Fulfilling Pharmacovigilance Obligations in Innovator Pharmaceutical and Generic Manufacturer Partnerships

Both the reduction in the number of new drug approvals and the increased competition from generic manufacturers due to an increase in patent expiries have put tremendous pressure on innovator pharmaceutical companies. The last decade has been characterised by a severe innovation drought that has seen the number of new medicines fall to little more than half the previous levels (Reuters, 2013), and it is estimated that more than USD 290 billion of prescription drug sales are at risk from patent expirations between 2011 and 2018 (Evaluate Pharma, 2012).

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The challenging market conditions (which include governmental demands and the weight of supporting global distribution channels) are driving the global pharmaceutical industry to explore new growth opportunities in emerging markets, to focus on operational efficiency and to move towards a mixed portfolio of innovative and generic products. Such changes are responsible for the substantial increase in the number of licensing and supply partnerships between generic manufacturers based in an emerging market and large to mid-sized global pharmaceutical companies – specifically for the marketing of pharmaceutical products.

SDEAs & Minimising the Regulatory Risk

These mutually beneficial partnerships allow big pharmaceutical companies to attain a mixed portfolio of innovator drugs and generics and expand into emerging markets while providing the generic manufacturers their sought after marketing capabilities.

However the increase in regulatory vigilance requires safety reporting responsibility to be clearly outlined and monitored. Pharmaceutical regulators (such as the FDA and EMEA) hold innovator pharmaceutical companies legally responsible for Pharmacovigilance (PV) within such licensing/outsourcing agreements. The Marketing Authorisation Holder (MAH)/Application Holder is ultimately responsible for maintaining compliance with the application itself, and applicable laws regarding good manufacturing practices, quality standards and adverse event reporting.

Safety Data Exchange Agreements (SDEA) between the partner companies afford an opportunity to manage the risk and are reviewed during regulatory inspections. By defining the responsibilities of each party with reference to each PV activity, these contracts ensure there are written procedures for safety data exchange and that the communication timelines are adequate to ensure regulatory compliance and prevent PV activity duplication.

Rooted in the framework of these agreements are the challenges associated with maintaining compliance with safety reporting due to liability on the biopharmaceutical company and responsibility for PV with the generic manufacturer.

In a majority of these agreements, the generic manufacturer is based in an emerging market and the regulatory and legal obligations of highly regulated markets are relatively new to them. They often have limited access to safety expertise and resources such as safety databases required for PV compliance.

Sourcing Models – Mitigating the Challenge

Typically such generic manufacturers are not adequately set up to cope with the intense regulatory requirements.

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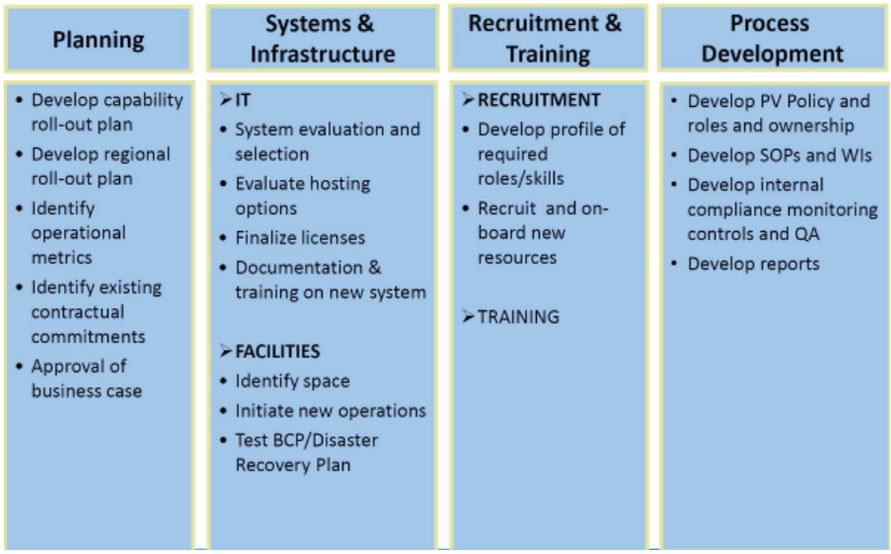


Figure 1: Implementing the Roadmap

Consultancy and education are essential for mitigating these challenges, and outsourcing PV to a neutral third party offers greater opportunity for its successful management.

The main strategic imperatives to consider when adopting a model to ensure a successful path to PV outsourcing are:

- Capability – Access to PV and regulatory knowledge to ensure compliance.
- Capacity – Access to scalable and resilient sources of talent and infrastructure.
- Cost – Ability to establish global PV centers in a low cost destination.

Various sourcing models can be considered, with the captive and the fully outsourced models at opposite ends of the spectrum. The fully outsourced model provides an attractive option if the outsourcing partner is competent, flexible enough to accommodate requirements arising from future partnerships of the MAH and if adequate controls are defined and implemented. More control is provided to the MAH in the captive model where global PV operations are set up in-house, but is a high risk and high cost model given the company's lack of knowledge and resources at the outset.

