Bangladesh Pharmaceutical Journal ***20****(1): 105-114, 2017*

Review on Pharmacovigilance Practice for Safety of Medication System in Bangladesh

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Received: January 15, 2017; Accepted: January 31, 2017; Published (Web): March 19, 2017

Abstract

Pharmacovigilance is a system that provides safety to the patients in case of medication. It mainly deals with adverse drug reactions. With the outbreak of new diseases new medicines are developing worldwide. So to ensure the safety of drug, pharmacovigilance is very necessary. National pharmacovigilance center of a country coordinates the overall activity of pharmacovigilance in collaboration with international regulatory authorities like WHO, the Uppsala Monitoring Centre etc. Integration of pharmacovigilance system in public health has positive impact on improvement of health care system. In Bangladesh Directorate General of Drug Administration (DGDA) is playing an active role to ensure the safety of medication system.

Key words: Pharmacovigilance, ADR, ADRM cell, ADRAC, paracetamol tragedy, diethylene glycol, substandard vitamin A, case report.

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Introduction

Pharmacovigilance is concerned with adverse drug reactions or ADR, which is described by World Health Organization (WHO) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (Suke *et al.*, 2015). Adverse drug reactions constitute the top ten leading causes of death (WHO, pharmacovigilance: ensuring the safe use of medicines, Geneva, 2004) The etymological roots for the word "pharmacovigilance" are pharmacon (Greek) meaning drug and vigilare (Latin) meaning to keep watch (pharmacovigilance, Wikipedia). Pharmacovigilance is gaining importance for doctors and scientists as the number of stories in the mass media of drug recalls increases. Because clinical trials involve several thousand patients, less common side effects and ADRs are often unknown at the time a drug enters the market (IFPMA position paper on pharmacovigilance principle for biotherapeutic medicine. April,2012). Even very severe ADRs, such as liver damage, are often undetected because study populations are small. Postmarket surveillance uses tools such as data mining and investigation of case report to identify the relationships between drugs and ADRs (Suke*et al.*, 2015; Yao *et al*., 2013). Pharmacovigilance is the science relating to detection, assessment, understanding and prevention of adverse effects particularly long term and short term side effects of medicines (Importance of pharmacovigilance, 2002). Generally speaking, 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, herbal products, vaccines, medical devices and traditional medicines.

Aims of pharmacovigilance

1. Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
2. Improve public health and safety in relation to the use of medicines.
3. Detect problems related to the use of medicines and communicate the findings in a timely manner.

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4. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit.
5. Encourage the safe, rational and more effective (including cost-effective) use of medicines.
6. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public (Safety of medicine in public health program. WHO, 2006. Amran *et al*., 2015).

Pharmacovigilance practice in Bangladesh

Pharmacovigilance study is very necessary for every country for maintaining proper healthcare system and safety issues regarding treatment. So in our county pharmacovigilance has been introduced and practiced, under the supervision of WHO-UMC (WHO-Uppsala Monitoring Committee). Adverse drug reaction monitoring (ADRM) cell was established in Directorate General of Drug Administration (DGDA), which is the drug regulatory authority of our country since 1996. Initially the cell circulated leaflets and posters bearing awareness slogans of drug use throughout the country. Also organized awareness meetings among the chemists (Retailers) of different area and published awareness instructions in the daily newspapers and broadcasted these awareness slogans on Radio Bangladesh. The cell has been trying from its inception to introduce a systematic mechanism for ADRs monitoring in Bangladesh through collection, analysis and compilation of ADRs, spontaneously reported by the medical and pharmaceutical professionals of all health services outlets of the country. For that reason, the Directorate General of Drug Administration has been organizing ADR Monitoring Workshops/meetings in the medical colleges and hospitals of the country and distributing printed ADR reporting forms to the doctors for spontaneous reporting of ADR cases since 2000.

The Ministry of Health & Family Welfare formed a 10-Member ADR Advisory Committee (ADRAC) on 6 July 1997 to evaluate, analyze and make recommendations for solving problems of ADR (Bangladesh National Formulary, 2015).

