The importance of pharmacovigilance in risk management

Business, Risk Management

Introduction

OBJECTIVE

Every medicinal product has its own risk-benefit ratio. The products, whose benefits to the patients overweigh its risk, are approved by the Competent Authorities (CA). The approved products do not mean that they have no side effects. Actually every medicinal product has some side-effects and it’s very important to identify the side-effects throughout its lifecycle. The process of constant monitoring of the medicinal product throughout the product lifecycle is called Pharmacovigilance. The aim of pharmacovigilance is to protect people by identifying, detecting, characterising, monitoring and communicating risk for rational and safe use of medicines. 1 These benefit-risk findings helps to take decision regarding safety of the medicinal product by regulators, company, physicians and patients. 2

BACKGROUND

In 1961, after disaster of thalidomide, it has been brought forward that post-authorisation data was not sufficient to detect early warning signs of the drug safety. 3 If Pharmacovigilance system were in place during that time; such a disaster would be minimised. To avoid any such disaster in future Marketing Authorisation Holder (MAH) & Competent Authority (CA) work together to ensure that pharmacovigilance system is maintained and patient’s safety is not compromised.

CONCEPT OF PHARMACOVIGILANCE

In general, pharmacovigilance have no boundaries and it should be performed to all medicinal products throughout its lifecycle. Rapid and

effective assessment of drug safety is achieved by early information of any unintended effect. Innovative and generic companies have to follow the same requirements with regards to updating the safety specification. 4

Currently, the pharmacovigilance system is set as per guidance,

Regulation EC/726/2004

Directive 2004/27/EC.

Volume 9A and

ICH guidelines

PHARMACOVIGILANCE RESPONSIBILITY

Marketing Authorisation Holder (MAH):

In current situation, it’s very difficult to identify a new product and new product application is expensive and time-consuming process. To make a blockbuster product; MAH focus thoroughly on Pharmacovigilance system to avoid any disappointment at the later stage of the product lifecycle as it’s very essential for survival of the company. The importance of Pharmacovigilance is that if successful product fails to detect early signals, company also fails to protect its brand identity.

The first step initiated by MAH is to ensure that proper pharmacovigilance system is set up to detect signal of any adverse effect and risk management plans should be in place to minimise its impact. 3

To perform above activities, MAH appoints a QPPV who is responsible for, 5

Collecting and collating all suspected adverse effects globally and establish benefit-risk balance to submit to CA.

Preparing and submitting Periodic Safety Update Review (PSUR), Individual Case Safety Review (ICSR), pre & post-authorisation studies to the CA through electronic reporting.

Reviewing safety issues and product defects.

Conducting internal audit of pharmacovigilance system and ensure management of database.

Along with Pharmacovigilance team, company also build Risk Management Team or Crisis Management Team who plays a vital role in minimising the impact of any adverse reactions on the product and the company.

Competent Authorities (CA)

Along with MAH, CA also develop their Pharmacovigilance team who performs studies like MAH to evaluate the safety performance of the medicinal product. It is also theresponsibilityof MAH to provide timely and correct information of any signal detected to the CA. CA also evaluate Pharmacovigilance system of the MAH by routine inspections conducted by national authorities to check the system and facilities are in accordance as mentioned in Detailed Description of Pharmacovigilance System (DDPS)6. Apart from routine inspections, certain factors that triggers the inspections are, 5

Delays in carry out safety reporting

Incomplete or poor quality reporting

Inconsistency between reports

Changes in benefit-risk balance andfailureto communicate to CA.

Hence considering the importance of Pharmacovigilance, both MAH and CA take joint responsibility to safeguard publichealth.

KEY STEPS IN PHARMACOVIGILANCE

Once the MAH Pharmacovigilance system is set, the key factors are,

Signal detection

Signal detection is initiated by MAH as well as CA. At any stage during the product lifecycle, if unintended effect is detected, it prompts to evaluate the reason for its happening. Generally MAH should be first to detect any signal, but if is detected by CA, it means that MAH pharmacovigilance system is not efficient and inspections are required to verify the pharmacovigilance set up.

