



Studies on Pharmacovigilance in Bangladesh: Safety Issues

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Review Article

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Abstract

An increase in drug safety concerns in recent years with some high profile drug withdrawals have led to raising the block by various stakeholders, more importantly by the regulatory authorities. The number of Adverse Drug Reactions (ADRs) reported, have also resulted in an increase in the volume of data handled. To understand pharmacovigilance a high level of capability is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. Positive pharmacovigilance throughout the product life cycle is the way forward and the future direction for drug safety. It is a challenge to arrange and regiment the act of signal detection and risk management in the context of clinical trials and post-marketing pharmacovigilance. While major advancements of the discipline of pharmacovigilance have taken place in the West, not much has been achieved in Bangladesh. However, with more clinical trials and clinical research activity being conducted in Bangladesh, there is an immense need to understand and implement pharmacovigilance. For this to happen in Bangladesh, the mind set of people working in regulatory agency and the Bangladesh Pharmaceutical companies need to change. The article highlights the various strategies and proposals to build, maintain and implement a robust pharmacovigilance system for various stakeholders and eventually make it happen in Bangladesh.

Keywords: *Pharmacovigilance, Drug, Safety, Bangladesh.*

Introduction

Before Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines ⁽¹⁾. Pharmacovigilance is a very significant and inseparable part of clinical research. Both clinical trials safety and post-marketing pharmacovigilance (popularly known as Post marketing studies or Phase IV clinical trials) are critical throughout the product life cycle. With a reasonably high number of recent high-profile drug withdrawals, both the pharmaceutical industry as well as various regulatory agencies across the globe have raised the bar. Early detection of signals from the post-marketing surveillance studies and clinical trials in early phases have now been adapted by major pharmaceutical companies in order to identify the risks associated with their medicinal product/s as early as possible. If any such risk is present then effectively managing the risks by applying robust risk management plans throughout the life cycle of the product is adopted. These risk management plans are also widely known as Risk Minimization Programs/Strategies. Thalidomide which is reintroduced for Multiple Myeloma and Lepa reactions through S.T.E.P.S. program (System for Thalidomide Education and Prescribing Safety) is a classic example. Signal detection and risk management/minimization has added a new dimension to the field of pharmacovigilance and has led it to be an evolving discipline; which requires ongoing refinement in order to increase its applicability and value to public health. Each year, in hospitals alone, there are 28,000 cases of life-threatening heart toxicity from adverse reactions to digoxin, the most commonly used form of digitalis (drugs that regulate the speed and strength of heart beats) in older adults. Since as many as 40% or more of these people are using this drug unnecessarily. Each year 41,000 older adults are hospitalized and 3,300 of these die from ulcers caused by NSAIDs (non-steroidal anti-inflammatory drugs, usually for treatment of arthritis). Thousands of younger adults are hospitalized. At least 16,000 injuries from auto



crashes each year involving older drivers are attributable to the use of psychoactive drugs, specifically benzodiazepines and tricyclic antidepressants. Psychoactive drugs are those that affect the mind or behavior. Each year 32,000 older adults suffer from hip fractures attributable to drug-induced falls, resulting in more than 1,500 deaths. In one study, the main categories of drugs responsible for the falls leading to hip fractures were sleeping pills and minor tranquilizers (30%), antipsychotic drugs (52%), and antidepressants (17%). All of these categories of drugs are often prescribed unnecessarily, especially in older adults. Approximately 163,000 older Americans suffer from serious mental impairment (memory loss, dementia) either caused or worsened by drugs. In a study in the state of Washington, in 46% of the patients with drug-induced mental impairment, the problem was caused by minor tranquilizers or sleeping pills; in 14%, by high blood pressure drugs; and in 11%, by antipsychotic drugs. Two million older Americans are addicted or at risk of addiction to minor tranquilizers or sleeping pills because they have used them daily for at least one year, even though there is no acceptable evidence that the tranquilizers are effective for more than four months, and the sleeping pills for more than 30 days. Drug-induced tardive dyskinesia has developed in 73,000 older adults; this condition is the most serious and common adverse reaction to antipsychotic drugs, and it is often irreversible. Tardive dyskinesia is characterized by involuntary movements of the face, arms and legs. About 80% of older adults receiving antipsychotic drugs do not have schizophrenia or other conditions that justify the use of such powerful drugs, so many of these patients have serious side effects from drugs that were prescribed inappropriately. Drug-induced Parkinsonism has developed in 61,000 older adults also due to the use of antipsychotic drugs such as haloperidol (HALDOL), chlorpromazine (THORAZINE), thioridazine (MELLARIL), trifluoperazine (STELAZINE), and fluphenazine (PROLIXIN). Pharmacovigilance aims to improve patient care and safety, public health, assessment of benefit, harm, effectiveness and risk of medicines, promotes understanding, education and clinical training.