Reasons of adverse drug reactions in Bangladesh

1. Self-medication
2. Poly pharmacy
3. Aggressive promotion and push sell of drug products
4. Unethical practice of healthcare providers
5. Irrational use of antibiotics, steroids and other drugs
6. Registration of more combination products where alternative options are there
7. Distribution/purchase of medicine from any unauthorized source
8. Improper storage and distribution of drugs

Necessity of pharmacovigilance study in Bangladesh

Bangladesh is an underdeveloped country. According to the DGDA, we are now exporting wide range of products to more than 130 countries of the world. It includes all major therapeutic class & dosage forms along with high-tech products like inhalers, nasal sprays, suppositories, IV fluids and injectablesetc (Mustansir *et al*., 2013). On the other hand a major portion of the people of Bangladesh are unconscious about the health and the drug they intake during diseases. They have limited ideas about their health and medicines. They face many serious health hazard (several drug induced diseases like- kidney damage, liver disease etc.). Due to these reasons pharmacovigilance study must be required for the safety of the people. From a recent questionnaire based survey on 292 community pharmacist/pharmacy technicians practicing in Dhaka, Bangladesh following result found. Findings of the study is shown in table 1 (Amin *et al*., 2015).

From this study it is clear that more than half of them were not familiar with the existence of ADR reporting body of Bangladesh though they were experienced ADRs. Many did not even know how to report, some were afraid of legal liabilities associated with reporting to ADRs. So it is very urgent to strengthen the pharmacovigilance practice and reporting system in our country for the safety of medication system, especially in case of self-medication which is very common in our country.

Another study conducted from December 2009 to December 2010 to find out response of reportingADRs in one teaching hospital and 10 private chambers revealed that response of reporting of ADR from private chamber was very poor (29%) whereas response from teaching hospital was more (55%) (Nahar *et al*., 2011)

Table 1. General ADR practices of respondent.

Demographic category of survey	Number	(%)
Respondent	203	69.5
Pharmacy technicians	152	74.9
Pharmacist	37	18.2
Master of science	2	0.98
Others	12	5.9
Respondent experienced ADR at their pharmacy	72	35.5
Respondent were not familiar with the existence of an ADR reporting body in Bangladesh	105	51.7

Adverse drug reaction overview in Bangladesh

In Bangladesh, importance of reporting ADRs is still underestimated with inadequate reporting, inappropriate data collection, improper storage and analysis of data. Present condition of ADRs in Bangladesh can easily presumed from studies carried out in different hospitals. One study carried out from November 2007 to April 2008 upon160 patientsat skin department of Dhaka Medical College,were randomly surveyed and among them 19 patients were found to have ADR with certain drugs. Among these reactions 31.58% were of mild type, 42.1% were of moderate and 26.32% were of severe in nature. The findings of the study are shown in tables 2 and 3 (Begum *et al*., 2012).

Table 2. Drugs responsible for ADR.

Drug	Number of ADRs	%
Antibiotics	9	42.86
NSAIDs	7	33.33
Steroids	1	4.76
Others	4	19.05

Table 3. Antibiotics associated with ADRs.

Name	Number	%
Fluoroquinolones	4	44.44
β- Lactams	2	22.22
Macrolides	2	22.22
Co-trimoxazole	1	11.11

The results of another study carried out in the department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2011 to December 2011, are shown in table 4 and 5 (Khondker*et al*., 2014).

Table 4. Distribution of patient by common drug reactions.

Common drug reactions	Number of patients
Fixed drug eruptions	9
Urticaria	4
Stevens-Johnson syndrome	3
Erythema multiform	2

Table 5. Drugs implicated in ADRs.

