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Pharmacovigilance obligations of the pharmaceutical companies in India

Deepa Arora

The decision to approve a new drug is based on its having a satisfactory balance of benefits and risks on the basis of the information available at that time. Once a product is marketed, new information will be generated, which may have an impact on the benefit-risk profile of the product. The detailed evaluation of the new information generated through pharmacovigilance activities is important for all products to ensure their safe use. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee an absolute safety when a product is marketed and prescribed in large populations with settings different from the clinical trials. Thus, a strong pharmacovigilance system is required to ensure the continuous monitoring and evaluation of the new safety data generated under the real-world conditions on the effects, side effects, contraindications, drug interactions, new indications and use in new populations of all drugs.

Indian market has mostly seen the launch of only those products that have been already approved and marketed in the regulated markets of USA, Europe, Japan or other countries. For assessing the benefit-risk profile of a drug and to take appropriate corrective actions, the Indian pharmaceutical companies as well as the regulators have been depending on the experiences gained from these markets where the drug was being used for several years before introduction in India, thus bypassing the requirement to establish a strong pharmacovigilance system of their own.

In recent years, many Indian companies are increasing the investment in research and development and are enhancing their capacity to develop and market new drugs with their own research efforts. Further, India is becoming a hub for clinical research activities due to its large population, high enrolment rate, and low cost. Moreover, the lag period when a drug is placed for the first time on the market in USA, Europe, Japan or somewhere else in the world, and its subsequent availability in India has decreased considerably. As a result, for such drugs the long-term safety data is not available and the time of their marketing in India. This is clear by the fact that all the high-profile drugs that have been recently withdrawn were available in Indian market. In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess benefit-risk balance of a drug, thereby stressing the importance of developing their own adequately designed pharmacovigilance system in India. All these factors have drawn the attention of not only Drugs Controller General of India (DCGI), but also of World Health Organization (WHO), and the pharmaceutical companies toward the inadequacy of pharmacovigilance systems in India. For an effective pharmacovigilance system to be functional and efficient, all the stakeholders need to be alert and attentive throughout the lifecycle of a medicinal product in the market.

The office of the DCGI has been making sincere attempts for the implementation the National Pharmacovigilance Program (NPP) in India. Further, the Schedule Y of the Drugs and Cosmetics Act 1945 was thoroughly reviewed and amended in 2005 to include and elaborate the pharmacovigilance obligations of the companies attempting to market/develop new drugs in India. This article provides the details of the pharmacovigilance obligations of the pharmaceutical companies marketing their products in India, for generic products, for clinical trials of new chemical entity (NCE) and Indian pharmaceutical companies with pharmacovigilance headquarters in India and subsidiaries in other countries.

Regulations Relating to Pharmacovigilance in India

In India, a pharmaceutical company holding the marketing license should ensure that they have adequate pharmacovigilance system in place to ensure the responsibility and liability of their marketed products, as specified in Schedule Y. When two or more marketed products are identical in all aspects except their trade names, each pharmaceutical company holding a marketing license is obliged to meet the pharmacovigilance obligations. This includes establishment and maintenance of appropriate pharmacovigilance system to collect, collate, and evaluate information about suspected adverse reactions. All these adverse reaction reports and the information about the benefit-risk analysis of a product need to be shared with DCGI. A pharmaceutical company can achieve this either by setting up in-house systems for pharmacovigilance or can enter into contractual arrangements with CROs specializing in pharmacovigilance function for meeting their pharmacovigilance obligations.
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Schedule Y

The legislative requirements of pharmacovigilance in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945. The Schedule Y also deals with regulations relating to pre-clinical and clinical studies for development of a new drug as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in India. Schedule Y was thoroughly reviewed and its latest amendment, dated 20th January 2005, indicates the continued commitment of DCGI to ensure adequate compliance of pharmacovigilance obligations of the pharmaceutical companies. In the amended Schedule Y, an attempt has been made to better define the responsibilities of pharmaceutical companies for their marketed products as well as relating to the reporting of adverse events from clinical trials. The section entitled post-marketing surveillance includes the requirement for submission of periodic safety update reports (PSURs), PSUR cycle, template for PSUR, and the timelines and conditions for expedited reporting.