AIMS & UTILITY OF PHARMACOVIGILANCE:

Pharmacovigilance (abbreviated PV or PhV) is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines ⁽²⁾. Generally, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to:

- Identifying new information about hazards associated with medicines
- Preventing harm to patients.

The etymological roots are *pharmakon* (Greek), "drug;" and *vigilare* (Latin), "to keep awake or alert, to keep watch." Pharmacovigilance is particularly concerned with adverse drug reactions, or ADRs, which are officially described as: "A response to a drug which is noxious and unintended,

and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."⁽³⁾

Recently, its concerns have been widened to include:

- Herbals
- Traditional and complementary medicines
- Blood products
- Biologicals
- Medical devices
- Vaccines.

Continuous monitoring of their effects, side effects, contraindications and outright harmful effects which can result in a high degree of morbidity and in some cases, even mortality, is essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the Country and outside. Because clinical trials involve several thousand patients at most; less common side effects and adverse drug reactions are often unknown at the time a drug enters the market. Even very severe adverse drug reactions, such as liver damage, are often undetected because study populations are small. Post marketing pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and adverse drug reactions. The drug regulatory agencies have the responsibility of having a well-established pharmacovigilance system to monitor adverse reactions of drugs. During the drug development phase and later during the life time of a marketed drug⁽⁴⁾.

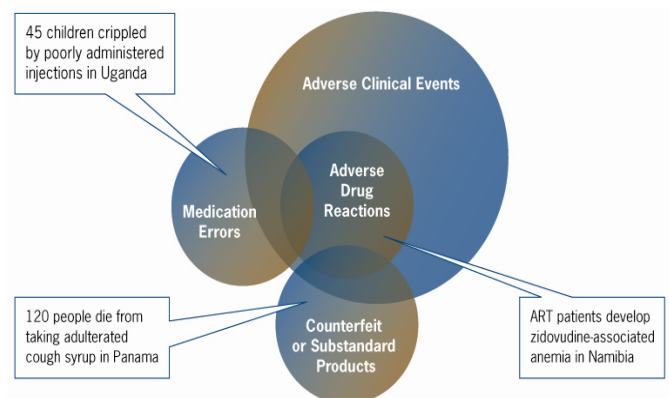


Figure 1: Scope of Pharmacovigilance

The identification and quantification of previously unrecognized adverse drug reactions (ADR). The identification of sub-groups of patients at particular risk of ADRs (the risk relating to dose, age, gender and underlying disease). The continued monitoring of the safety of a product, throughout the duration



of its use, to ensure that its risks and benefits remain acceptable. This includes safety monitoring following significant newly approved indications. The comparative adverse drug reaction profile of products within the same therapeutic class. The detection of inappropriate prescription and administration. The further elucidation of a product's pharmacological/toxicological properties and the mechanism by which it produces adverse drug reactions. The detection of significant drug–drug interactions between new products and co therapy with agents already established on the market, which may only be detected during widespread use. In a word it is said that the aim of pharmacovigilance is to improve patient's care and safety, public health, assessment of benefit, harm, effectiveness and risk of medicines, promotes understanding, education and clinical training⁽⁵⁾.

When a pharmaceutical drug is introduced in the market there are still a lot of things that are unknown about the safety of the new drugs. These medicines are used by various patients for different diseases. These people might be using several other drugs and must be following different traditions and diets which may adversely affect the impact of medicine in them. Also the different brands of same medicine might differ in the manner of their production and ingredients. Additionally, adverse drug reactions might also occur when drugs are taken along with traditional and herbal medicines that have also to be monitored through pharmacovigilance. In some cases, adverse drug reaction of certain medicines might occur only in one country's or region's citizens. To prevent all undue physical, mental and financial suffering by patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country with the support of doctors, pharmacists, nurses and other health professionals of the country. The importance of pharmacovigilance are⁽⁶⁾ safety monitoring of medicinal products, drug monitoring, pharmaceutical preparations - adverse effects, adverse drug reaction reporting, product surveillance, post marketing , legislation.

