New Pharmacovigilance Obligations for MAHs in India

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On September 29, 2017, the Secretary, Ministry of Health and Family Welfare, Government of India, released the *Pharmacovigilance Guidance Document for Marketing Authorization Holders (MAHs) of Pharmaceutical Products*. While practical issues pertaining to implementation of this mandate are yet to be encountered, it is obvious that 2018 will go down in history as the year of pharmacovigilance's metamorphosis from an elite add-on to an essential component of the pharmaceutical industry in India.

According to this Document, the term "MAH" refers to the manufacturer or importer of the drug, who has a valid manufacturing or import license in India. The Document has been prepared and published by the Indian Pharmacopoeia Commission, the National Coordination Centre for the Pharmacovigilance Programme of India (PvPI), under the aegis of and in collaboration with India's drug regulatory agency, the Central Drugs Standard Control Organization (CDSCO). This Document aims at enabling MAHs to set up a Pharmacovigilance system in their organizations in line with the recent amendment to the Drugs & Cosmetics Act (1940) and Rules (1945). This Guidance Document (Version 1.0) is set to be effective as of January 2018.

Module 1

Industry's most important obligation established by this Document is the need to identify a Pharmacovigilance Officer In-charge (PvOI), as defined in Module 1 of the Pharmacovigilance System Master File (PvMF), who shall have sufficient authority over the pharmacovigilance system and be responsible for compliance. As a unique feature, the PvOI is mandated to be a Medical Officer or a Pharmacist trained in the collection and analysis of Adverse Drug Reaction (ADR) reports. This PvMF Module further elucidates on the MAH organizational structure pertaining to pharmacovigilance, its relationships with contract research organizations, sources of safety data, pharmacovigilance processes, standard operating procedures, computerized databases, quality management system, and pharmacovigilance system performance. This is a phenomenal change in the history of regulatory pharmacovigilance in India, as this is the first time that such a detailed description for a pharmacovigilance system required of a MAH has been announced by the competent authorities. While pharmaceutical companies with mature pharmacovigilance systems may have just a little difficulty in fine-tuning their systems per the newly detailed requirement, a huge number of manufacturers/importers with valid licenses find themselves in oblivion due to their lack of prior exposure to pharmacovigilance as an industry practice.

Module 2

Module 2, which deals with Individual Case Safety Reports (ICSRs), provides reasonable detail on the different sources of ADRs into which the MAH must tap. The requirement for monthly literature review using electronic literature database has been stated for the first time. In addition, screening of medical inquiries, internet/digital media, solicited reports, special populations, and reports from contractual partners, have been explained. All ICSRs received by MAHs are mandated to be submitted to PvPI in XML-E2B format, a significant development as it implies the indispensable need for an electronic pharmacovigilance database. The MAH is required to code ADRs using a dictionary but no specific dictionary has been recommended. However, indications of the suspected and concomitant drugs must be coded using the latest version of the International Classification of Diseases, which allows room for redundancy. The Document lists the WHO-UMC causality assessment scale as the preferred tool for causality assessment. It also states that causality assessment by MAHs is mandatory for new drugs. The document establishes the timelines of reporting to PvPI as 15 days for serious adverse events/ADRs and 30 days for non-serious adverse events/ADRs. However, it is not clear on whether serious adverse events/ADRs need to be reported to both the regulatory authority and PvPI or if reporting to one of them will suffice. In addition, the requirement for serious unexpected ADRs to be reported to the licensing authority (which may be the CDSCO or any of the State Drug Licensing Authorities) paves way for ambiguity due to opening of multiple reporting channels. Lack of efficacy cases and medication errors must also be reported.

Module 3

Module 3 defines the recommended format, content, and timeline of submission of Periodic Safety Update Reports (PSURs) in conformity with Schedule Y of the Drugs and Cosmetics Act (1940) and Rules (1945). PSURs shall be submitted every six months for the first two years after approval of the drug and annually for the subsequent two years, unless extended by the licensing authority in the interest of public health. PSURs due must be submitted within 30 calendar days of the last day of the reporting period. All dosage forms and formulations as well as indications for new drugs should be covered in a single PSUR, with separate presentations of data given for these special situations. The PSUR must provide separate line listings of ICSRs received from India and from the rest of the world. While most of these PSUR regulatory requirements were already in force, a key change is that the PSUR submission must be made to the PvPI in addition to the regulatory authority. It is understood from other sources that the original submission is expected to be made to CDSCO as a hard copy, with a soft copy of the PSUR emailed to PvPI.

Module 4

Module 4 focuses on the QMS in the MAH organizations and outlines the quality cycle of the pharmacovigilance system, quality objectives for pharmacovigilance, responsibilities of the quality system, training of MAH personnel, and required facilities and equipment, with special emphasis on compliance management, record management, documentation of the quality system, and critical pharmacovigilance processes. It also stresses the importance of business continuity plans. It also explains monitoring the performance and effectiveness of the pharmacovigilance QMS.

Module 5

Module 5 exclusively provides insight into the planning, conducting, reporting, and follow-up of pharmacovigilance inspections by the competent authorities in India. The module lays out the objectives and distinguishes between routine and targeted inspections. It also sketches the inspection planning and procedures, classification of the findings, inspection follow-ups, responses to findings, and types of regulatory actions, and also dwells briefly on inspector training.

Module 6

Module 6 provides a summary approach towards Risk Management Plans (RMPs), including the objectives of RMPs, their content and risk minimization activities, and highlights specific pharmacovigilance activities. The general understanding is that an RMP must be submitted at the time of product approval and/or on request by the competent authorities, although it is not explicitly mentioned in the module. While the module states that the regulatory authority shall approve every RMP for every product, it is not clear whether this condition applies to products already in the market or only to products that would be introduced prospectively. Moreover, the format in which a RMP has to be prepared and submitted by a MAH has not been provided.

There is no dedicated module for signal detection despite it being referred to in the modules on PvMF and PSURs.

Conclusions

The announcement of the Pharmacovigilance Guidance Document for MAHs (in conjunction with the two other guidelines applicable to Vaccines and to Similar Biologics, released earlier in 2017) has effectively placed the evolution of pharmacovigilance obligations for MAHs in India at its crossroads. Although complying with the pharmacovigilance requirements pronounced by this Document may be quite challenging, especially for that part of the Indian pharmaceutical sector that was hitherto unexposed to pharmacovigilance, there are provisions for outsourcing most of its mandated activities. With India serving as the global capital of pharmacovigilance outsourcing today, impacted MAHs may make use of these provisions and quickly augment their pharmacovigilance systems by choosing appropriate pharmacovigilance partners.

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