Module XIII – Pharmacovigilance (PV) Agreements

Contents

1. Introduction to Pharmacovigilance (PV) Agreements

Recently, there has been a significant increase in the collaborations, partnerships, in-licensing and out-licensing. While some companies specialize in compliance with Good Manufacturing Practices (GMP) and manufacturing of the medicinal products, there are many other companies who have well-developed marketing networks in one or several countries. Such companies often collaborate to make the best use of their specific expertise.

Thus, for a product, it may happen that the active ingredient is supplied by one company and the finished formulation may have been manufactured by another company. This finished formulation may be the procured by several companies for marketing in different countries.

Thus, due to the involvement of several parties, the responsibility for PV and thus, continuous assessment of the benefit risk analysis of the medicinal product may either be overlooked, or it may happen that all of them are conducting various PV activities, thus, leading to the duplication of work.

Therefore, it is critical to develop PV agreements to define the responsibilities of each partner for activities related to drug safety.

A well-drafted PV agreement ensures regulatory compliance and prevents the duplication of PV activities by various partners. As the name itself indicates, PV agreements are written contracts developed between two or more pharmaceutical companies working together, to define the responsibilities of each party with special reference to each and every activity related to PV agreements covering the responsibilities of each party for the sharing of data with other party, in the context of receipt of adverse reactions, processing of Individual Case Safety Reports (ICSRs), literature searching, submission of periodic reports, signal detection, single evaluation, development and implementation of risk management plans (RMPs).

Therefore, PV agreements are also known as Safety Data Exchange Agreements (SDEA).

To ensure timely preparation and appropriate implementation of the PV agreements, coordination between the business groups and the pharmacovigilance team is a must. Business groups need to keep PV teams informed of new associations, master agreements as well as change partnerships or expiry / cancellation of the master agreements.

Many times, companies need to outsource some PV activities to third parties. Appropriate and updated contracts and agreements defining the responsibility of each party and responsibilities of each party and responsibilities for sharing the information should be in place with these companies.

This chapter explains various types of PV agreements and provides details regarding the format and contents of these agreements. This chapter also covers timelines for preparing PV agreements, its periodic review and various practical aspects of implementing PV agreements to ensure effective implementation.

2. Contents of PV Agreements

Pharmacovigilance agreements should be drafted to clearly define who will be responsible for the following activities.

- Maintenance of Global safety database.
- Maintenance / updating Company Core Safety Information (CCSI)
- Call receipt
- Case processing including medical assessment and follow-up.
- Regulatory reporting for expedited reporting of initial reports as well as for significant follow-up.
- Preparation of Periodic Safety Reports (PSRs) and submission to regulatory authorities in various countries.
- Literature review
- Signal evaluation
- Signal detection
- Updating Summary of product Characteristics (SmPC) / Package Inserts (PI), Patient Information Leaflets (PILs) / Medication Guides and other relevant documents.
- Archiving of PV documents.
- Development, review, evaluation and implementation of RMPs.
- Continuous benefit-risk assessment.

Where alliances extend to more than one country, the PV agreement should define the responsibilities for each country considering the local regulatory requirements. There can be two scenarios.

- Two different companies are responsible for PV in two different countries. In such cases, regulatory requirements of reporting foreign adverse reactions should be taken into consideration. One should also consider who will be doing the medical assessment as

per local SmPC / PI. Usually serious, unexpected “foreign” adverse reactions are reportable within 15 days; therefore, PV agreement should specify the timelines for exchange of serious adverse reactions. Usual practice is to share the initial report of serious adverse reactions within one working day on initial receipt date. However, this may be longer if company receiving the initial adverse reaction is also responsible for the data entry and medical assessment against both PIs. Similarly, while defining the timelines for exchange of safety data, companies should also consider the data lock point for PSRs, languages constraints and translation requirements if any for submission to local regulatory authorities.

- Only one company is responsible for PV across the world. In such circumstances, PV agreements should clearly outline how data that may unintentionally reach other company will be passed to the company responsible for PV, so that adverse reaction reports and other information can be appropriately processed and reported.

Although it’s critical to define the timelines for exchange of serious adverse reactions (SAEs), it is also essential to include timelines for exchange of non-serious adverse reactions. Non-serious adverse reactions may be exchanged monthly along with the reconciliation of serious adverse reactions which have been exchanged promptly. This will ensure that all non-serious cases are also appropriately included in the PSRs.

As a good practice, it is also important for companies to define the responsibility and appropriate communication lines for handling /exchange of information on the following:

- Urgent Safety Restrictions (USRs)
- Product complaints & Quality issues
- Recalls
- Non-approvals / withdrawals related to safety
- Clinical trial reports / results of ongoing pre-clinical studies
- Other regulatory actions related to the safety of medicinal products

These may be a part of PV agreement or some other agreement.