PHARMACOVIGILANCE FRAMEWORK⁽⁷⁾:

METHODOLOGIES OF PHARMACOVIGILANCE:

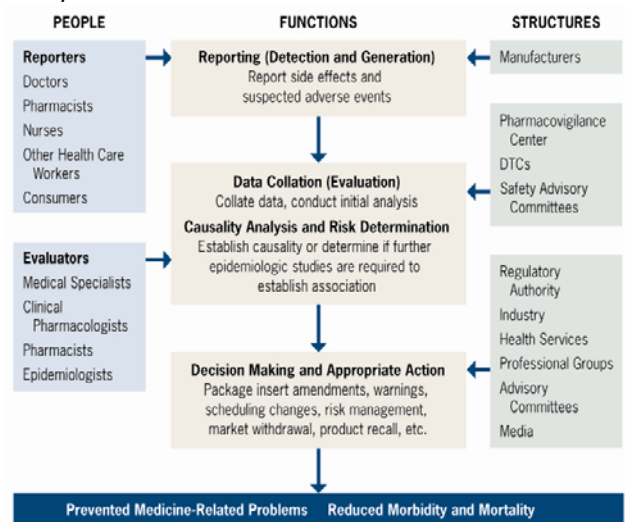
Methods used in pharmacovigilance

The activities undertaken in the name of pharmacovigilance can be roughly divided into three groups: regulatory, industry, and academia. Regulatory pharmacovigilance is driven by the aim to provide drugs with a positive benefit-harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by a description of the methods used to detect new ADRs and a discussion of the pros and cons of each method.

Clinical trial data insufficient to evaluate drug risk

The main method currently used to gather information on a drug in the pre-marketing phase is to conduct a clinical trial. Pre-marketing clinical trials can be divided into three phases.

Phase III studies are often double-blind randomized controlled trials; these are considered to be the most rigorous approach to determining whether a cause-effect relationship exists between a treatment and an outcome. However, when it comes to monitoring the safety of a drug, this study design is not optimal. Due to the limited number of patients participating, it is generally not possible to identify ADRs that occur only rarely. Post-marketing studies can be descriptive or analytical. Descriptive studies generate hypotheses and attempt to describe the occurrence of events related to drug toxicity and efficacy. Analytical studies test hypotheses and seek to determine associations or causal connections between observed effects and particular drugs, and to measure the size of these effects. Descriptive studies are widely used in post-marketing surveillance because they are able to generate hypotheses that will become starting points for analytical studies⁽⁸⁻¹¹⁾.



Spontaneous reporting

In 1961, a letter from the Australian physician WG McBride was published in Lancet. In this letter, he shared his observation that babies whose mothers had used thalidomide during pregnancy were born with congenital abnormalities more often than babies who had not been exposed to thalidomide *in utero*. In the years to come it became evident that thousands of babies had been born with limb malformations due to the maternal use of thalidomide. In order to prevent a similar disaster from occurring, systems were set up all over the world with the aim of regulating and monitoring the safety of drugs. Spontaneous reporting systems (SRS) were created, and these have become the primary method of collecting post-marketing information on the safety of drugs. The main function of SRS is the early detection of signals of new, rare and serious ADRs. By means of a SRS it is possible to monitor all drugs on the market throughout their entire life cycle at a relatively low



cost. The main criticism of this approach is the potential for selective reporting and underreporting. In a review article. Underreporting can lead to the false conclusion that a real risk is absent, while selected reporting of suspected risks may give a false impression of a risk that does not exist. However, underreporting and selective reporting can also be seen as advantages. Because only the most severe and unexpected cases are reported, it is easier to detect new signals of ADRs because the person reporting the reaction has already pinpointed what may be a new safety issue. Against this background, the system should perhaps be called 'concerned reporting' instead of spontaneous reporting, seeing as those reporting the issues are highly selective of what they are reporting⁽¹²⁻¹⁸⁾.

