbiased assessment makes recommendations regarding whether the safety information meets FDA criteria for IND safety reporting. Also, by analyzing similar events, sponsors ensure they meet the need to evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in the placebo or active comparator group.

Thorough review and analysis of all aggregate data in real time is particularly important in the context of the FDA's guidance. This timely reporting of meaningful safety information allows the FDA to consider whether any changes in study conduct should be made beyond those initiated by the sponsor and allows investigators to take any essential steps to protect subjects. Besides ongoing safety data review, it is also imperative to evaluate efficacy of the investigational product across clinical trial sub-groups and closely partner with key stakeholders to develop the emerging benefit-risk profile prior to final drug dossier submission for gaining marketing approval.

Post-marketing approval, management of all key PV activities for the approved product gains precedence and establishing a comprehensive PV organization in-house can be quite challenging. This is because dedicated and experienced professionals are required to manage both PV operations as well as the enabling technology architecture/infrastructure. On the technology side, implementing validated, regulatory-compliant PV systems requires significant investment in a robust quality management system (QMS) and the right expertise to select, implement and support the right solution(s). Yet, the amount of the safety data is often relatively low and volume surges are highly unpredictable, therefore not always justifying the expenditure.

Similarly, on the PV operations side, associated responsibilities such as aggregate safety reporting, benefit-risk evaluation, signal detection and management and development of risk management plans are becoming more complex and resource-intensive. Across Europe and several other countries, including Australia, Canada and Japan, specific regulatory mandates have included the need to have a qualified person responsible for PV (QPPV), which poses additional operational challenges to SMEs.

SMEs can benefit by embracing newer strategies to manage their responsibilities during clinical development and in the post-approval phase. Specifically for management of safety activities, an optimized solution can be achieved by using functional service providers (FSPs), who can provide end-to-end integrated safety support including reporting and assessment of all safety data in a centralized database, compliance to required clinical safety monitoring norms and standards (e.g., SSP, SAC) and essentially partner with the pharmaceutical company to help market the product by setting up required PV systems and processes to efficiently manage end-to-end PV activities for the marketed product. Using niche FSPs that specialize in areas of statistical design and analysis, clinical data management and PV, while using the best-fit CROs to optimize patient recruitment and manage clinical trial conduct ensures the best strategy is implemented.

SMALL BIOTECHS AND EUDRAVIGILANCE

Small biotechnology companies' needs are focused on supporting the clinical development program for novel therapies using new technologies. Because of this, we have seen that the resources as well as the experience these companies have can be somewhat limited when it comes to PV, which typically comes in at a later stage and may not be high on the priority list.

Another big challenge observed, particularly for non-EU-based companies, in recent years is around registration with the European Medical Agency (EMA) and EudraVigilance (EV). The many U.S.-based small biotech companies often know the PV regulations in the U.S., but they are not aware that European agencies have more lengthy and complicated processes. EMA requires a legal representative (LR) for conducting trials in the EU region and need a responsible person (RP) for performing safety tasks. These are two different entities playing different roles, which can be confusing to organizations new to the European market. With the recent changes in EV, the EMA has actually made this process more streamlined, but only experienced companies or individuals understand the nuances involved.

Small and medium biotechs can invest in getting an experienced individual who can project-manage this according to the steps and the processes described by EMA. There are specific forms and authorization letters along with cover letters that both LR and sponsor/company should duly sign. The RP needs to then upload these and register themselves with EV for the particular company and then create users who can take over the functions within EV and start submitting SUSARs.

With the changes in the regulations and the requirements, it is advisable to take help from an experienced service provider who can manage this end-to-end.

COMMON REGULATORY AND SAFETY-RELATED PITFALLS DURING THE PRODUCT LIFECYCLE

Compliance to safety regulations is of the utmost importance. Regulatory compliance may be compromised if appropriate standard operating procedures (SOPs) and safety management practices are not in place. Suboptimal processes and non-compliance issues can in turn lead to higher costs through missed work, rework or low-quality output. Regulatory authorities such as the U.S. FDA issue warning letters for critical regulatory violations observed during inspections. Consequences of the warning letters can be serious, such as the loss of trust by patients and health care practitioners, damaging effect on stock prices or negative impact on approval of future submissions. The FDA's enforcement actions can include product recall, seizure, injunction, administrative detention and civil money penalties and/or prosecution.

Figure 1 depicts several critical safety and regulatory related activities that are part of the product lifecycle, from preclinical development through Phase IV. However, smaller organizations are often unable to prioritize these activities and may not have the expertise or resources to undertake all activities themselves. These companies typically have a small team that is responsible for all of the clinical, safety and regulatory activities. Not having distinct and specialized teams often impacts the appropriate prioritization of the various critical activities.

