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REVIEW ARTICLE

Pharmacovigilance Requirements for Biologic Products in India

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ABSTRACT

The term Pharmacovigilance mean all scientific and data gathering activities related to the detection, assessment, and understanding of adverse events. It principally involves the identification and evaluation of safety signals. It also requires detection of any change in benefit-risk balance during its entire life cycle. With the increasing complexity of medications available today, a comprehensive ADR monitoring system is necessary to detect, evaluate, and develop mechanisms to prevent ADRs. Risk assessment during product development should be conducted thoroughly and rigorously; however, it is impossible to identify all safety concerns during clinical trials. Therefore, postmarketing surveillance which may be passive or stimulating has a significant role in assessing the actual safety aspects of the vaccine product.

KEYWORDS

ADR, Safety signal, Post-marketing surveillance

INTRODUCTION

Indian pharmaceutical industry is the third largest industry regarding volume and thirteen most significant regarding valve. It has also emerged as a hub for clinical trials and drug development process with the frequent increase in new drug delivery system, devices and chemical entities. Vaccines are among the safest tools of modern medicine that help in protecting against disease by inducing immunity. Pharmacovigilance system originated with thalidomide incident that caused ten thousand birth defects in children. Regulatory systems were established soon to bring an improvement in post-marketing surveillance for the safest medicines.[1]

Pharmacovigilance of vaccines differs mostly from drugs as vaccines are complex biological products which may include multiple antigens, live organisms, adjuvants, and preservatives. So each component has unique safety implications which require different information to capture as compared to other drugs.[1]

Objectives

1. To aid to the marketing authorization holders (MAH) and other allied stakeholders (industry and agencies) who play an active role in launching, distribution and bringing the vaccine products to its end users.
2. To identify the risks, formulate the risk profile of a vaccine and its administration programme, design of the appropriate Pharmacovigilance plan to mitigate s uch risks and to explore the missing critical information which did not emerge during premarket phase I /II / III trials, and

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therefore safety profile had not been established.[2]

DISCUSSION

Although vaccines are considered to be medicines with an anti-infective activity that work by immunological action and administered for prophylaxis, Pharmacovigilance of vaccines differs mostly from drugs because, vaccines are complex biological products which may include multiple antigens, live organisms, adjuvants, and preservatives. So each component has unique safety implications which require different information to capture as compared to other drugs.

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use regarding subject characteristics and the number of patients exposed. In particular, during the early post-marketing period, the product might be used in settings different from clinical trials and a much more significant population might be exposed in a relatively short timeframe. Once a vaccine is marketed, new information might emerge, which may have an impact on the benefits/risks ratio of the product. Evaluation of this information should be a continuing process in consultation with regulatory authorities.

The licensing authority may also advise the MAH to conduct Phase IV trial in case of demonstration of product safety, efficacy and dose definitions. These trials may not be considered necessary at the time of new drug approval, but may be required by the licensing authority for optimizing the product use.

Similarly, the immunization division under the Ministry of Health and Family Welfare collects information on adverse event related to vaccines on a regular basis. Information on serious adverse events is collected in the case report form (CRF), and details of the investigation of the reported incident are received in the Preliminary Case Investigation Form (PCIF) and final case investigation form (FCIF) in which the state AEFI committee assigns the causality. The AEFI secretariat will share limited line list (in excel format) with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited line list to include state, age, sex, date of vaccination (DOV), antigens administered, manufacturing details (name, batch number and expiry date) and the reason for reporting.[2]

Roles and Responsibilities of Authorities

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with the Indian Pharmacopoeia Commission (IPC), Ghaziabad have initiated a nationwide Pharmacovigilance program for protecting the health of the patients by assuring drug safety. The programme is coordinated by the Indian Pharmacopoeia Commission, Ghaziabad as a national coordinating center (NCC). The center operates under the supervision of a steering committee.

Role of a Pharmacovigilance Program of India at IPC

- To monitor Adverse Drug Reactions in Indian population.
- To create awareness amongst health care professionals about the importance of ADR reporting in India.
- To monitor benefit-risk profile of medicines and vaccines.
- Generate independent, evidence-based recommendations on the safety of medicines.
- Support CDSCO for formulating safety-related regulatory decisions for medicine.
- Communicate findings with all key stakeholders.