Clinical presentation	Number (%)
Sulfonamides	8 (40)
NSAIDs	6 (30)
Quinolones	3 (15)
Metronidazole	2 (10)
Anticonvulsants	1 (5)

Diethylene glycol tragedy in Bangladesh

Diethylene glycol is a highly toxic organic solvent that causes acute renal failure and death when ingested. Its toxicity became apparent in the 1930s when it was used to prepare a sulphanilamide elixir in the United States. The deaths of at least 76 people from ingestion of this sulphanilamide elixir prompted the promulgation of the United States Food, Drugs, and Cosmetics Act in 1938, which regulates the evaluation and use of new drugs or foods (Hanif*et al.*, 1995). Diethylene glycol is occasionally identified in medical preparations or foods, though rarely in lethal concentrations. Drug toxicity due to formulation alteration is very much

common. There are a lot of examples of this type of malpractices. It gets importance because of some recent incidence. In 2009, 26 children died due to formulation alteration in case of paracetamol syrup, where propylene glycol was replaced by diethylene glycol as a solvent. Health officials in the country said that so far 26 children aged between 11 months and three years have died after taking paracetamol (acetaminophen) syrup contaminated with diethylene glycol that was manufactured by local drug producer Rid Pharmaceutical Co (Mustansir *et al*., 2013; Arrest warrants issued after DEG kills 26 infants in Bangladesh). The trade name of the drug was Temset (paracetamol suspension). In addition, three hundred thirty nine (339) deaths attributed to paracetamol syrup contaminated with diethylene glycol in 1990-1992 (Mustansir *et al*., 2013; Health news BD; Helali *et al*., 2014). This incidence shows that, the formulation alteration by harmful chemical can pose a serious threat to health care system.

Substandard vitamin A tragedy in Bangladesh

Vitamin A deficiency may be a major threat to the health and survival of children and mothers. Effects of vitamin A deficiency extend much beyond blindness alone. Vitamin A deficiency increases the risk of child deaths from diseases such as measles and diarrhea. These infections contribute to over one-third of deaths among children aged 0-5 years in Bangladesh (UNICEF- Bangladesh media center, 6 June 2009). For this reason the Government of People's Republic of Bangladesh conducts National vitamin A plus campaign every year. In 2013 due to ingestion of substandard vitamin A capsule many children became sick, and online reports talked about some patients experiencing vomiting sensation and feeling unwell. Children were reported sick at Chittagong, Cox's Bazaar and Lakhsmipur among other places. Rumors of death were also reported with one report claiming a child had died from administration of Vitamin A capsule which were supplied by Indian source, Olive healthcare. (Manobkontho reports on substandard vitamin A Capsules, 09 March 2013).

Adverse Drug Reaction Monitoring (ADRM) cell as National Drug Monitoring Centre

In Bangladesh, pharmacovigilance started in 1999, but became dormantdue to a lack of legislation, motivation,inadequate knowledge and attitude,as well as a lack of coordination and communication between stakeholders, resulting in many ADRs not being properly reported.In 2013 the United Nations agency for international development (UNAID)'s System for Improved Access to Pharmaceuticals and Services (SIAPS) program provided support to the DGDA for reviving the cell and committee in the directorate as a part of health system strengthening. For this purpose, a monitoring cell, known as Adverse Drug Reaction Monitoring (ADRM) was established and designated as the National Drug Monitoring Centre by the Ministry of Health & Family Welfare of Government of People's Republic of Bangladesh. An Adverse Drug Reaction Advisory Committee (ADRAC)has also been formed to evaluate, analyzeand make recommendations on adverse drug event (WHO Uppsala report, April 2015). As a result ADRM cell and ADRAC have become fully functional, with meeting taking place at regular interval. When the cell took up its responsibilities, it applies to MOHFW, requesting recognition as the national drug monitoring center for Bangladesh, and on 3 September 2013 the ministry issued a notification declaring ADRM cell as National Drug Monitoring Cell(NDMC) for the country. ADRM cell is responsible for the collection of adverse event report received from healthcare facilities, hospital and pharmaceutical companies(Bangladesh National Formulary, 2015). As the concept on pharmacovigilance is very new to Bangladesh but the number of ADRs report obtained is increasing day by day, in the year 2014 ADRM cell collected 265 reports and in 2015, 441 reports were submitted to ADRM cell. In addition, ADRM cell is responsible for the maintenance and analysis of adverse event database, including the data entry or quality assurance and to share adverse event information with WHO Uppsala monitoring center. The adverse drug reaction advisory committee is responsible for providing technical assistance on causality assessment, risk assessment, and case investigation. In order to make recommendation for DGDA to take regulatory action the national center will collaborate with WHO-

UMC to further strengthen their capacity and for ensuring medicine safety and of good quality for people of Bangladesh. Till now 30 medical colleges including Dhaka and Rajshahi Medical College and Chittagong Medical College also are working with ADRM cell regarding pharmacovigilance practice. Besides this ADRM cell also impose the responsibility of reporting ADRs upon 30 top selling pharmaceutical companies in Bangladesh.