Data mining in spontaneous reporting

In the past, signal detection in spontaneous reporting has mainly occurred on the basis of case-by-case analyses of reports. In recent years, however, data mining techniques have become more important. The term 'data mining' refers to the principle of analyzing data from different perspectives and extracting the relevant information. Algorithms are often used to determine hidden patterns of associations or unexpected occurrences, i.e. signals, in large databases. Although the methodology of the various data mining methods applied in pharmacovigilance differ, they all share the characteristic that they express to what extent the number of observed cases differs from the number of expected cases⁽¹⁹⁾. Moreover, clinical information described in the case reports is not taken into account; consequently, there is still the need for a reviewer to analyze these events.

Intensive monitoring

In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (Intensive Medicines Monitoring Program) and the UK (Prescription Event Monitoring). These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored. These data are collected and analyzed for new signals. The methodology of these intensive monitoring systems have been described in depth elsewhere. The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spontaneous reporting because the former only monitors selected drugs during a certain period of time. Through its non-interventional character, intensive monitoring provides real world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. This approach, however, also has recognized limitations. Although the intensive monitoring methodology was developed more than 20 years ago, this methodology has received renewed interest in the last years. In the European Commission consultation 'Strategy to better protect public health by strengthening and rationalizing EU pharmacovigilance' intensive monitoring is mentioned as one tool that can improve the Pharmacovigilance system⁽²⁰⁻²⁴⁾.

Database studies

In order to test a hypothesis, a study has to be performed. The study can be conducted using a variety of methods, including case-control studies and cohort studies. The limitations of these methods include power considerations and study design. In order to be able to conduct retrospective cohort and case-control studies, data which have been collected in a reliable and routine fashion needs to be available⁽²⁵⁾.

LIST OF THE COMPETENT PERSONS & RELEVANT ORGANIZATIONS TO BE INVOLVED IN PHARMACOVIGILANCE STUDIES⁽²⁶⁾:

The Prescriber

The prescriber is the spear point in the execution of any REMS strategy. The prescriber must be thoroughly familiar with the benefits and risks associated with the therapy. He or she must be willing to attest to this knowledge and agree to abide by the requirements for therapy initiation and ongoing maintenance. Responsibilities will include counseling and educating the patient regarding the product benefits and risks, as well as documentation of these discussions. To initiate therapy, the prescriber will enroll the patient in the required registry or REMS program as established by the manufacturer sponsor. The prescriber will conduct all testing required for diagnosis and monitoring, submit any required documentation, and will report any subsequent adverse events. The most successful commercialization process recognizes that these requirements place an additional administrative burden on the prescriber. The manufacturer can mitigate some of this additional burden, frequently through the services provided by its Coordinating Center to offer support and direction on navigating the process of REMS compliance.

The Patient

The patient is also a key stakeholder, in that while reaping the benefits of the product, the patient will be the individual experiencing the risks. The patient must take ownership of the decision to initiate and maintain therapy by enrolling in the required registry or REMS program, and by attesting to understanding and acceptance of the risks of therapy. The patient may also be required to submit to required baseline and ongoing testing to monitor the responses to therapy, which may expose the patient to additional financial burden associated with the cost sharing requirements of their insurance coverage. Testing may also be required to facilitate identification of adverse events. The reporting of adverse events is an important responsibility of patients taking any



pharmacotherapy, but particularly those operating under REMS.

The Coordinating Center

The Coordinating Center is the nexus of REMS commercial activity, acting as the central point of contact and repository for all enrolled patient and prescriber information. The Coordinating Center is frequently the voice of the manufacturer with respect to communication of REMS structure and requirements to all key stakeholders, and provides assistance and direction to ease any barriers to appropriate access resulting from the REMS requirements. In addition, the Coordinating Center manages the ETASU conditions by collecting and analyzing all product dispense records, as well as ensuring that all testing requirements have been met. Some models utilize a prospective method of REMS management, where the Coordinating Center will provide authorization to the dispensing pharmacy allowing the patient dispense, ensuring that no product is dispensed without the appropriate approvals. In other models, the specialty pharmacy obtains required testing information, and the Coordinating Center will retrospectively review records to ensure that all pharmacies have appropriately collected and reported required data with regard to testing compliance. The Coordinating Center will report any adverse events received within the conduct of its activities; it will also receive reports of adverse events from the specialty pharmacy network.

The Coordinating Center will then aggregate these data, and report to the manufacturer for reconciliation to ensure that all reported adverse events have been received and appropriate action taken. Finally, the Coordinating Center will provide data necessary to conduct the knowledge, attitude, and behavior (KAB) surveys that are required by the FDA to gauge REMS effectiveness and impact in the marketplace.