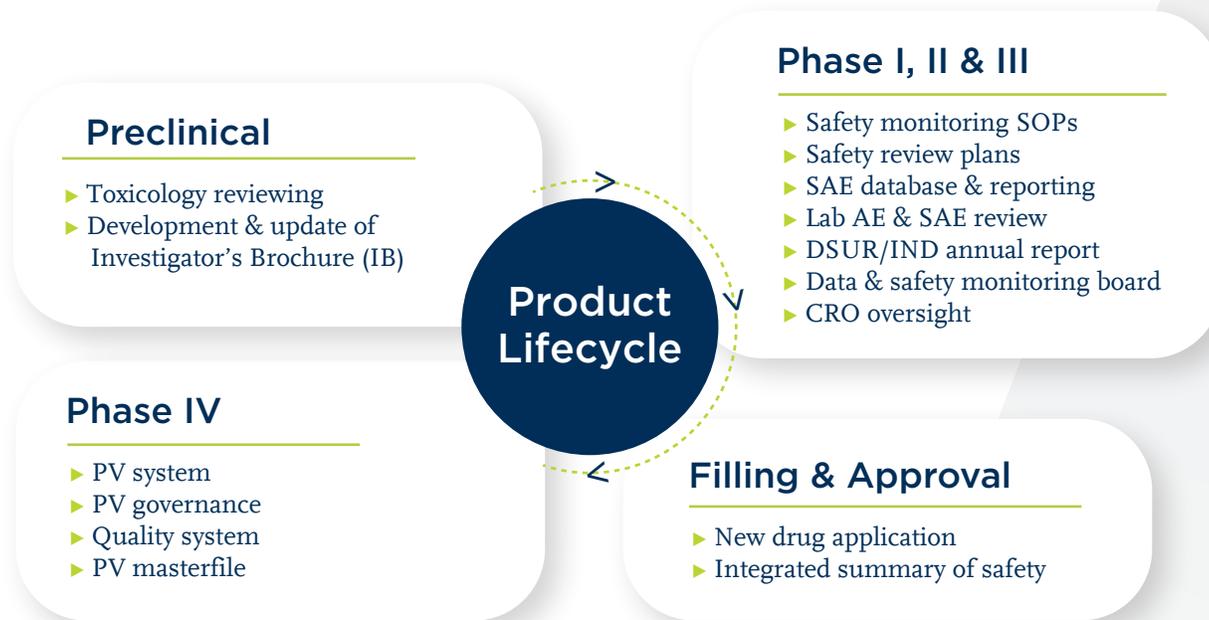


Figure 1: Critical safety and regulatory activities during the product lifecycle.

The most common pitfalls in safety monitoring during the product lifecycle include failure to:

- ▶ Integrate multiple safety databases, required for comprehensive aggregate safety review
- ▶ Develop robust written SOPs and work instructions for safety management
- ▶ Perform safety activities in accordance with those SOPs
- ▶ Analyze, review and document all pertinent clinical safety data (adverse events, events of interest, laboratory data and other investigations)
- ▶ Review and update IB on a timely basis
- ▶ Coordinate case submissions to regulators, ethics committees and investigator sites across multiple clinical studies, as required and within timelines
- ▶ Submit DSUR/IND Annual Reports per schedule and applicable regulations
- ▶ Manage the Development Core Safety Information and assess expectedness according to EU requirements
- ▶ Ensure audit and inspection readiness at all times

The analysis and reporting of safety data from clinical trials may not be of the desired robustness and quality, which may cause lengthy delays in submissions even if the patient recruitment timelines are met. This would have significant financial implications, particularly for smaller companies.

OUTSOURCING – KEY DECISION DRIVERS

There are three key areas of consideration that determine and drive an organization's decision process to outsource clinical, safety and regulatory activities: people, process and technology (Figure 2).



Figure 2: Key considerations for outsourcing clinical, safety and regulatory activities.

THE PEOPLE FACTOR

Work force limitations with respect to cost and flexibility are an important consideration for SMEs, and external vendors can provide a flexible flow of qualified, competent and specialized personnel. Expertise across distinct work streams including safety, medical, clinical, biometrics, regulatory and technology can be easily leveraged to get the full range of expertise necessary for meeting expected quality standards and regulatory compliance. All of this is possible without the need for the companies to themselves recruit, train and retain dedicated staff.