National Pharmacovigilance Program

This is a nation-wide program, sponsored and coordinated by the country’s Central Drugs Standards Control Organization (CDSCO) to established and manage a database of adverse drug reactions (ADRs) for making informed regulatory decisions regarding marketing authorization of drugs in India for ensuring safety of drugs. NPP sponsored by WHO and funded by World Bank became operational since 1 January 2005. The details of this program are beyond the scope of this article. Some of the major functions of this program include the monitoring of spontaneous ADRs, review of the PSURs submitted by the pharmaceutical companies and assessing the safety information so as to make appropriate recommendations on product label amendments, product withdrawals and suspension. NPP has its own form for spontaneous ADR reporting. The data elements of this form are almost similar to that of CIOMS form or MedWatch Form 3500A. The protocol of NPP provides guidance to healthcare professionals on completion of the spontaneous adverse event reporting form and describes the activities at various centers of pharmacovigilance.[5]

As there is limited guidance available in Schedule Y as well as the protocol published by the NPP, it becomes imperative for the Indian pharmaceutical companies to consult the guidance documents available from International Conference of Harmonization, US FDA, and European Agency for the Evaluation of Medicinal Products (EMEA) so as to develop well laid down procedures for optimally meeting their pharmacovigilance obligations for NCEs as well as for the generic drugs.

Pharmacovigilance Activities for the Generic Drugs in India

To fulfill the pharmacovigilance obligations for its marketed products, as per regulations, a generic company in India is mainly required to carry out the following activities: collection, monitoring, and reporting of spontaneous adverse reaction reports, including expedited reporting of serious unexpected adverse reactions and preparation of the PSURs. The latter activity implies that the pharmaceutical company should also develop adequate systems and expertise for literature searches, management of safety data, signal detection, and risk-benefit analysis of its marketed products.

Spontaneous Adverse Drug Reactions

Spontaneous reporting of ADRs is an important tool for gathering the safety information required for early signal detection. As the information gathered by the spontaneous reporting of adverse reactions is the one collected under real-world conditions, this is considered to be an important tool for conducting the risk-benefit analysis of new drugs. However, due to a high degree of subjectivity and geographical variation in the frequency of reporting of ADRs, it is generally not considered to be a high-quality tool.

Schedule Y specifies that all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. As follow-up all available clinical information regarding the reaction should be provided. Individual adverse reaction reports should be included in the next periodic safety update report, and not necessarily in an urgent manner.

Further, in situations where even if the pharmaceutical company is aware that a physician has reported an adverse reaction of its products directly to DCGI, the pharmaceutical company is still required to report the adverse reaction. For some specific drugs, DCGI on its approval letter for that particular drug, device or biotechnological product mentions that all ADRs reported for that drug should be reported to DCGI. In all such cases, pharmaceutical companies also report all spontaneous adverse events individually as CIOMS/NPP forms besides reporting the spontaneous ADRs routinely in PSURs. It is not clear, however, that how this duplication of reports is managed at DCGI/Pharmacovigilance Centers.

As further details regarding the capture, evaluation and follow-up of adverse reactions, have not been addressed in the Schedule Y, the guidance document from ICH, ICH E2D[6] is referred to develop detailed procedures for handling of spontaneous adverse events. These procedures include defining the minimum four criteria to validate the adverse reaction reports, collection of relevant information for spontaneous adverse reactions, handling of the reports received from patients or their relatives, evaluation of the spontaneous adverse reactions for their seriousness and listenedness/expectedness, follow-up of spontaneous adverse reactions reports, minimum follow-ups required, close out of the case, etc.

National Pharmacovigilance Program has its own form for the reporting of spontaneous ADRs. Generation of separate NPP forms along with CIOMS forms may imply a lot of duplication of work for the pharmaceutical companies who are marketing their drugs in various countries. DCGI, however, also accepts the CIOMS forms for spontaneous adverse event reports. This was clarified by Director General of India in one of the symposium conducted at New Delhi.[7]

Management of the Safety Database

No specific guidelines are available from the Indian regulators regarding the management of safety data or maintenance and update of Company Core Data Sheet or Company Core Safety Information. Generally, all the data collected during the literature searches, spontaneous adverse
event reports, clinical and non-clinical studies or from all other sources are collected and saved in the product safety file.

