BRIEF TO EXECUTIVES AND OTHER HIGH-LEVEL STAKEHOLDERS ON PHARMACOVIGILANCE (MEDICINE SAFETY) IN RESOURCE LIMITED SETTINGS

January 2023

PhArmacoVigilance Africa (PAVIA)

Brief to Executives and other High-Level Stakeholders on Pharmacovigilance (Medicine Safety) in Resource Limited Settings

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3.1.2.1 Administrative Issues/ Executive Orders

Expected Roles and Responsibilities would depend on the position occupied and other activities in routine work. There is utmost need for persons to be fully aware of the need to monitor the intended benefits of medicines and be aware of the potential or unexpected adverse events, thus defining the changing balance of benefit and risks. This will ensure that there is an acceptable balance which guides its stay or exit from the pharmaceutical market. The expected intervention may be formal or informal, direct or indirect.

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Abbreviations

ADR: Adverse Drug Reaction

AEFI: Adverse Event Following Immunization

COVID-19: Coronavirus Disease 2019

CSR: Corporate Social Responsibility

FDA: Food Drug Administration

IOM: Institute of Medicine

PDUF: Prescription Drug Users Fee

PV: Pharmacovigilance

RLS: Resource Limited Settings

UMC: Uppsala Monitoring Centre

WHO: World Health Organization

Importance of this manual

Medicines constitute an important tool for the treatment of diseases. In most Resource Limited Settings (RLS), there is the perception of medicines being a panacea for all diseases. To this large audience, the use of medicines is considered to be always beneficial and is not associated with risks or any form of harm. Humans take a lot of medicines both orthodox and non-orthodox underscoring the quote by Sir William Osler (1849 – 1919), 'the desire to take medicine is perhaps the greatest feature which distinguishes man from animals. However, adverse effects are inextricably linked to the use of medicines. The quote alluded to Paracelsus, the Swiss physician (1493 – 1541) that, 'all things are poisons and nothing is without poison; the dosage alone makes it so that a thing is not a poison' is also apt.

In line with the dictum of Hippocrates re-echoed by the Institute of Medicine (IOM) 'First do no harm' in Latin 'Primum non nocere', it is pertinent to address the issue of medicine intake and the consequential harmful effects that might follow intake.

The harm caused by medicines is enormous ranging from being asymptomatic (without symptoms), mild to moderate symptoms to severe morbidity and eventual mortality. In this discourse, the burden of adverse effects from medicines, the potential role and responsibilities of persons in different sectors of the polity with a view of preventing or reducing this subtle carnage is highlighted. It is of utmost importance to note that the safe use of medicines is everybody's business and not limited to some eggheads in health institutions or government agencies.

The recent COVID -19 pandemic highlighted the intricacies in the development of a cure and the potential problems specifically untoward effects with the new potential medicinal products and vaccines. The concerted effort of all stakeholders - health and non-health professionals inclusive, drive and establish the machinery to ensure the safety of these products. The development and deployment of vaccines required the engagement of all stakeholders and the continuous monitoring also calls for their elaborate participation to further characterize the safety element of newly introduced vaccines.

1 Introduction

1.1 What is Pharmacovigilance (*Terminology and Definition*)

The term 'Pharmacovigilance' is Greko-Latin; derived from 'Pharmakon' meaning Drug or medical substance in Greek and 'Vigilare' (Latin) meaning to keep watch. It is believed to have been coined by a group of French Pharmacologists and Toxicologists in the 1970's. The WHO (2002) defines Pharmacovigilance as *'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem'.*

In this brief, the term 'Medicine Safety' which is essentially synonymous with Pharmacovigilance (PV) will be used interchangeably for better understanding of the subject matter so as to avoid the use of a medical jargon in non-medical circles. In a number of instances written and spoken, the abbreviation 'PV' may also be used.

1.2 Historical perspective from pre thalidomide to post thalidomide era

There are several documented adverse events in the last century following the use of medicines which have impacted on health care. Their occurrence has facilitated the development of a system to limit and mitigate such harmful event and ensure the safety of medicines.

This includes to mention a few, the sulphadiazine elixir disaster in the mid 1930's in the US where a poisonous diluent was used

in the formulation of the antibacterial drug for children resulting in over a hundred deaths. This event resulted in the establishment of the US FDA Act. Another major event was that of thalidomide, a sedative manufactured in Germany which when taken by pregnant women resulted in marked malformations of babies; some being born without or with malformed limbs and malformations of other organs (Appendix 2.1: **Thalidomide**). This was a wakeup call that resulted in legislations and articulate plans by nation states to prevent the future occurrence of such tragedy. Over the years the global coalition coordinated by the WHO resulted in the establishment of the Program for International Drug Monitoring, which is supported by the Uppsala Monitoring Centre, Sweden. Other notable adverse events include skin and mucosal lesions by practolol (*now withdrawn*). Other important effects were seen in the blood (haematological) such as – aplastic anaemia from chloramphenicol, anaemia by the antiviral agent zidovudine, biochemical effects such as raised blood sugar by the thiazide diuretics and the atypical antidepressant clozapine.

