Outsourcing pharmacovigilance activities is a standard business practice in a continuously expanding market segment. In the past, outsourced safety services were limited due to concerns about confidentiality, data security, and liability in cases of regulatory non-compliance, which are all still important considerations today. Because of the changing technology and regulatory environments, sponsors are reevaluating the advantages and disadvantages of outsourcing their pharmacovigilance obligations. The benefits of outsourcing include lower costs for staffing (based on reduced effort), recruitment, management, and training, along with access to clinical trial staff in non-traditional lower-cost regions (e.g., the Philippines, India, or China). Sponsors also gain access to unique expertise, intellectual property, multidisciplinary knowledge, and an unbiased view. With stricter regulatory requirements, however, the hiring of experienced safety personnel has become highly competitive.
INTRODUCTION

According to “The New 2015 Trends of Global Clinical Development Outsourcing Market” published by Research and Markets in 2015, the global clinical trial service market will likely reach more than $64B by 2020, representing a CAGR of 9% between 2015 and 2020. By 2020, the average clinical trial outsourcing penetration will likely approach 72%. The best relationships between sponsors and contractors are those that are well defined from the beginning. This white paper outlines the best practices for ensuring success when outsourcing pharmacovigilance services.

BACKGROUND

Pharmaceutical companies traditionally outsourced case processing activities including expedited reporting and occasional aggregate report generation. For large pharma, the benefits of outsourcing were reduced costs and smaller infrastructure, as well as increased flexibility in scalability of operations to match data volume fluctuations.

However, the increasing pharmaceutical product safety regulations are increasing demands for pharmacovigilance capacity and expertise. This is moving the landscape of outsourcing to more complex activities such as signal detection, benefit-risk management, support for risk management plans, and newer fields such as pharmacogenomics. Sponsors may not always have the ability to perform these services in-house because of resource constraints or limited infrastructure/geographical presence. These changes have led to a reevaluation of the way pharmacovigilance services are outsourced.

OUTSOURCING ADVANTAGES

The benefits of outsourcing in general also hold true for pharmacovigilance services. Fixed resource costs are converted into flexible workload-oriented costs. In the outsourcing model, pharmaceutical and biotech companies reduce costs because significantly less effort is needed for recruitment, management, and training of staff. The special benefits of outsourcing pharmacovigilance services include access to unique expertise and multidisciplinary insight and protection for intellectual property at the time they are actually needed. The service provider focuses its attention on the outsourced task, a benefit that is enhanced by strong staff motivation. Because the contracted experts are external, they can provide an unbiased view. This impartiality is of special value in a decision-making process, for example, related to improving the in-house pharmacovigilance system or regarding signal detection and risk management activities required for a drug.
What Services are Outsourced?

All pharmacovigilance tasks are currently outsourced. Sponsor companies also request specialized services such as:

- Audit preparation for inspections
- Delegation of the role of a qualified person for pharmacovigilance
- Development of product information, process design, and standard operating procedures (SOPs)

With growing demand by regulators, sponsors also seek support developing risk management programs. Although all tasks related to pharmacovigilance and risk management are generally outsourced, the needs of individual companies vary significantly. Company size, the size of the pharmacovigilance department, and existing license or development partnerships influence outsourcing decisions.

**PHARMACOVIGILANCE & PATIENT SAFETY DURING PRODUCT LIFE CYCLE**

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Figure 1: Pharmacovigilance & Patient Safety Services - Product Life Cycle
The External Perspective

The following example demonstrates how the involvement of an external consultant can result in a successful product approval:

As a prerequisite for the marketing authorization of a known product with a new formulation, European regulators requested an active surveillance study to detect rare and serious adverse events for risk minimization. The negotiations between the pharmaceutical company and the regulatory authorities on the risk management program had been unsuccessful for several years. This is when the company sought advice from a risk management expert. The expert coming from the outside with a fresh and unbiased approach to the issue quickly understood the problem and recommended slight changes to the proposed safety surveillance approach. It was also proposed to include a methodology debate on appropriate pharmacovigilance study designs and considerations about signal investigation and proposed actions. Based on the revised risk management plan, the product received marketing authorization. This involvement of an external consultant ultimately helped the company resolve an issue that had delayed marketing authorization. The company’s time and cost savings were tremendous.

Small Biotech

Small biotech companies typically do not have drug safety departments, and routinely outsource all safety services including the safety database. Only high-level activities, such as analysis and decision-making, are conducted in-house. This system not only reduces internal expertise, but it limits the resources available for managing. The sponsor’s limited experience and unclear decision-making processes are common causes of dissatisfaction.

Mid-Size Pharma

Mid-size pharma companies generally have the knowledge and resources to accommodate the demands of the global pharmacovigilance environment. They typically require support to meet fluctuating resource needs associated with a changing product development pipeline. For example, support will be needed to meet medium-term resource challenges such as increased serious adverse event (SAE) volume arising from a new clinical program. They also have limited geographic coverage and often require additional support in unrepresented countries.