3. Various types of PV agreements

A company may be executing a pharmacovigilance agreement as a manufacturer, Marketing Authorization Holder (MAH), co-licensor, supplier for clinical trials on its own marketing authorization (MA) or for the transfer of MA. The approach and the roles and responsibilities of pharmacovigilance team members will differ under each condition.

As PV is the responsibility of MAH, MAH takes the initiative to draft a pharmacovigilance agreement. The MAH should take care that following are included in the pharmacovigilance agreement with manufacturer:

1. Manufacturers are responsible for notifying the MAH of adverse reactions associated with products complaints.
2. As the manufacturer's name and contract details may appear on the contracted for reporting of adverse reactions or product complaints. The PV agreement should outline the responsibility of manufacturer to appropriately direct such reports to the MAH.
3. Manufacturers are also responsible for notifying the MAH of USRs, product recalls, withdrawals, regulatory actions associated with safety in other countries.

Sometimes companies get orders to supply a medicinal product for clinical trials on their own Marketing Authorization (MA). The product may be used as a comparator or concomitant or rescue medication.

Consider an example where a company that is marketing Drug A gets an order to supply the Drug A for a clinical trial where Drug A will be used as a concomitant medication. Pharmacovigilance agreements in such situation are drafted to ensure that the sponsor of the trial informs MAH of all adverse events reported in the clinical trial where Drug A is a suspect drug. As MAH may need to expedite serious, unexpected cases, timelines should be defined for the reporting of serious as well as non-serious cases.

Now, consider a case where Drug A as well as the investigational medicinal product that is being tested in the clinical trial, both are suspect drugs. In such a situation, if the sponsors of

the clinical trial as well as the MAH for Drug A, both are expediting the case this will result in duplicate reporting. Therefore, it is advisable to define expedited reporting requirements in pharmacovigilance agreements in such a manner that there is no duplication. Generally, sponsor of the trial remains responsible for the expedited reporting of all SUSARs. This is appropriate also as reporting of serious, unexpected cases would also require unblinding and it may not be appropriate for the sponsor to share the unblended data with the MAH.

Further, MAH should also be made aware of the SUSARs that have been reported by the sponsor. The agreements should be further refined considering the reporting obligation of MAH in order countries (foreign reports) and information collected after the trial is unblended at the end of the study.

It must be remembered that PV is the responsibility of MAH. Whenever, MA is transferred, new MAH becomes responsible for the pharmacovigilance obligations of the medicinal product. Therefore, during the transfer of MAs, the partner who is receiving MA should proactively draft the pharmacovigilance agreement to ensure the exchange of complete safety data including existing safety database with all adverse reaction reports, list of deleted cases, all PSURs submitted, result of single detection, frequency tables, lists of expedited reports, regulatory communications regarding safety etc; in fact depending on the safety profile of the medicinal product this list can be quite exhaustive.

When Should PV Agreements be drafted?

As collaborations are usually driven by business development terms; companies focus on the commercial agreements and financial aspects. Thus, PV agreements may not get adequate attention in the beginning and are usually rushed up and completed at the last moment.

Therefore, it is advisable to prepare a draft acceptable to both parties at the earliest possible while the business negotiations are still ongoing. This will give PV teams from various partners enough time to understand each other's structure, processes, expectations and regulatory requirements. Such an approach will facilitate realistic commitments by PV teams.

Review of PV Agreements

Pharmacovigilance agreements are reviewed periodically, whenever there in change in the legislation or regulatory requirements or change in the business agreements.

Partners may increase the scope, for example increase in the number of products under partnership or an extension of the territories covered by an existing partner. This, the scope of pharmacovigilance agreements also changes with the increase in the number of products and now, it should also cover new products and / or territories. It may happen that, business development terms miss to inform PV teams about such change in scope.

Therefore, PV agreements may not be updated to reflect an increase in the number of products or an extension of the territories. Regular communication and reconciliation between PV and business groups is a must to ensure that PV agreements are current and updated as per the business agreements.

Agreements with Service Providers

Appropriate and legally binding agreement should be developed with third parties to whom one or more pharmacovigilance activities have been outsourced. These agreements should describe details of the services that have been outsourced. Sponsors/ MAHs should develop elaborate procedures for auditing and monitoring of third parties to ensure compliance with MAHs obligations relevant to PV. One must remember that even when outsourced, MAH remains responsible for PV function.

Who executes the PV Agreements?

Pharmacovigilance agreements should be reviewed and approved by the person who has an overall responsibility of PV in consultation with local PV representative, regulatory and legal staff.