Pharmacovigilance Plan

The MAH will develop a comprehensive Pharmacovigilance plan as listed below**.**

1. Pharmacovigilance Methods

It includes

A) Individual Case Study Reports

B) Periodic Safety Update Reports (PSUR)

C) Post Marketing Trials (Phase IV)

A) Individual Case Study Reports

These are further subdivided into

i. Passive surveillance

ii. Stimulated reporting

iii. Active surveillance[2]

Passive Surveillance – Spontaneous Reports

- Spontaneous reports play a significant role in the identification of safety signals once a drug is marketed.
- A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a MAH, regulatory authority that describes one or more adverse drug reactions in a patient who was given one or more biological products and that does not derive from a study or any organized data collection scheme.
- Spontaneous reports can also provide valuable information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions.
- The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors, including the time since launch, Pharmacovigilance-related regulatory activity, media attention, and the indication for the use of the drug.

Stimulated Reporting

- Stimulated adverse event reporting in the early post-marketing phase can lead MAH to notify healthcare professionals of new therapies and provide safety information early in use by the general population.
- Stimulated reporting includes on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting, and incomplete information.
- During the early post-marketing phase, MAH might actively provide health professionals with safety information and at the same time encourage the cautious use of new products and the submission of spontaneous reports when an adverse event is identified.
- Stimulated reporting should be regarded as a form of spontaneous event reporting, and thus data obtained from accelerated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.[2]

Active Surveillance

- Active surveillance, in contrast to passive surveillance, seeks to completely ascertain the number of adverse events via a continuous pre-organized process.
- It includes the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and permit later contact.
- It is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

All the Serious Adverse Events during the period of Post Marketing Surveillance or Periodic Safety Update Report shall be reported within 15 days to the Licensing Authority in the prescribed format - Vaccine Adverse Event Reporting System (VAERS).

B) Periodic Safety Update Reports

- PSUR are essential Pharmacovigilance documents.
- These provide an opportunity for MAHs to review the safety profile of their products and ensure that the Summary of Product

Characteristics (SmPc) and Package leaflet within the reasonable time frame.

- PSURs present the world-wide safety experience of a medicinal product/vaccines at defined times post-authorization, in order to report all the relevant new safety information from appropriate sources; relate these data to patient exposure; summarize the market authorization status in different countries and any significant variations related to safety; create periodically the opportunity for an overall safety re-evaluation; indicate whether changes should be made to product information in order to optimize the use of the product

It is recommended that the MAH can submit the PSUR data either in schedule Y format or in conformity with Periodic Benefit-Risk Evaluation Report (PBRER) as per ICH E2C (R2) according to the current practices of the developed countries and developing countries and continue to monitor the safety of the vaccines throughout the lifecycle of the product and produce the report as and when required by the licensing authority.(2)

C) Post Marketing Trials (Phase IV)

- Postmarketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s).
- These trials may not be considered necessary at the time of new drug approval, but may be required by the licensing authority for optimizing the new drug's (vaccine's) use.
- Phase iv trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g., mortality/morbidity studies, epidemiological studies, etc.

2. Development and Use of Risk Minimization Action Plans

The goal of risk minimization is to minimize a product's risk while preserving its benefits. The MAH shall develop, implement and evaluate the risk minimization action plan which shall include

(1) Initiating and designing plans called risk minimization action plans or risk MAPs to minimize identified product risks,
(2) Selecting and developing tools to mitigate those risks,
(3) Evaluating risk MAPs and monitoring tools.

A product is considered safe if it has an appropriate benefit-risk balance for the intended population and use. Benefit and risk information emerges continually throughout a product's lifecycle (i.e., during the investigational and marketing phases) and can reflect the results of both labeled and off-label uses. Assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient factors. To help ensure safe and effective use of their products, sponsors have always sought to maximize benefits and minimize risks.

Communication of risks and benefits through product labeling is the cornerstone of risk management efforts for prescription drugs. Routine risk minimization measures such as labeling practices describing the conditions in which the drug can be used safely and efficiently, updated from time to time to incorporate information from post-marketing surveillance or studies revealing new benefits (e.g., new indications or formulations) or risk concerns. A risk MAP targets one or more safety-related health outcomes or goals and uses one or more tools to achieve those goals.