Spikes and boluses (both planned and unplanned) are a reality in PV, especially with marketed products, and companies need to be ready with a plethora of options to handle different types of spikes (of varying intensity and duration), as seen in Figure 3. Working with an outsourcing partner allows convenient access to a broader pool of staff within the supplier's organization. Resources can be trained and deployed within weeks to manage the increased workload (for planned as well as unplanned volume surges/boluses) and can then be withdrawn as needed, providing flexible and cost-effective resourcing solutions for surge management.

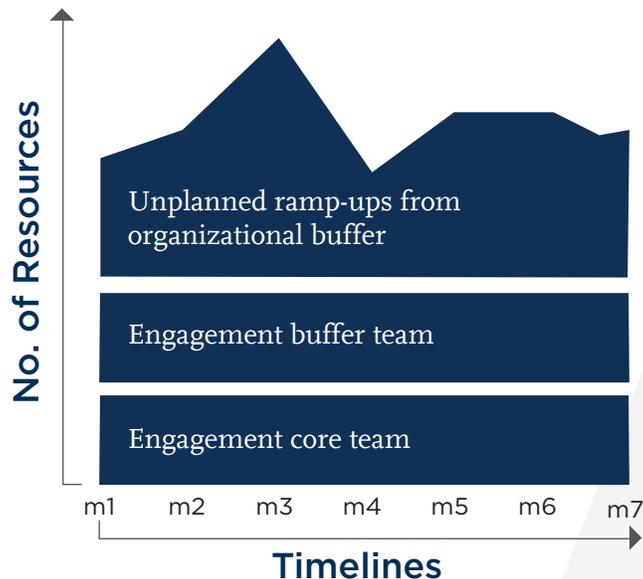


Figure 3: Companies need to be prepared for planned and unplanned spikes and boluses.

THE PROCESS FACTOR

Developing the right processes to support end-to-end clinical development, regulatory and PV activities is both very costly and laborious. Specialty outsourcing organizations can provide ready-to-go, robust, tested and audited systems and procedures, eliminating the time and expense of starting from square one. These processes can be configured to the company products, processes and requirements. Further, these processes are updated on an ongoing basis to adapt to changing regulatory requirements and technological advances.

THE TECHNOLOGY FACTOR

Information technology is essential to enabling a robust safety and risk management operation and outsourcing vendors are able to provide ready-to-go infrastructure and technology services, as well as knowledgeable and experienced technology staff. This also ensures strong business continuity and disaster recovery plans.

Specialized vendors employ best-in-class quality systems and oversight with well-defined quality management plans, robust SLA compliance frameworks, and metrics, analytics and reporting. Such vendors can help build pragmatic and compliant systems to meet company requirements and development plans.

ADVANTAGES & BENEFITS OF SPECIALIZED SAFETY AND REGULATORY SOLUTIONS

In order to tackle the breadth of challenges in safety and risk management, the best strategy incorporates a holistic customer-centric approach that brings together an end-to-end PV solution comprised of safety, technology and advisory services (Figure 4). The model is further enhanced when a single vendor who can offer services in any area of PV that the sponsor company elects to outsource is employed. This integrated, flexible and shared services outsourcing model ensures regulatory compliance, quality data, product safety, lower risks, greater cost savings and allows the sponsor to focus on their core capabilities while developing and delivering new medicines to the market.

The effective combination of domain expertise, agile processes and robust technology results in high quality and compliant operations, increased efficiency and time savings. At the product level, this integrated approach

allows real-time tracking of benefit-risk profile and enables the sponsor to make quicker and more informed decisions on risk minimization, ultimately supporting maintenance of efficacious and safer medicines in the market. An automated technology platform (as part of the integrated solution) plays a key role in effective PV management by fostering collaboration between disparate teams, enabling seamless processes and effective analysis of safety data.