Signal detection
All the safety data collected from various sources should be evaluated for signal detection. If a trend becomes apparent during the signal detection, the necessary action should be initiated.

Indian population is unique, not only because of its composition and genetic make up but also due to several other reasons like majority of the population approaching general practitioners for most of their diseases, high prevalence of polypharmacy, simultaneous consumption of medicines from alternative systems of medicines, particularly herbs. As in India, as it is very common for the people to consult practitioners from different streams of medicine, such as Ayurveda, Homeopathy or Unani, it is advisable to include a direct question regarding the consumption of herbal drugs in the spontaneous adverse event monitoring. Further, pharmaceutical market in India is not well regulated; therefore, in India even prescription only medicine can also be available freely like the over-the-counter drugs. Thus, a more diverse cross-section of the population is likely to be exposed and a careful evaluation of the adverse events and signal detection can help in revealing a lot of new aspects related to a drug. Therefore, a generic drug company in a country like India should have very strong systems and expertise for signal detection. However, in practice the requirement for establishing a strong AE signaling program is overshadowed by the small number of spontaneous adverse reaction reports, lack of the relevant data on spontaneous ADR reports, the unavailability of the trained staff for signal detection, and the lack of the push/drive from the regulatory agency.

Generally, Indian generic companies follow the global updates of the innovator’s label.

Periodic safety update reports
Periodic safety update reports have been designed to provide the regulators with an update of the worldwide safety data of a marketed drug, biological product or device at defined time intervals. It is considered to be an important pharmacovigilance tool as it is designed to include the safety data on a particular drug from all the sources and geographical regions. Like other regulators, DCGI also recommends a single PSUR for all dosage forms, formulations, and indications for one active substance. Within a single PSUR, data for different dosage forms, indications or populations should be provided separately. License holders are expected to include succinct summary information along with the critical evaluation of the safety profile of a marketed drug in the light of new changes during post-authorization period. A PSUR should also mention whether further investigations need to be carried out and what changes need to be made in the package insert.

Format of PSURs
Format of PSUR provided in the Schedule Y is similar to that of ICH E2C format, although it does not elaborate the contents of the data to be incorporated under each and every heading. For all practical purposes, a PSUR prepared in accordance with ICH E2C format should be acceptable to DCGI.

PSUR reporting cycle
Schedule Y also recommends that for all new products, PSURs should be submitted every 6 months for the initial 2 years and thereafter annually for the next 2 years. It is quite similar to the reporting cycle requirements of European Union (EU), where PSURs are required to be submitted every 6 months for the first 2 years, annually for the three following years and every 3 years, thereafter. In EU, it is generally acceptable to the regulators that the generic companies skip the 6-monthly cycles of initial 2 years and submit the PSURs every 3 years from the date of marketing approval. Reporting requirements of US FDA are, however, different. The US regulations require quarterly reports during the first 3 years and annual reports, thereafter. Like other regulatory authorities, DCGI can also extend the total duration for the submission of PSURs if it is considered necessary in the interest of public health.

Like other major regulatory authorities, Indian regulations also require that PSURs should contain the relevant clinical and non-clinical safety data only for the period of report (interval data). Although it is not specified in Schedule Y, as per ICH E2C requirements, PSURs submitted to DCGI contain cumulative data on the regulatory status information on authorization applications and renewals, as well as data on serious, unlisted adverse reactions.

Periodic safety update reports due for a period must be submitted within 30 calendar days for the last day of the reporting period. As there is no guidance available on the data lock, generally pharmaceutical companies follow the recommendations from ICH E2C for the data lock.

Period of reporting in PSURs
Schedule Y further states that if the marketing of a new drug is delayed after obtaining the approval to market, such data may be submitted on a deferred basis beginning from the time the new drug is marketed. This is in sharp contrast to EU regulations, where a pharmaceutical company is required to meet pharmacovigilance obligations of all the products for which it holds marketing authorization, irrespective of the marketing status of the products.