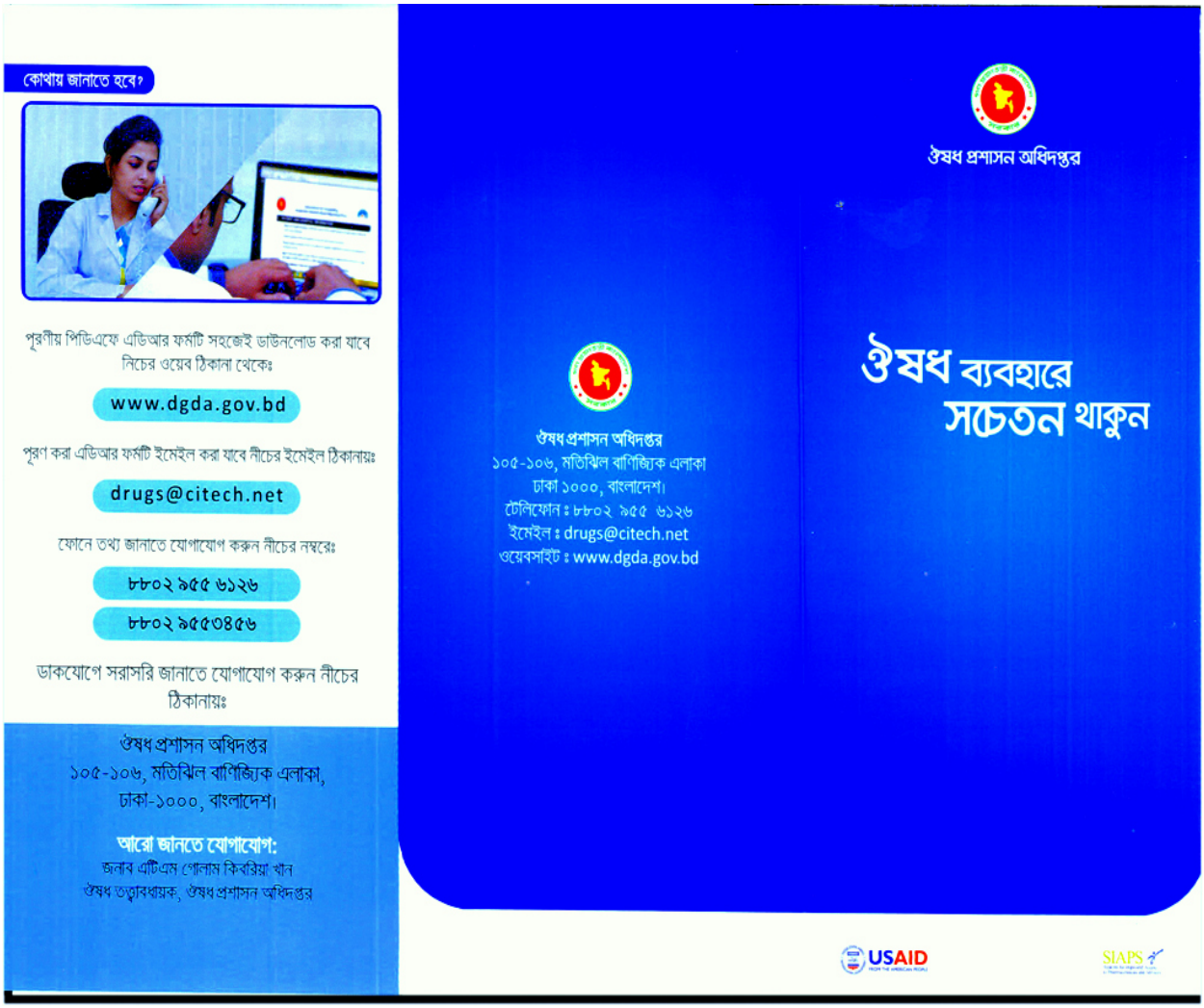


Figure 1. Leaflet of DGDA to increase awareness about pharmacovigilance (side-1).