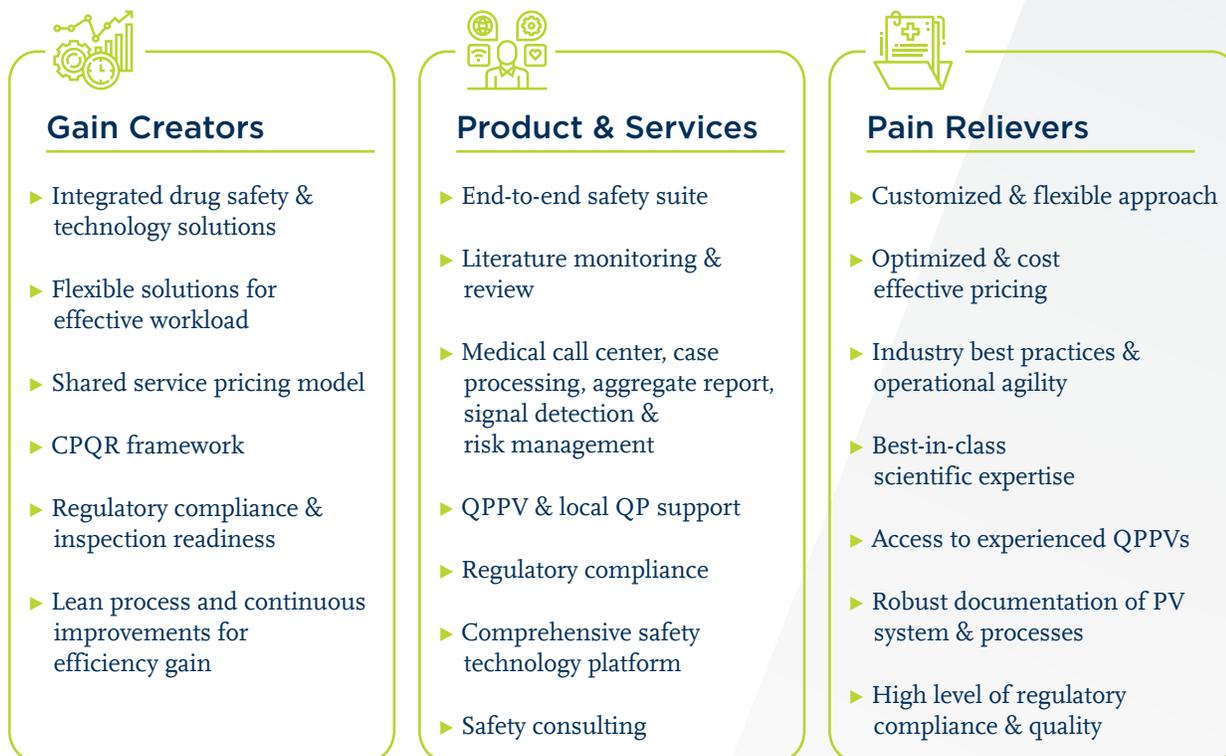


Figure 4: Integrated regulatory and PV shared service model, encompassing end-to-end activities from safety database and call center implementation, to case processing and medical review, to safety surveillance and risk management.

Efficient study designs and the right analysis and reporting can significantly enhance the success rate of clinical trials. Similarly, teams that specialize in market access strategies and have an understanding of the regulatory environment in various markets can advise on the submission requirements for regulatory approvals, especially in semi-regulated or non-regulated markets. Such specialized clinical and regulatory support will increase the chances of successful clinical development programs and ultimately of the commercial success of the products.

CONCLUSION

Both clinical trials and post-marketing activities for medical products continue to grow in complexity and scope. Furthermore, in this constantly evolving and more stringent regulatory environment, the task of managing patient safety in clinical trials is more demanding than ever. With this in mind, it is interesting to note that while most of the industry’s risk management efforts have focused on post-marketing drug safety, the clinical trial process holds a broad array of other potential risks that could jeopardize a company’s product development investment, including regulatory delays.

A common challenge across small- and medium-sized life science companies is how to create, develop and implement effective clinical, safety and regulatory operations that can scale and ensure regulatory compliance for their growing product portfolio. Some companies need advice and direction to get their operations started, while others who have processes in place may need help selecting and maintaining technology (e.g., safety database) and services (e.g., medical call center) to centralize and automate their operations.

In addition, obligations and imperatives span a wide array of areas, including clinical development, managing regulatory submissions and approvals, market access decisions and product launches across geographies. All of these require a breadth of experience that can be realized only through professionals who specialize in individual areas. It is not practical for small- to mid-sized companies to have all the required expertise and experience in-house. It's also not possible for many niche CROs to have the quality of experience across all these areas.

Employing a comprehensive regulatory intelligence framework and ensuring that processes and SOPs are always compliant is challenging, given an organization's limited resources. The requirement for a SAC in the recent draft guidance for IND safety reporting is a case in point. Aggregate review in real time by an independent team is critical, for which it's important to have all the safety data consolidated in a single database. This has implications on a company's strategy to source safety services right from the early clinical development stage.

Smart outsourcing and quality services are dependent on effective business (scientific) processes, well-defined governance structure and long-term commitment to continuous improvement. Partnering with a provider who offers a scalable and agile solution with a suite of integrated products such as Covance's specialized and customized clinical development and regulatory solutions will go a long way in enabling sponsor companies to stay ahead of the curve. This strategy will help organizations achieve commercial success, get products to patients faster and remain compliant with regulatory requirements, while being focused on patient safety and optimal benefit-risk evaluation of their products at all times.

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