The adverse effect signal can be detected by:

Constant monitoring in-house studies conducted by MAH.
Spontaneous ADR reporting: where a healthcare professional reports any adverse effect to the MAH or CA from patients experiences as well as from his own studies. 5

MAH evaluates if a casual or suspected relationship is determined between adverse reaction and medicinal product. Once it is confirmed that relationship exists, MAH should inform CA within 15 days of the occurring of the adverse reaction. 5

For cases where patient contacts the MAH directly regarding any adverse reaction, MAH should advice the patient to contact the healthcare professional. Once the adverse reactions are confirmed by healthcare professional, it should be documented by MAH as spontaneous adverse reactions.

Prescription Event Monitoring (PEM): It is a hybrid method of data collection from surveillance as well as spontaneous adverse effects. Here all the prescriptions when dispensed are collected and analysed to give an idea of which patients are exposed to which medicines, time of exposure and any signal detected during their therapy. 3
Worldwide reports published for ICSR published on Medline or Embase etc helps MAH to be aware of the incidents and can get prepared for such adverse reaction incidents. 5 Such literature or internet references should be reviewed atleast once or twice fortnight.

If the product is authorised by CP, it should be reported to Eudravigilance, but if the product is authorised through MRP or DCP, CA of the RMS should be reported. Here RMS takes the leading role and contacts respective CMS regarding of reporting any such adverse reaction. 25

All the regional wise signals detected are collected by local affiliates and then they are reported to the main office The MAH collects this information globally through local affiliates and reporting to the central office as well as collecting information through websites.

Benefit-risk Assessment

Once the signal is detected, benefits of medicinal product are assessed on the information of cure or improve rate of the symptoms, the response rate and quality of life. The risk involved is assessed as spontaneous adverse reactions, frequency and presence of risk factors, epidemiological data as well as overdose, misuse or medication errors. 5 MAH should try to improve the benefit-risk balance to optimise safe use of the medicines.

To effectively monitor the safety performance of the medicine by the CA, it is decided to report periodically which is known as Periodic Safety Update Review (PSUR).

Pharmacovigilance during pre-authorisation

From drug discovery till the application is submitted, MAH performs several non-clinical and clinical studies to establish benefit-risk balance. Once the product is in application but not granted, if any unintended effect is seen, MAH evaluate the impact of unintended effect and inform to the CA. But there are several limitations to pre-authorisation stages like, 5

limited people population,
limited time of exposure of medicine,
limited age & sex, geographical, ethnicity people &
limited scope of interactions with other medicines.

Pharmacovigilance during post-authorisation

But when the product is authorised, it is widely prescribed in different class of patients. This gives more opportunity to identify any unintended risk or potential risk which was not identified during pre-authorisation studies.

Hence post-authorisation studies are very essential to detect any such changes in benefit-risk balance and its reporting is through PSUR.

To make the post-authorisation robust, MAH maintains the list of information regarding safety, indications, dosing and pharmacology which is called Company Core Data Sheet (CCDS). CCDS proves as a reference to evaluate the change in benefit-risk balance. If any new adverse reaction is reported, CCDS data is updated to reflect changes. 27

PHARMACOVIGILANCE REPORTING

Periodic Safety Update Reports (PSUR)

PSUR is intended to review worldwide safety profile of the product and ensure that SmPC, labelling and leaflet are up-to-date. It is performed to evaluate the data of latest safety reports and to conclude that safety benefit-risk balance is not changed. If there is any change in safety data, appropriate actions should be taken for amendments of current information through increased market surveillance. 7 Single PSUR is required to be submitted per MA which include all indications, dosage forms and route of administration.

The main contents of PSUR are, 5

Executive summary

Introduction

Worldwide market authorisation status

Update to regulatory authority

Changes to reference safety information

Patient exposure

Individual case histories

Overall safety evaluation

Conclusion

Appendix: company core data

PSUR reporting to CA is derived from the date of birth of the medicinal product. The date when the medicinal product was approved is call International Birth Date (IBD). 5

Considering IBD, PSUR is submitted,

Every six months from authorisation until it is placed in the market

Every six months for first two years

Annually for next two years and thereafter every 3 years

Product submitted for renewal

In certain cases, where PSUR is not submitted on time, additional 30 days are allowed to submit PSUR. For generic and well established product, PSUR submission dates can be amended depending on the benefit-risk profile of the product. But in all cases, prior permission should be taken from CA. 5

During renewal submission, the PSUR report should cover 4 years and 4 months. Renewal can be submitted before 6 months. 5 As PSUR submission is calculated as per IBD, renewal should not be affect by PSUR reporting and similar reporting cycle should be followed.