Reporting system in Bangladesh

It is important to recognize the adverse drug reaction first and according to the identification or observation action is taken. Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs (Bangladesh National Formulary, 2015)

1. Ensuring that the medicine prescribed is the medicine received and actually taken by the patient at the dose advised.
2. Verification of the fact that, the onset of the suspected ADR was after the drug was taken, not before. Anddiscuss carefully the observation made by the patient.

3. Determination of the time interval between the beginning of drug treatment and the onset of the event.
4. Evaluation of the suspected ADR after discontinuing the drugs or reducing the dose and monitoring the patient's status.
5. Analysis of the alternative causes (other than the drug) that could on their own has caused the reaction.
6. Usages of relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction.
7. Reporting any suspected ADR to the person nominated (if any) for ADR reporting in the hospital or directly to the ADR Cell of the Directorate General of Drugs Administration.

Figure 2. Leaflet of DGDA to increase awareness about pharmacovigilance (side-2).

What to report?

The reporter should bear in mind that he will often be reporting only suspicions in his own mind that a drug has caused particular adverse effect. He should not wait until he feels certain that a causal link can be considered proven or disproven. In any case of doubt it is better to report than not to report. A case report in pharmacovigilance can be defined as, "a notification relating to apatient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine."

Adverse drug reaction reporting form is available in the web site of Directorate General of Drug Administration (DGDA). This form can be downloaded from the website, and reporter can fill upthe form easily by giving some important information about the reaction and other relevant information.

Who can report?

1. Consumers (affected person)
2. Doctors
3. Nurses
4. Pharmacists
5. Other health workers

How to report ADRs?

1. Patient should immediately report any type of adverse drug reaction due to the use of any medication to their primary doctor and help the doctor fill out the special ADR form.
2. Doctor, nurses, pharmacist and health workers can fill out the ADR form in PDF format and send it back to the DGDA.
3. Government/Private Hospitals/Clinics: Every hospitals and clinics must decide for itself how the reporting system should be operated and by whom.

Generally, the physicians themselves act as reporters, completing the reporting form, keeping a record and sending them to the ADRM Cell, Directorate General of Drug Administration, Aushad Bhavan, Mohakhali, Dhaka-1212, Bangladesh**.**

The hospital pharmacist may also act as a reporter, completing the forms in consultation with the reporting physician. He should report:

1. Apparent ADRs previously unknown to the reporter
2. Serious ADRs
3. All suspected ADRs to new drugs
4. Cases of suspected dependence

Elements should be in a case report

1. The patient: age, sex and brief medical history.
2. Adverse event: description (nature, localization, severity, characteristics) of adverse drug reactions. Results of investigations start date, course and outcome
3. Suspected drugs: name (brand or ingredient name + manufacturer) dose, route, start/stop date, indication for use.
4. All other drugs used (including self-medication): names, doses, routes, start/stop dates.

   Risk factors (e.g., impaired renal function, previous exposure to suspected drug, previous allergies).
5. Name and address of the reporter (to be considered confidential and to be used only for date verification, completion and case follow-up).

Collaboration with WHO

After evaluation of ADR reports by the Adverse Drug Reactions Advisory Committee (ADRAC), the ADRM Cell of the Directorate General of Drug Administration, Aushad Bhavan, Mohakhali, Dhaka-1212, Bangladesh may provide the essential ADRs data to WHO collaborating center for International Drug Monitoring & Exchange of Drug Information.