As there is limited guidance available in Schedule Y as well as the protocol published by the NPP, it is very important for the pharmacovigilance team of an Indian pharmaceutical company to consult the guidance documents available from ICH, US FDA, and EMEA so as to develop well laid down procedures for optimally carrying out the pharmacovigilance of new as well as generic drugs. Some additional activities that are generally carried out by a generic pharmaceutical company, however, have not been covered above include literature searches, generation of alerts, communications to healthcare professionals, and execution of pharmacovigilance agreements.

Safety Reporting During Clinical Trials
In a clinical trial, all adverse events experienced, irrespective of the causality should be monitored, accurately documented and adequately reported in a timely manner following the local regulatory requirements. As per amended Schedule Y, the sponsor’s responsibilities include reporting of SAEs as mentioned:
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Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study (Appendix XI).

Although Schedule Y mentions that only the unexpected adverse events should be reported, it does not provide any guidance on the procedure to determine the expectedness of an adverse event.

Appendix XI of Schedule Y, titled “Data Elements for reporting of serious adverse events occurring in a clinical trial” has contents similar to the SAE forms from the other authorities.

Further under the responsibilities of the investigators for a clinical trial, Schedule Y mentions that during the conduct of a clinical trial or its follow-up, it is the responsibility of an investigator to ensure adequate medical care to the subjects suffering with adverse events. Regarding reporting responsibilities of the investigators, Schedule Y states that: Investigator(s) shall report all serious and unexpected adverse events to the sponsor within 24 h and to the Ethics Committee that accorded approval to the study protocol with 7 working days of their occurrence.

Unlike other regulations, Schedule Y does not specify the rules regarding the reporting of foreign cases from multinational trials, and lacks further details on the procedures for unblinding, coding, data monitoring committees, annual safety reports, and handling of the adverse events associated with placebo or comparator drugs.[9]

Pharmacovigilance Obligations of Indian Companies with Subsidiaries Abroad

India multinational companies who have subsidiaries across the world, particularly in Europe are facing a new challenge. Although Schedule Y does not specify anything regarding the expedited reporting of serious adverse reactions from other countries, Eudralex Volume 9A - Guidelines on Pharmacovigilance for Medicinal Products for Human Use, clearly specifies the requirement for the reporting of foreign cases and the case reports from literature searches. Thus, it is a more convenient to collect data centrally and report to relevant authorities where the product is marketed. Thus, it makes sense for such Indian companies with subsidiaries in Europe to establish and maintain the safety databases for their products in India and centralize the pharmacovigilance activities such as literature searches, generation of CIOMS forms, signal detection, risk-benefit analysis, and preparation of PSURs in India and have a QPPV locally in Europe for regulatory interactions, including reporting and receiving pharmacovigilance communications from the respective Competent Authorities.

Conclusion

Till recently, in India there was never a compulsion to have a strong pharmacovigilance system to detect adverse reactions of the marketed drugs. However, the increased interest of Indian regulatory authority in pharmacovigilance is clearly reflected by several instances including the amendment of Schedule Y, organizing several seminars, and training programs with WHO and several press releases from DCGI from time to time stressing the importance of a strong pharmacovigilance system in India, including the recent press release announcing the setting up of an independent pharmacovigilance team to review the safety of the anti-diabetic drug rosiglitazone. Thus, the pharmaceutical companies who have been marketing generic drugs in India are now faced with greater regulatory reinforcement and increased accountability demands for ensuring a favorable benefit-risk balance of their products are required to take a more active approach to pharmacovigilance. This includes monitoring and reporting of spontaneous adverse reactions, submission of PSURs, conducting the risk-benefit analysis of new drugs, and relevant communications. For the companies conducting clinical trials in India, the regulatory timelines for reporting and the conditions for expedited reporting have been clearly defined.

As there is limited guidance available in Schedule Y as well as the protocol published by the NPP, it becomes imperative for the Indian pharmaceutical companies to consult the guidance documents available from ICH, US FDA, and EMEA so as to adequately define their procedures for conducting various pharmacovigilance activities. Some of the challenges faced by the pharmaceutical companies in India are a very low level of reporting of spontaneous ADRs, lack of training of general practitioners on drug safety and adverse drug reaction reporting, non-availability of staff trained in pharmacovigilance, lack of the guidance from the Indian regulatory authority due to the lack of expertise and experience.

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