The Specialty Pharmacy

The Specialty Pharmacy (SP) is another key stakeholder, with primary responsibility for management of the prescription. The SP provides access to the medication through its dispensing responsibilities, ensuring that only appropriate patients receive product. The SP is responsible for reporting data on all patient activities to the Coordinating Center as contracted by the manufacturer. In addition, the SP ensures that any required materials, to include medication guide, are included in product shipments in accordance with the REMS requirements. The SP provides REMS-required mandatory patient counseling, in addition to patient counseling consistent with standard pharmacy practice. As with all other stakeholders in the process, the SP is responsible for reporting adverse events to the manufacturer, generally within 24 hours, and to the Coordinating Center through the data exchange. Because the SP is in regular contact with the prescriber and the patient, the SP shares responsibility with the Coordinating Center for clear communication of the service offering and REMS management process. It is important to note that in many cases, activities unique to a particular REMS program may be outside the standard operating procedures for the

specialty pharmacy; this will be an important consideration in network selection, contracting and ongoing management.

The manufacturer

While the prescriber, patient, Specialty Pharmacy, and Coordinating Center all have vital roles, it is the manufacturer that is the ultimate stakeholder and primary driver of the successful commercialization of its REMS program. From the inception of the process, the manufacturer is responsible for the conceptual design of its REMS commitment, and the overall vision of the market experience associated with the product. To accomplish this successfully, the manufacturer must align between and among all of its clinical and commercial resources. The clinical and brand teams must cooperate to ensure that all tactics developed and implemented meet both sets of needs. The manufacturer must develop and submit its proposed REMS plan and work in collaboration with the FDA to obtain approval. Following approval, the manufacturer is responsible for the training and communication of REMS elements with all staff and supporting vendors. The manufacturer provides educational materials to patients, prescribers, sites of care, and other involved parties, ensuring compliance with FDA marketing requirements. Once the product has been introduced in the marketplace, the manufacturer must conduct audits of the Coordinating Center and Specialty Pharmacies to ensure compliance with REMS requirements. As with all marketed products, the manufacturer must manage and reconcile all adverse events according to FDA-mandated pharmacovigilance standards.

PHARMACOVIGILANCE STUDIES IN BANGLADESH:

Finally, as part of the agreed-upon REMS, the manufacturer commits to report to the FDA with regard to the various elements of the risk mitigation program. This may include specific data elements regarding the particular risk under management (i.e. number of adverse events, pregnancies, etc.) measuring the effectiveness in achieving the goal of continued benefit from the drug with minimization of the risk. The manufacturer-conducted REMS assessment may also include surveys of prescribers and patients, to understand knowledge, attitude, and behaviors (KAB) related to the understanding of the risks to the therapy, with the ultimate goal being to determine the effectiveness of the REMS plan in aggregate. Depending upon the results of these evaluations, the manufacturer may seek to modify the REMS to improve its effectiveness and acceptability in the marketplace over time.



Necessity of pharmacovigilance study in Bangladesh

Bangladesh is an underdeveloped country. But it has a vast population. But the history of pharmaceutical export from Bangladesh dates back to the late 80's. So, far we have exported our pharmaceuticals to 55 countries. We are exporting wide range of products covering all major therapeutic class & dosage forms along with high-tech products like Inhalers, Nasal sprays, Suppositories, IV fluids, Injectable etc.

On the other hand most of the people of Bangladesh are ignorant. They have only a few ideas about their health. They faces many serious health hazard (several drug induced diseases like- kidney damage, liver disease etc.). Above these reason pharmacovigilance study is must be required for the safety of the country people.

Diethylene glycol tragedy

Drug toxicity due to formulation alteration is very much common. There are a lot of examples of this. Only diethylene glycol create this problem worldwide. It gets importance because of some recent incidence. Recently 28 children died due to formulation alteration in case of paracetamol syrup, where propylene glycol replaces by diethylene glycol as a solvent.

- In Bangladesh this types of incident occur two times.
- Health officials in the country say that so far 26 children aged between 11 months and three years have died after taking paracetamol (acetaminophen) syrup contaminated with DEG that was manufactured by local drug producer Rid Pharmaceutical Co. The trade name of the drug was Temset (paracetamol suspension).
- Bangladesh was also affected by one of the worst cases on record, with 339 deaths attributed to paracetamol syrup contaminated with DEG from propylene glycol in 1990-92.