Suspected Adverse Event Reporting Form

Identities of reporter, patient, institution, and product trade name(s) will remain confidential

ADR report number_____ (For office use only)
Date received_____

A. PATIENT AND HOSPITAL INFORMATION

Name of health facility (if applicable) _____

Patient name_____ **Registration #**_____

Patient address

_____

_____

Contact number_____

Age_____ **Weight (kg)**_____ **Height (cm)**_____ **Gender** ◯Male ◯Female

Pregnant ◯Yes ◯No ◯Unknown ◯Not applicable

B. SUSPECTED ADVERSE EVENT INFORMATION

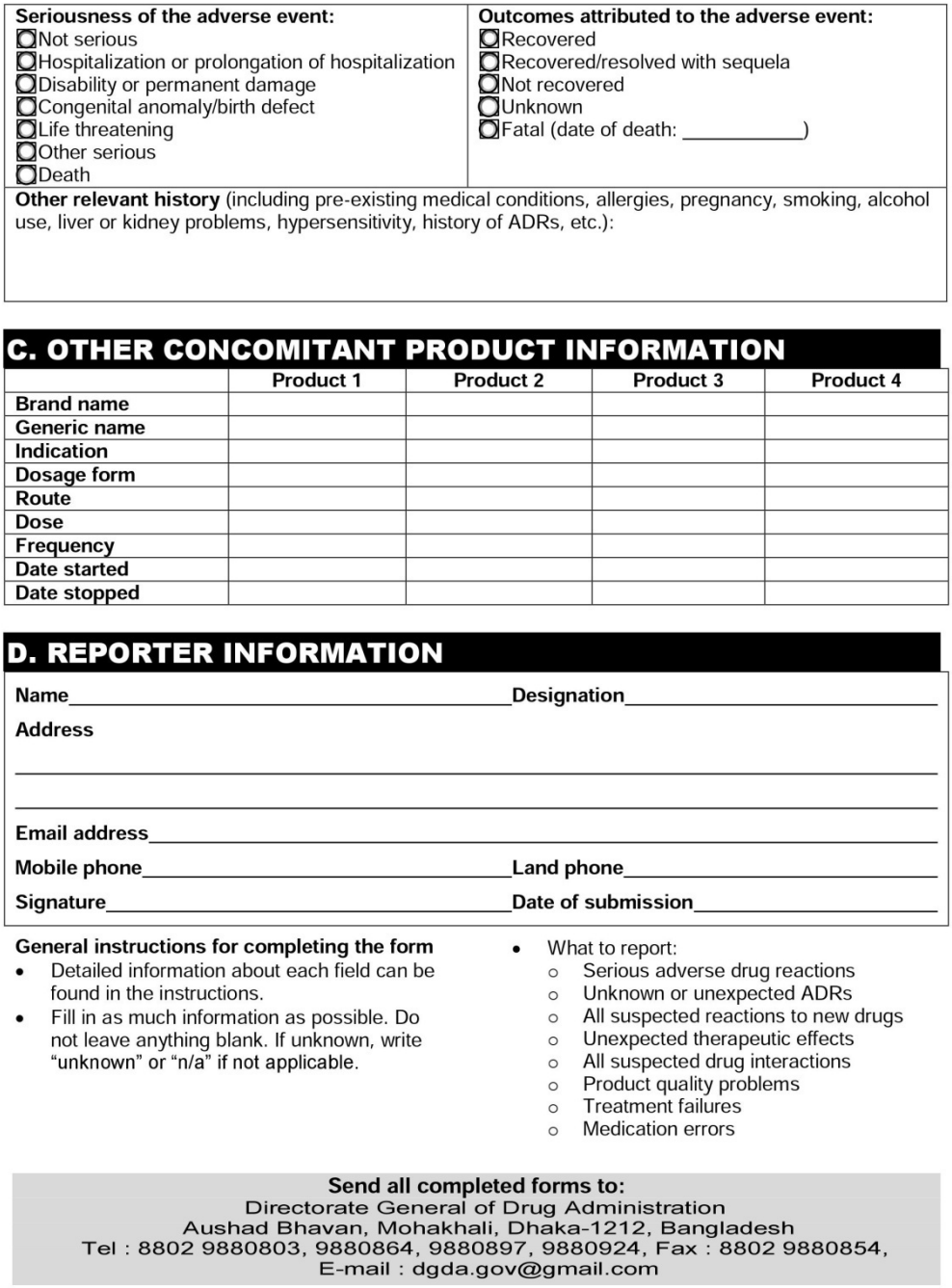
Type of event	**Suspected product**
◯Adverse drug reaction	Brand name_____ Generic name_____
◯Product quality problem	Indication_____
◯Medication error	Start Date _____ End Date _____
	Dose [strength, unit]_____ Dosage Form_____
	Frequency _____
	Batch/Lot number_____ Manufacturer_____