Other intermediate approaches may be considered in place of the fully outsourced model if the manufacturer wants to retain direct control over specific aspects of the global PV operations or is mandated by the SDEA to do so. Build-Operate-Transfer model (BOT) is a relatively low risk and low cost outsourcing model, whereby the third party takes full responsibility of regulatory compliance and safety reporting for a pre-determined period of time before handing over the responsibility to the now-readied generic manufacturer.

This model can be challenging for the third party provider unless the generic manufacturer has a few key senior management members with good understanding of safety obligations and who can facilitate and support decisions to enable the provider to act towards attaining compliance. There is also a risk that the company may not be fully ready to bring everything in-house by the agreed time.

With the hybrid model, the manufacturer can identify elements which could be managed by third party providers (eg, case processing, aggregate reporting, literature surveillance). For the elements to be retained in-house, either the BOT or captive model can be utilised. Such a model encapsulates the shared approach with continued long-term consultancy. As the responsibility is shared between the generic manufacturer and the third party and is not completely handed back, the model de-risks compliance with long term regulatory obligations.

The choice of model also depends heavily on the scale of the partnership (number of products and number of countries/ regions) and projected increase of the complexity of the portfolio.

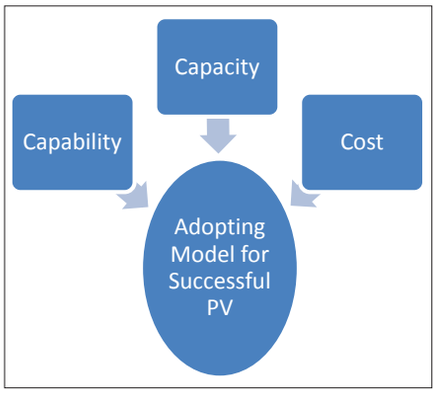
A multi-partner ecosystem is becoming more common and adds a different dimension of complexity requiring high levels of expertise, both on domain and on process. For example, cases received from one partner need to be sent to another partner. Such involvement of multiple parties and multiple hand-offs may result in insufficient turnaround time for cases or even worse, compliance/ reporting risk.

Ownership of the global safety database has to be determined upfront and interoperability of different safety databases ensured. There is also a need to drive agreement on document format for receipt (source documents, e2b, MedWatch, CIOMS, etc). Working with a third party provider that specialises in all of these elements may prove to be the best solution is such scenarios.

The Hybrid-BOT Model: A Case Study

A hybrid-BOT model for PV outsourcing has recently been implemented in a partnership between a well-known global pharmaceutical and an Indian generic manufacturer. The model's definition and implementation in that specific partnership embodies a roadmap that other similar partnerships may well find useful, specifically highlighting the questions and processes which must be actioned.

Firstly, the strategic objectives of the model are identified which should include access to capability, efficiency and leadership. Through the employment of a current state/situational analysis, together with a thorough understanding of organisational limitations, it is then possible to establish the scope involved and what needs and issues require immediate attention.



With the scope in place, an efficient operating model can be defined by asking questions about the process, technology and organisational changes that are required, and how plans for current initiatives will change on implementation of an operating model. It is essential to employ a change management process in order to meet the set objectives. This may involve establishing a completely new working environment or amending current practices, and must allow for the measurement and management of success through quantifiable metrics around regulatory compliance and operational efficiency. Such issues can be raised through the use of a risk/benefit analysis, which is an important process in identifying the level of investment required, what risks must be managed, and how the probability of realising the objectives can be increased.

This initial planning process should take approximately 4-9 months and should be undertaken before implementing the strategy. It is important to ask questions pertaining to what areas should be implemented immediately, which pilot programs should be instigated to ensure the success of the implementation strategy, and if the evaluation process is viable and sustainable.

Questions should also be asked on which business units or geographies require involvement, and if implementation should occur in certain phases over a given timeframe. In terms of execution, metrics, SLAs and measurement are vital, but it is also imperative to derive a strategy to scale the model across different geographies and the entire organisation. The timeframe is obviously dependent on the scale of activity, which in the case of our partnership example is over a few years.

The implementation of the roadmap involves planning, systems and infrastructure, recruitment and training, and process development, and is summarised in figure 1.

In this example, certain responsibilities were transferred to the manufacturer at the end of the agreed period and Sciformix continued to own other tasks and responsibilities such as aggregate reporting, safety surveillance and Quality Assurance.

Conclusion – Successful Management of PV

It is clear that in any partnership of the type described here, meeting regulatory obligations heavily depends on the successful management of Pharmacovigilance. This success hinges on several key factors, specifically in the context of the partnerships and various sourcing models outlined above. Of paramount importance is clarity and universal understanding that the responsibility for PV obligation fulfilment and its integrity rests with the MAH, and that there should be only a single, global process owner. The requirement for transparency extends to the performance and workflow management systems, and the need for evaluation is exemplified by the required measurement of key metrics such as compliance and workload.

Management commitment must also be evident in ensuring all departments share the same regulatory vision and goals, and the SOPs must be global in true sense with a centralised operation team to ensure consistency in processes and quality criteria across regions.

In conclusion, special considerations in terms of regulatory obligations are required in the setting up of global PV operations in the manufacturing and marketing partnerships discussed here. The characteristics of these partnerships are often unique, and although there are some similar considerations taken when addressing PV, there will be unique challenges and complexities which require careful planning. ■

References

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