Mid-Size Pharma Services Example

The sponsor delegated to a vendor all submissions of expedited Individual Case Safety Reports (ICSRs) and cumulative line listings and annual safety reports to health authorities, ethics committees/institutional review boards, and investigational sites for all clinical trials. The vendor’s services included assessing the country-
specific reporting obligations for each SAE in more than 35 trials conducted in 50+ countries. The vendor implemented a system for electronic distribution of safety letters to investigators, which considerably reduced costs associated with the submission of approximately 4800 monthly safety alerts. The vendor’s centralized team effectively assumed responsibility for reporting from the pharma company’s understaffed local affiliates. This centralization mitigated a problem many pharma companies face: global consistency. Regulators thoroughly review a company’s global pharmacovigilance practices. Local affiliates often operate under different standards and work practices that cause conflicts when a global product is reviewed by regulators. Global pharmacovigilance departments are often unable to place any pressure on local affiliates to ensure consistency with global practices. Outsourcing to a vendor places the responsibility with one party who is responsible for ensuring global compliance.

**Large Pharma**

Large pharma companies have comprehensive expert pharmacovigilance departments with global infrastructures and databases. Large pharma companies typically outsource to reduce costs or support peak workloads; however, reducing costs using low-cost or off-shore outsourcing may result in quality issues and regulatory non-compliance. It is necessary to maintain oversight and engagement with the outsourcing partners or vendors. Large pharma companies must have processes in place swiftly to identify and mitigate quality and compliance issues.

**SOLUTIONS**

**Selecting the Service Provider**

Outsourced pharmacovigilance activities vary significantly. The range of contracted services is determined by the type of safety service providers, including individual consultants, specialty CROs, large, full-service CROs, and global service providers under the umbrella of business process outsourcing. To achieve a successful cooperative relationship, it is crucial to select the provider best suited to the current need. The first step should always be to establish a clear definition of the tasks to be contracted and assess the expertise and resources required.

When evaluating the consultant’s or vendor’s expertise, the sponsor must determine whether the knowledge and experience are available in-house to support the provider selection and assist in quality control (QC) during the collaboration. Outsourcing medium or large projects enables internal resources to focus on increasing QC demands, signal detection/risk management plans, etc. Other provider selection considerations include:
• What are the future outsourcing plans?
• Is this the first in a series of contracts for similar or different services?
• Is this a one-time request for consultancy?
• How are various outsourced services connected?

Checking provider references that illustrate past/actual performance is highly recommended as the first step in due diligence. The technical expertise and tenure of senior vendor staff are critical considerations. Important information also may be derived from audits of the providers’ pharmacovigilance processes and quality management systems. A record of regulatory compliance and low rates of non-conformity usually indicate a robust quality management system. When these factors are combined with procedural flexibility, the prerequisites for high-quality and tailored services are satisfied. Taken together, these data are a solid basis for an informed decision.

Sponsors tend to underestimate the time required to conduct a thorough vendor selection process. Shortcuts in the selection process will most likely need to be compensated for when the project is underway, when ambiguities or unresolved details will have had an impact on performance. A timeline that is too short yields a poorly defined scope of work (SOW) and an inappropriate outsourcing model that impacts contractual agreements with poorly defined tasks and responsibilities.

There may be instances when outsourcing is the only possible solution due to unplanned resource shortages or unanticipated workload (eg, during a pandemic). Under these circumstances the vendor selection and contract negotiations must be completed as quickly as possible; completing the process described above will not be an option. The SOW may become a “moving target,” while budget constraints place additional pressure on all parties, increasing the risk of regulatory non-compliance. Outsourcing may still be a positive experience if the sponsor and vendor communicate openly and address issues immediately. Such situations require extreme flexibility by both sponsor and vendor.

Success Checklist

• Define scope of work
• Assess expertise required for each outsourced task
• Check internal expertise available for vendor selection
• Determine internal expertise available for vendor quality control
• Define duration of collaboration
• Evaluate vendor’s expertise
• Check references
• Verify technical expertise of vendor staff
• Assess tenure of vendor’s senior managers and technical staff
• Audit vendor’s processes
• Audit the vendor’s quality system
• Assess quality of proposal
• Engage with the vendor team at the bid defense

Outsourcing Business Models to Consider

The selection process should also include an evaluation of the business models offered for the requested service. The model selection will be governed by key factors such as complexity and variability versus standardization, the volume of work involved, and the duration of the project. A time and materials budget—with or without a cap—is often the best option for consultancy or other ad hoc services when timing, volume, and complexity are unknown or are likely to evolve. A well-defined scope over a limited period can be sufficiently covered in a fixed-price contract. Should a fixed budget over several years be agreed upon, both parties may wish
to review the budget and actual costs on a regular basis. If the tasks are well-defined but the volume of work is challenging to estimate, the answer may be to negotiate unit prices. For large projects, a workforce-based contract, such as a full-time equivalent model, is often preferable to a unit-based agreement. If significant fluctuation in workload is likely, the business model must ensure that sufficient trained resources are available on demand.