Describe event including relevant tests and laboratory results:

Date the event started	**Date the event was reported**	**Date the event stopped**
_____	_____	_____

Was the adverse event treated? ◯Yes ◯No
If yes, please specify

Action taken after the reaction	**Did reaction subside after stopping/reducing the dose of the suspected product?**
◯Dose stopped ◯Dose reduced ◯No action taken	◯Yes ◯No ◯Not applicable **Did reaction appear after reintroducing the suspected product?** ◯Yes ◯No ◯Not applicable



Seriousness of the adverse event:	**Outcomes attributed to the adverse event:**
☐ Not serious ☐ Hospitalization or prolongation of hospitalization ☐ Disability or permanent damage ☐ Congenital anomaly/birth defect ☐ Life threatening ☐ Other serious ☐ Death	☐ Recovered ☐ Recovered/resolved with sequela ☐ Not recovered ☐ Unknown ☐ Fatal (date of death: _____)
Other relevant history (including pre-existing medical conditions, allergies, pregnancy, smoking, alcohol use, liver or kidney problems, hypersensitivity, history of ADRs, etc.):	

C. OTHER CONCOMITANT PRODUCT INFORMATION

	Product 1	Product 2	Product 3	Product 4
Brand name				
Generic name				
Indication				
Dosage form				
Route				
Dose				
Frequency				
Date started				
Date stopped				

D. REPORTER INFORMATION

Name_____ **Designation**_____

Address

_____

_____

Email address_____

Mobile phone_____ **Land phone**_____

Signature_____ **Date of submission**_____

General instructions for completing the form

- Detailed information about each field can be found in the instructions.
- Fill in as much information as possible. Do not leave anything blank. If unknown, write "unknown" or "n/a" if not applicable.

- What to report:
  - Serious adverse drug reactions
  - Unknown or unexpected ADRs
  - All suspected reactions to new drugs
  - Unexpected therapeutic effects
  - All suspected drug interactions
  - Product quality problems
  - Treatment failures
  - Medication errors

Send all completed forms to:
Directorate General of Drug Administration
Aushad Bhavan, Mohakhali, Dhaka-1212, Bangladesh
Tel : 8802 9880803, 9880864, 9880897, 9880924, Fax : 8802 9880854,
E-mail : dgda.gov@gmail.com

Figure 3. Adverse drug reaction reporting form used in Bangladesh.

Conclusion

Safety on medication is the great concern in the health care system. Every drug has beneficial as well as adverse effects and its very common scenario. Pharmacovigilance is the way that can best protect the public health from the problem. The Directorate General of Drug Administration (DGDA) is working for ensuring safe, quality and effective medicines to safeguard the health of the people of Bangladesh. Involving patients in adverse drug reaction reporting can also improve the efficiency of the pharmacovigilance system and collaboration and commitment between the partners (Doctors, pharmacists, nurses and patients) are necessary to meet

future challenge of pharmacovigilance in Bangladesh. Also training, capacity, allocation of budget and logistic support required for effective reporting. Regulation of clinical trials, vaccines, biological and herbal medicines is one of the important functions of pharmacovigilance. So to maintaining safety of medication pharmacovigilance system should be strictly controlled. The day is not very far when adverse drug reaction monitoring (ADRM) cell of Bangladesh will be able to perform its role like other developed countries.

Acknowledgement

The authors would like to acknowledge the support received from Directorate General of Drug Administration (DGDA) during this work.