ASSESSMENT OF PHARMACOVIGILANCE & REGULATORY SYSTEMS (COMPLETE FRAMEWORK FOR FURTHER STUDY ON THE PERSPECTIVE OF BANGLADESH):

Pharmacovigilance and the methods used need to continue to develop in order to keep up with the demands of society. In recent years, three publications have been of utmost importance in terms of providing guidance on the future of pharmacovigilance. Pharmacovigilance experts from all over the world, representing different sectors, emphasize the role of communication in drug safety with the following statements:

- Drug safety information must serve the health of the public.
- Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for health care providers.
- All the evidence needed to assess and understand risks and benefits must be openly available.
- Bangladesh needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all.

- Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated.
- The active involvement of patients and the public in the core debate about the risks and benefits of medicines, and in decisions about their own treatment and health.
- The development of new ways of collecting, analyzing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it.
- The pursuit of learning from other disciplines about how pharmacovigilance methods can be improved, alongside wide-ranging professional, official and public collaboration.
- The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clinicians, patients and the general public, based on the demonstrable benefits of pharmacovigilance to public.

It is believed that these factors will help risks and benefits to be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

Despite several advances made in supply chain management for reproductive health commodities in Bangladesh with support from USAID over the past few decades, there are still documented challenges on procurement process management, storage and distribution of health commodities, as well as monitoring consumption which is the primary source of information for forecasting and quantification. Registration of imported health commodities, management of TB commodities and overall quality assurance in the health supply chains have continued to be areas of concern.

Following the successful work of SPS, SIAPS has extended its support to the Directorate General of Health Services (DGHS), the Directorate General for Drug Administration (DGDA), Central Medical Store Depot (CMSD), and the National TB Program (NTP) of the MOHFW. The SIAPS goal of the expanded support to the MOHFW will be to strengthen the ability of policy makers, health care providers and institutions to improve commodity management, with an emphasis on governance, procurement, institutional capacity building and other system strengthening initiatives, aimed at ensuring continuous availability of goods required to support health care delivery and the timely availability of reliable data to support evidence based decision making.

Specific objectives of the program in Bangladesh are to



- Strengthen the procurement management systems,
- Strengthen warehousing, distribution and logistics management systems,
- Strengthen commodity management information systems,
- Promote commodity security,
- Improve drug registration systems, and
- Strengthen pharmaceutical management systems for TB.

Recommendations

• Building and maintaining a robust pharmacovigilance system

So far, considerable work has been put in place by the dedicated staff at the Drug Control Committee (DCC) to develop a robust pharmacovigilance system. But experience till date clearly points that this is not enough as more needs to be done to meet the challenges of ensuring that all data is captured and analyzed for rapid detection of signals and for putting effective measures in place to overcome the risks. The DCC could go a step ahead to invite experienced private firms to help, train and set up the pharmacovigilance system to combat the problems of inexperience and shortage of trained personnel.

• Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections

The Government of Bangladesh's Health Ministry needs to pass a law and make Pharmacovigilance reporting mandatory. This should be valid not only for the multinational companies (MNCs) operating within Bangladesh and the Bangladeshi Pharmaceutical Companies but also for various medical colleges and health care professionals in the country. A department for Pharmacovigilance Inspections should be incorporated within the DCC with the view of starting inspections in all pharmaceutical companies operating in Bangladesh.

• High-level discussions with various stakeholders

A high-level discussion with various stakeholders, i.e., Ministry of Health, Pharmacy Council, Nursing Council, Dental Council, Pharmaceutical Companies and their associations, Consumer Associations, nongovernmental organizations (NGOs) working in this field and Patient Groups should be initiated in order to make them aware of how the DCC is planning to improve and develop a robust system in pharmacovigilance and to understand and resolve their queries and problems.

• Strengthen the DCC office with trained scientific and medical assessors for pharmacovigilance

Intensive training should be given in all aspects of pharmacovigilance to officials working within the pharmacovigilance department of the DCC and the peripheral, regional and zonal centers. This should be an ongoing activity with training scheduled twice a year.

• Creating a clinical trial and post marketing database for SAEs and ADRs for signal detection and access to all relevant data from various stakeholders

Create a central database for all protocols and clinical trials run within Bangladesh along with clinical study reports and results (both for preclinical toxicology studies and clinical trials) across various therapeutic areas with specific registration numbers. Registration numbers should be given at the time of starting the trial and should cover both drug and nondrug therapies and be therapeutically aligned.