RISK MANAGEMENT PLAN (RMP)

As all actual or potential side-effects are not identified during studies, so along with pharmacovigilance activities which detect any unintended effects, there should also be Risk Management Plan (RMP) to minimise the impact of any such unintended effects.

RMP identifies the risk, clarifies the safety profile and decide alternative ways to minimise risk to the patients. 15 As every product has different pharmacological actions and differ in safety profiles, separate RMP should be designed for each product. RMP should also identify multiple risks. RMP comprised of 4 steps: 5

Risk detection

Risk assessment

Risk minimisation

Riskcommunication

EU Risk Management Plan

All products authorised within the EU should have approved EU-RMP maintained throughout the product lifecycle. EU RMP contains,

Safety Specification – These are certain data which are not clearly addressed during non-clinical and clinical trials like toxicity, drug interactions, pharmacology & pharmacological class, population not studied, epidemiology and adverse events.

Hence it is the summary of important identified risks, potential risk and some missing information. 13 It should also highlight the population at risk and

highlights the requirement for further study. The safety specification is itself a stand-along document along with pharmacovigilance plan and the specific elements are incorporated in CTD. 5

A Pharmacovigilance Plan – It is based as per safety specifications. For certain products where less risk is expected, routine Pharmacovigilance plan is designed. For certain product which involves more complexity and were less safety specifications are available, additional steps are taken to ensure that any signal detected is evaluated in early stages. Action plans are prepared depending on the safety issue. The main points for action plan are safety issue, objective of proposed action, action proposed, rational for proposed action, monitoring and finally evaluating & reporting. 5

Risk minimisation activities – It can be achieved through knowledge of Safety Specifications by restricting adding suitable warning on the labelling and package leaflet. Medication errors should also be considered withrespectto brand names, presentations & instructions for use. 5 Appropriate warning should also be mentioned if it can be life-threatening due to improper use of route of administration or due to mixing of different strength. Risk can be minimised through additional studies, legal status of medicines, control at pharmacy level and prescription size and validity.

Risk communication – Risk communication is a much appreciated step for risk minimisation. Risk should be communicated to healthcare professionals through literatures, educational trainings and informative internet sources so that they can take corrective steps while prescribing to the patient and can minimise the risk. 5

EU-RMP is required to be submitted for, 5

Application for new active substance, paediatric product, biological product or generic product where more information is required for reference medicinal product.
Application for significant change in MA like new dosage forms, route of administration or change in manufacturing process
On request of CA or if any safety issue arises of the product.

EU-RMP plan is submitted in Module 1. 8. 2 for evaluation by pharmacovigilance and risk management experts. 5

PHARMACOVIGILANCE PENALTIES

Every MAH has to adhere to pharmacovigilance system. Non-compliance in the UK will have fine upto ? 5000 or if it is conviction it is unlimited fine and imprisonment for upto 2 years to QPPV or company management.

As per EU laws, if non-compliance is intentional or negligent, the fine is upto 5% of the annual sales or 2. 5% per day average or if it is failure to co-operate or providing misleading information, the fine is upto 0. 5% of total annual or per day average sales. Apart from fine, it gives a signal that company is not looking about patient’s safety, putting their profits first and an embarrassment in the industry.