It includes

A) Nature and rate of known risks versus benefits

B) Targeted education and outreach

C) Performance linked access systems

A) Nature and Rate of Known Risks versus Benefits

Comparing the characteristics of the product's adverse effects and benefits may help clarify

whether a risk MAPs could improve the product's benefit-risk balance. The characteristics to be weighed might include the

- Types, magnitude, and frequency of risks and benefits;
- Populations at high risk and/or those likely to derive the most benefit;
- The existence of treatment alternatives and their risks and benefits; and
- Reversibility of adverse events observed.

Serious adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for risk MAPs.

A risk minimization tool is a process or system intended to minimize known risks. Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appropriate situations or patient populations. Some tools are available and may be used as required. A variety of tools are currently used in risk minimization plans. These fall into three categories.[2]

i) Targeted education and outreach

ii) Reminder systems

iii) Performance linked access systems

i) Selective Education and Outreach

It is recommended that MAH holders consider tools in the targeted education and outreach category.

- When routine risk minimization is known or likely to be insufficient to minimize product risks or
- As a component of risk MAPs using reminder or performance-linked access systems.

Sponsors are encouraged to continue using tools, such as education and outreach, as an extension of their routine risk minimization efforts even without a risk MAP. Tools which may be used as routine risk minimization efforts even without a risk MAP may be:

- Training programs for healthcare practitioners or patients.
- Continuing education for healthcare practitioners such as product-focused programs developed by sponsors
- Prominent professional or public notifications
- Patient labeling such as medication guides and patient package inserts.

Promotional techniques such as direct-to-consumer advertising highlighting the appropriate patient use or product risks

- Patient sponsor interaction and education systems such as disease management and patient access programs
- Healthcare practitioner letters.

ii) Reminder Systems

Tools in the reminder systems category can be used in addition to the tools in the targeted education and outreach category when targeted education and outreach tools are known or likely to be insufficient to minimize identified risks. Tools in the reminder system include systems that prompt, remind, double-check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving or using a product in ways that minimize risk.

Examples of tools in this category are as follows:

- Patient education includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are often called 'consent forms'
- Health care provider training programs include testing or any other documentation of the physician's knowledge and understanding.
- Enrollment of physicians, pharmacies, and/or patients in specialized data collection systems that also reinforce appropriate product use.
- A limited number of dose in any single prescription or limitations on refills of the product.[2]

iii) Performance Linked Access Systems

Performance-linked access systems include systems that link product access to laboratory testing results or other documentation.[3]

Tools in this category are very burdensome and can disrupt usual patient care, should be considered only when

- Products have significant or otherwise unique benefits of a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and
- Routine risk minimization measures, targeted education and outreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.

In choosing tools for a risk MAPs, it is recommended that sponsors:

- Maintain the broadest possible access to the product with the least burden to the health care system that is compatible with adequate risk minimization.
- Identify the key stakeholders who can minimize product's risks and define the anticipated role of each group.
- Seek input from the key stakeholders on the feasibility of implementing and accepting the tool in usual health care practices, disease conditions.
- Acknowledge the importance of using tools with the least burdensome effect on healthcare practitioner-patient, pharmacist-patient and/or other healthcare relationships.

It is recommended that MA holders periodically evaluate each risk MAPs tool to ensure it is materially contributing to the achievement of risk MAPs objectives or goals.[4]

CONCLUSION

India needs a standard Pharmacovigilance system for the monitoring of the adverse effects of the drugs, biosimilars and assuring patient safety. Despite all the efforts made by CDSCO for the establishment of a global Pharmacovigilance system for the country, a lot of challenges need to be overcome for successful implementation of Pharmacovigilance like lack of awareness among pharmacists, nurses, patients and a shortage of technical staff for reporting ADRs. The need of the hour is to educate the pharmacists, physicians to encourage them to report ADRs that occur in patients. Standard guidelines for Pharmacovigilance in India, inspired by the Good Pharmacovigilance Practices devised by EMA, will genuinely serve the purpose of ensuring the safety of our patients and establishing a global system for drug safety monitoring.

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