• List all new drugs / indications by maintaining a standard database for every pharmaceutical company.

A list should be maintained by the regulatory authorities and pharmaceutical companies for all new drugs/indications in the database. All new issues need to be put under heightened surveillance. Pharmaceutical companies in these circumstances should have meetings set up with the DCC to outline their risk management plan (RMP) for the safety issues in question and describe how they would put effective strategies in place to mitigate them.

• Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.

• Collaborating with pharmacovigilance organizations in enhancing drug safety.

With advancements in information technology, there has been the emergence of new opportunities for national ⁽²⁷⁾ and international ⁽²⁸⁾ collaborations that can enhance postmarketing surveillance programs and increase drug safety. The Uppsala Monitoring Centre (UMC) of WHO, is an example for an international collaboration to establish a harmonized post marketing surveillance database. The system is based on the exchange of adverse reaction information among national drug monitoring centers in 80 countries.

• Building a network of pharmacovigilance and pharmacoepidemiologists in Bangladesh

Pharmacovigilance and pharmacoepidemiology being relatively new fields in Bangladesh, it is absolutely essential for a group of experts to come together to formulate guidelines for the set-up and implementation of relevant processes within pharmacovigilance. A core group will need to be formed which will have representatives from Bangladeshi pharmaceutical companies and personnel from the regulatory authority (e.g. DCC). Epidemiologists, pharmacists and other like-minded people can also contribute to the development of the system.

• Interaction with the IT sector in building a robust pharmacovigilance system for Bangladesh

Bangladesh boasts a highly developed IT sector. Since pharmacovigilance and



pharmacoepidemiology deal with large numbers of ADRs, it would be wise for pharmacovigilance experts to collaborate with software professionals to develop and build a robust systems. Software programs developed can be used for collection and analyses of data sets, determining trends of drug usage in various disease areas, compliance, medication errors and drug interactions leading to ADRs. In specific areas where knowledge is inadequate, i.e., pregnancy, pediatric population, patients with liver and renal dysfunction and the elderly, pharmacokinetic software programs can help in optimizing drug dosages in individuals in various diseased conditions. This will be useful not only in rational drug therapy but would also be an important asset in therapeutics. A step in this direction has already been taken by the DCC, however the private interest of the IT firms are making things quite difficult for the DCC office.

Conclusion

Pharmacovigilance is a complex process and robust systems are essential to undertake the activity. The foundation for building a robust pharmacovigilance system has already been done to some extent by the DCC staff. However, the system needs to be refined with the help of pharmacovigilance experts in collaboration with information technology (IT). DCC should take some tough decisions and make commitments to make pharmacovigilance mandatory and start the culture of pharmacovigilance inspections. Pharmaceutical companies will need to show both regulators and consumers that they are doing everything possible to assure drug safety, while finding more effective approaches to manage drug safety data. This will require the ability to pull and analyze data from adverse event reporting systems in conjunction with other internal company data or external data sources to respond to any ad hoc safety queries or issues from the regulators. In order to do so, an integrated approach to a data system and pharmacovigilance along with appropriate business processes need to be developed and put in place. The companies need to be reassured that by reporting continuously monitoring for signals and developing risk management plans for products, they can actually still keep marketing their product. Reporting of ADRs after marketing should be actively encouraged and should involve all those concerned including doctors, pharmacists, nurses, patients and pharmaceutical companies. To enhance and facilitate this, a culture of learning about pharmacovigilance should start early in the professional training of healthcare students. This will help healthcare professionals to understand the subject and also create awareness by giving adequate information to patients at the start of any treatment about the potential benefits and risks of the therapy. Bangladesh is now considered to be a hub for drug export. The DCC will show its commitment to ensure safe use of drugs by establishing the National Pharmacovigilance Program. Healthcare professionals, consumer groups, NGOs and hospitals should appreciate that there is now a system in place to collect and analyze adverse event data. They should start reporting adverse events actively and participate in the National Pharmacovigilance Program to help ensure that people in Bangladesh receive safe drugs. With the help of all

stakeholders, let us pledge to make this happen in Bangladesh and build a world-class pharmacovigilance system. We can surely make this happen if we work together.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.