References

Amin, M.N., Khan, T.M. and Dewan, S.M.R. 2016. Cross-sectional study exploring barriers to adverse drug reactions reporting in community pharmacy settings in Dhaka, Bangladesh. *Br. Med. J. Open*. **6**.

Amran, M.S. Introduction to Pharmacy. January 2015.pp. 159-161.

Arrest warrants issued after DEG kills 26 infants in Bangladesh.

https://www.securingindustry.com/pharmaceuticals/arrest-warrants-issued-after-deg-kills-26-infants-in-bangladesh/s40/a206/#.V5JyhtJ97IV

Bangladesh National Formulary (BDNF), 2015.

Begum, Z.A., Sultana, S., Umar, B.U., Ferdous, A.H., Uddin, M.K. and Islam, S.M.H. 2012. Study of adverse drug reactions in out-patient department of a teaching hospital. *Bangladesh J. Pharmacol.* **7**, 104-107.

Edwards, R. 2012. An agenda for UK clinical pharmacology, pharmacovigilance. *Br. J. Clinical Pharmacol.* **73**, 979-982.

Hanif, M., Mobarak, M.R., Ronan, A., Rahman, D., Donovan, J.J. and Bennish, M.L. 1995. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. *Bri. Med. J.***311**, 88-91.

Health news BD. Diethylene glycol tragedy.

http://winksite.com/xhtml/ms_fo_pg_v?fid=21583&id=17623&susid=30373

Helali, A.M., Iqbal M.J., Islam, M.Z. and Haque, M. 2014. The evolving role of pharmacovigilance and drug safety: The way forward for Bangladesh. *Int. J. Pharm. Res* .**6**, 31-37.

IFPMA position paper on pharmacovigilance principle for biotherapeutic medicines. April 30, 2012.

Khondkar, L. and Khan, M.S.I. 2014. Clinical profile of cutaneous drug reactions. *J. Pakistan Associ. Dermatologist.* **24**, 160-163.

Manobkontho reports on substandard vitamin A capsules, 09 March, 2013.

http://www.talukdershaheb.com/2013/03/13/manobkontho-reports-on-substandard-vitamin-a-capsules-09-03-2013/

Mechanism of toxicity of diethylene glycol.

https://en.wikipedia.org/wiki/Diethylene_glycol

Mustansir, M.A., Saha, D., Paul, S., Rahim, Z.B. and Hosen, S.M.Z. 2013. Studies on pharmacovigilance in Bangladesh: Safety Issues. *Int. J. Pharm. Teachi Practice*. **4**, 613-621.

Nahar, N., Karim, A., Paul, P.C., Khan, T.H. 2011. Response of reporting adverse drug reactions.

among medical practitioners. *Bangladesh Med. J.* **40**, 13-18.

Official newsletter of California poison control system. 2012. p. 10.

http://www.calpoison.org/hcp/2012/callusvol10no4.htm

Pharmacovigilance,http://www.bionity.com/en/encyclopedia/Pharmacovigilance.html.

andhttps://en.wikipedia.org/wiki/Pharmacovigilance.

Safety of medicine in public health program. 2006. WHO.

Schep, L.J., Slaughter, R.J., Temple, W.A. and Beasley, D.M. 2009. Diethylene glycol poisoning. *Clin. Toxicol.* **47**, 525-535.

Suke, S.G.,Kosta, P. and Negi, H. 2015. Role pharmacovigilance in India: An overview. *Online J.Public Health Informatics.***7**, p. 223.

The importance of pharmacovigilance, Safety monitoring of pharmaceutical products, 2002.

UNICEF Bangladesh-Media center-Bangladesh conduct Vitamin A supplement campaign for more than 20 million children on 6 June, 2009. http://www.unicef.org/bangladesh/media_5123.htm

WHO. Pharmacovigilance ensuring the safe use of medicines. WHO policy perspective on medicines, Geneva. 2004.

WHO technical report series. International drug monitoring, the role of national center. **498.**

WHO Uppsala report. April, 2015.

Yao, B., Zhu, L., Jhing, Q. and Xia, H.A. 2013. Safety monitoring in clinical trials. *Pharmaceutics.* **5**, 94-106.