**Outsourcing Case Study**

A “virtual” biopharmaceutical company decided to outsource all back-end functions (i.e., data management, biostatistics, medical writing, and safety and risk management) to a single service provider. This left them free to select the best clinical CRO for a particular study and enabled them to leverage efficiencies in study set-up and execution for their clinical programs. The discussion between the sponsor and the CRO to define delegated responsibilities revealed that the sponsor’s confidence in the reliability of the vendor was limited.

The sponsor was extremely concerned that the CRO would not comply with agreed processes (such as expedited reporting of ICSRs to regulatory authorities without sponsor approval). The sponsor considered implementing a cumbersome process involving the CRO in the expedited regulatory reporting to mitigate the CRO’s compliance risk. The proposed process would have incurred a high risk of late reports and required additional expensive reconciliation steps between the involved parties to ensure compliance for both expedited and periodic safety reporting. Several meetings to discuss the details of the collaborations helped build confidence and trust. The final agreed work flows achieved a robust process with low risk of late reports, in which the sponsor controlled critical decisions.

**CLEAR PATH TO SUCCESSFUL COOPERATION**

Successful sponsor/provider relationships are built on contractual agreements with well-defined tasks and responsibilities in a structure that matches the SOW. At the beginning of the collaboration, it is important to define individual responsibilities, communication pathways, escalation procedures, and contingency plans for both parties.

The contingency approach should always consider that regulators will ultimately hold the sponsor or marketing authorization holder responsible. If third parties (such as co-license partners) are involved, they must also be included in the communication flow. If a long-term engagement is the goal, investing in face-to-face meetings at the start of the relationship and scheduling frequent formal and informal communication is a prudent approach.
Good relationship governance should employ an **oversight committee of executives from both parties** and the project teams (sponsor and vendor). In regular meetings, the committee assesses the ongoing relationship and the operational situation. The committee is responsible for high-level senior management overview, for providing strategic direction, and for oversight of the business relationship to ensure all parties’ needs are addressed and that a high-quality, compliant service is delivered. Investment in face-to-face time yields significant rewards when it comes to:

- Harmonization of processes and business values
- Issue resolution
- Contract change control

Although such relationship models affect the project budget, they are **smart business practices**. A strategic approach provides optimal results as sponsors maintain the relationship and product life cycle through the following:

- Joint commitment
- Shared values
- Trust
- Governance
- Aligned core competencies
- Optimized resource and cost efficiencies
- Aligned corporate vision

**Decisions about processes** are important and can drive cost. If individual components are outsourced, as opposed to full process outsourcing (such as steps in the case management process or use of the sponsor’s database), adherence to the sponsor’s SOPs can be advantageous. If the responsibility for a process or task lies mostly or completely with the service provider, that organization’s SOPs will best cover the required specifications. Agreement on deviations from individual process steps may be sufficient to adjust the process to the project. In rare instances, the development of project-specific SOPs can be the only way to clearly document processes. In most instances, project plans referring to SOPs are sufficient.

A **thorough QC process** will ensure that the service provider is meeting the sponsor’s expectations. Audits during the cooperation—whether by in-house staff or an external auditor—are the best tools to reconfirm that the provider meets standards and implements adjustments in an evolving regulatory environment.
CONCLUSION

Outsourcing pharmacovigilance activities is a standard business practice in a rapidly expanding market segment. The outcome will be a positive experience if the guidance outlined in this white paper is implemented:

• The service provider has the qualification to perform the service.
• The contractual agreement includes well-defined responsibilities.
• Communication and escalation paths are clearly defined during start-up.

Regardless of the level of sponsor involvement, a clear, strong agreement must be established and maintained, as success in pharmacovigilance is built on collaborative effort. This is the key to success.

Successful Long-Term Cooperation Example

A CRO serves as the safety data entry unit for a mid-size pharmaceutical company. Individual safety reports are received via email. The drug safety team at the CRO has Web access to the sponsor’s safety database and processes the safety data according to the sponsor’s SOPs, user manual, and entry/coding conventions. The working relationship began with support for a few individual studies. After a few years, work increased to cases from 3 products in 5 indications resulting from clinical trials and spontaneous reports. Since the sponsor’s drug safety team provided training to CRO staff at the beginning of the relationship, the CRO is responsible for training new staff (train-the-trainer principle). Regular audits without critical findings have proven the effectiveness of this concept. As many as 40 individual task orders were executed simultaneously under the master service agreement. This model provides the flexibility to include additional services in some task orders (such as expedited reporting to health authorities in some countries). Budget estimates are based on agreed units; compensation is earned on a time-and-materials basis. Due to the long-term relationship, the drug safety team at the CRO has become extremely efficient. In several clinical studies, the time spent per standard unit is lower than estimated. Due to the budget model, the efficiency is immediately passed on to the sponsor.

ABOUT PRA’S PHARMACOVIGILANCE & PATIENT SAFETY

PRA’s Pharmacovigilance & Patient Safety team has more than 380 experts in Europe, North America, Latin America, and Asia who assist pharmaceutical, biotech, vaccine, and device companies implement and conduct safety and risk management duties throughout their products’ life cycles.
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For further information, or to discuss any aspect of PRA’s services offered in the field of safety and risk management, please contact your PRA account director or the PRA employee below:

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