EUDRAVIGILANCE

From November 2005, electronic reporting became mandatory. The reporting of European pharmacovigilance activities is supported by software called Eudravigilance. Eudravigilance maintains the database of adverse

reactions reported for any medicinal product which are subject to clinical trials. 8 Eudravigilance provides access of adverse reactions to CA, healthcare professionals, patients as well as pharmaceutical industry. It also maintains the data of ICSR and other suspected adverse reactions. While reviewing the pharmacovigilance system, it helps to identify adverse events to the rapporteur by creating regular overview of adverse events throughout the lifecycle of medicinal product. Also Eudravigilance interfaces with EU-RMP in providing systemic description of risk in terms as defined by MEDdra. 8 It is found that 40% of safety issues can be detected earlier if Eudravigilance is used in addition to other PV sources. 9 The typical flow of information from PV and EU risk management strategy implication are,

PRACTICAL APPROACH TO PHARMACOVIGILANCE

Pharmacovigilance system is dependent on reporting and analysis of unintended effects. But all the side effects cannot be classified as unintended effects. Hence its MAH decision to classify which they consider as serious unintended effects.

As physician did not get any feedback of their reporting of unintended effect which ends up in reluctance to report to the MAH. 10

In the EU as the products are granted through different procedures, the requirements for labelling are different which makes it difficult to understand benefit-risk balance which pose a risk to public health. 10

MAH along with manufacturers should responsible for overall detecting and evaluating the adverse effects of the medicinal product.

Duplication of work is involved for reporting by both generic and innovator companies for same medicinal product and lack of communication between

them. 10

Important safety information should be treated as priority instead of documenting, validating, evaluating and reporting all experiences with the same degree of urgency.

PSUR reporting is complex as it involves different presentations, different approval times and country specific labelling. 10

As per innovation in healthcaretechnology, Pharmacovigilance system should be developed to identify the potential association of side effect with a comparison of patient who was given medicine v/s patient who has not taken the medicine. 10

NEW 2010 PHARMACOVIGILANCE LEGISLATION

The current legislation will amended by Regulation EU/1235/2010 and Directive 2010/84/EC from July 2012. 39 The new legislation aims to minimise duplication of reporting system & simplifies reporting of adverse drug reactions and PSUR. It also aims to inform patients about benefit-risk aspects and encourage patient to report any effects through online forms, have explanatory wordings on patient leaflet and SmPC for special safety monitoring medicines. The main implications are, 40

MAH have to submit ADR reports only to Eudravigilance and not required to submit to individual national CAs.

PSUR will have single assessment for same active substance hence all variations; maintenance should be done through union procedure to maintain harmonisation.

PSUR reporting is not required for low risk or established molecules unless

there is some safety concern. So generic companies will be benefitted by not submitting PSUR unless requested.

Currently DDPS will be replaced by Pharmacovigilance System Master File (PSMF) which should be permanently available for submission or inspection on request of national CA.

All pharmacovigilance referrals will be discussed by Pharmacovigilance Risk Assessment Committee (PRAC) and to avoid duplication CMDh should agree on the single opinions for all member states.

Environmental risk factors should be considered as safety of the people in the particular area of the EU.

SUCCESS EXAMPLES OF PHARMACOVIGILANCE

In last few years, there were certain medicinal products which were showing positive benefit-risk balance during approval, but on constant monitoring for 5 to 10 years, their safety profile has changed and they started to show negative benefit-risk balance. The few products are,

Avandia

Avandamet

Acomplia

Vioxx etc.

Avandia and Avandamet have shown good management ofdiabetes, but along with that they also pose a risk of cardiovascular events which were unintended adverse effects. MAH have provided extensive research documents to support their product, but finally it was found that benefits were less compared to risks imposed. Hence considering the public safety,

these products are withdrawn at their maturity stages. As a part of pharmacovigilance studies, it was found that due to long exposure time of the medicine, it has shown adverse effects which were not possible during pre-authorisation studies. Also it proved the strength of pharmacovigilance studies, which has avoided any such disaster among the patients.

CONCLUSION

Pharmacovigilance plays very important part in healthcare system. As the new molecules are complex with limited reports, pharmacovigilance is the tool to monitor the safety benefits. Though it creates more and more hurdles to the MAH with respect to provide more data and justification, it actually provides more safety towards the public health. Without accurate pharmacovigilance system, it may end up with lot of life-threatening incidence globally.

New legislation from July 2012 will bring a major change in current pharmacovigilance system, but it is more acceptable in terms of avoiding duplication of work, systematic reporting and monitoring and harmonised approach.

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