In instances where the scope of PV agreements also includes products approved in the European Union (EU), the EU QPPV (Qualified Person for Pharmacovigilance) should have an overview and direct access to all pharmacovigilance agreements. The EU QPPV is legally

responsible to ensure that pharmacovigilance agreements reflect the current regulatory requirements and are timely executed.

As in EU, the EU QPPV is legally responsible for execution and implementation of pharmacovigilance agreements, the EU QPPV can sign off these agreements.

Template of PV Agreements and Checklist

For companies that are entering in different types of collaborations with various companies, it is quite useful to develop the standard template for PV agreements as a ready reference. It will also be useful to develop a checklist to ensure that all relevant PV activities have been covered by the agreements.

An example of checklist is provided in Section 5 below. This checklist can be further modified as per country and company specific requirements. There should be processes in place to ensure that PV agreements are signed, training of the team responsible for execution of these agreements have been conducted and copies of these agreements are accessible to all responsible for PV.

Indexing of PV agreements- Readiness for Inspections

During inspections, inspector usually request for the list of PV agreements and thereafter, they may request for the copies of some executed agreements. Therefore, maintaining a ready list/index of PV agreements comes quite handy at the time of pharmacovigilance inspections. Such a list may include the following

- The name of the partner
- Date of Agreement
- Date of next review
- Type of agreements explaining the responsibility (MAH / manufacturer / clinical trial supply / transfer of MA / co-licensor / co-developer etc)

Inspectors also expect that companies should have the Standard Operating Procedures (SOPs) and the templates for pharmacovigilance agreements

Although small companies with few agreements in place can manage with an excel sheet, large companies that have hundreds of such agreements across the world, it will be useful to maintain a database of PV agreements along with remainders for periodic revision dates and alerts to revise these PV agreements if and when there is a change in the local regulations.

This database of PV agreements can also be linked with business groups to ensure that PV agreements are updated as and when the business agreement covers a new product or there is an expansion of the territory. This database of PV agreements can also be linked to regulatory database to enable the sharing of updates of approved package inserts and other regulatory actions with the partners.

Similarly, in small companies ICSRs are exchanged manually, for large companies with multiple agreements or for products with relatively large number of ICSRs, it will be very cumbersome and possibility of missing distribution of ICSRs to the partners increases. In large companies, the exchange of ICSRs and reconciliation can be carried out by suitably configuring the distribution servers of the global safety database.

Conclusions

Pharmacovigilance agreements are legally binding as well as auditable documents. Failure to prepare the PV agreements or poorly drafted PV agreements may potentially result in non-compliance as each company may assume that the other partner is doing PV activities, like expedited reporting, literature searching, signal detection and preparation of PSRs.

At other times, it may also result in duplication of activities with each party preparing PSURs and conducting literature review. As PV agreements are one of the most important documents reviewed during PV inspections, it is important to pay due attention to preparation and implementation of these agreements so as to ensure a smooth sailing during PV inspections.

4. References

1. Medicines and Healthcare Products Regulatory Agency. Frequently Asked Questions. Available on Website –
   http://www.mhra.gov.uk/howweregulate/medicines/inspectionandstandrads
   /goodpharmoacovigilancepractice/frewuentlyaskedquestions/index.htm#55

2. Medicines and Healthcare Products Regulatory Agency. Good Pharmacovigilance Practices Guide. Pharmaceutical Press 2009

5. Check-list for Pharmacovigilance Agreements

Check-list for pharmacovigilance agreements is exhaustive and should include a cross-check of all activities mentioned above, “Contents of pharmacovigilance Agreements”. Additionally, Pharmacovigilance agreements should also be reviewed to cross check the inclusion of the following points:

- Include definitions for clarity
- Includes key contacts for each partner.
- Signed and dated by all parties
- Method of termination
- Data of next review and the review procedure
- Territories covered by each partner
- Responsibility of maintenance of Global Safety database including updating the reference safety information in labels in different territories.
- Call handling
- Case Processing including medical assessment against CCSI and each label.
- Follow-up of cases
- Regulatory reporting for expedited reporting of initial reports as well as for significant follow-ups
- Timelines for sharing of case reports.
- Preparation of PSURs and submission to regulatory authorities in various counties

- Literature searching and review
- Signal detection
- Archiving of pharmacovigilance documents
- Development, implementation and modification of Risk Management Plans (or Risk MAPs or REMS)
- Conducting Post Authorization Safety Studies (if any agreed with regulatory authorities)
- For products authorized in Europe, check list should also include:
- Responsibility of QPPV
- Role of QPPV
- Responsibility for electronic reporting of ICSRs.