It is important to know that adverse effects of medicines can affect any organ-system in a human being e.g., in the liver, hepatitis is induced by medicines like the antipsychotic chlorpromazine and anaesthetic agent halothane. The recent occurrence reported from Gambia of deaths in children linked to cough syrup underscores the need for regulatory diligence (https://www.reuters.com/world/africa/gambia-police-link-child-deaths-cough-syrup-imported-by-us-firm-2022-10-11/)

1.3 The development of drugs and vaccines

The development of Medicines (including vaccines) is a process which goes through tests in laboratories using animal cells/tissues followed by use of different species of live animals (preclinical) progressing to human (clinical phase). Initially the human phase is carried out in normal volunteers (subjects) followed by studies in patients with the disease in view and thereafter in patients with other concomitant morbidities. It is pertinent to note that the capturing of adverse drug reactions to the medicines during this developmental phase cannot be exhaustive due to the limitations regarding the patient exposure: too few in numbers, too narrow in age (extremes excluded), too short a duration of observation etc. In all, by the time a medicine is being licensed only a total of 3,000 to 5,000 persons have been exposed which in most instance excludes persons at the extremes of age – children, pregnant women and elderly as well as those with other concomitant diseases. Again, especially when there is urgent need for a medicine (e.g., emergency use authorization being applied), far fewer numbers of persons would have been exposed prior to the medicine reaching the larger population. For various reasons, findings during animal experimentation cannot be extrapolated to man.

Figure 1: Formulations and Presentation of medicines
(Source: Departmental File)

1.4 Scope of Pharmacovigilance and Products of Concerns

The scope of Pharmacovigilance is broad encompassing but not limited to the following: Adverse drug reactions, Medication Errors, Drug – drug interactions, Substandard and Falsified Medicines, Lack of Effectiveness etc.(**Figure 2: Scope of Pharmacovigilance**.)

Adverse drug reactions are pre-eminent and focus is usually placed on the various untoward reactions that develop following intake of medicines. However, other adverse effects are equally important and professionals devote much time to detect them timely since they can result in significant number of deaths. **Figure 2 Figure 2**gives an overview of examples of Medicine Safety issues.

The products of concern in Pharmacovigilance are shown in Figure 3 and include the following: Medicinal Products, Traditional and Complementary Medicines including Herbal Products, Biologicals, Vaccines, Blood Products, Medical devices. In some instances, specific arrangements are made to address some of the concerns (e.g., Haemovigilance) for blood products and also for medical devices).

This brief is not intended to provide details however notable examples are further elaborated in the APPENDICES.

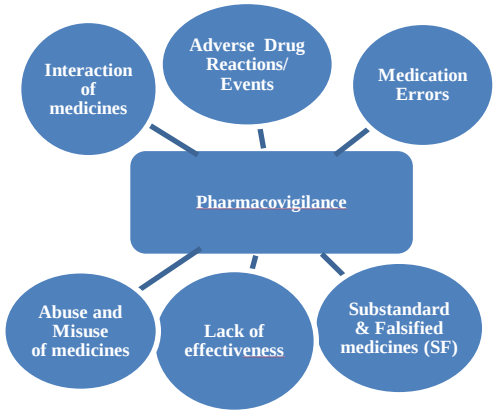

Figure 2: Scope of Pharmacovigilance

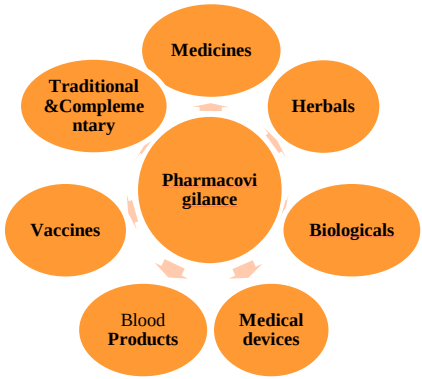

Figure 3: Products of Concern

2 The need for Pharmacovigilance.

Essentially, pharmacovigilance is concerned with Patient (and Public) care and safety regarding the use of medicines and vaccines as well as other medical and paramedical interventions. The public health dimension is of utmost importance recognizing the use of medicines and vaccines in large scale as in deployment for treatment of various diseases such as with the vaccines in the COVID-19 pandemic.

As mentioned above, during the development phase of medicines with the few patients studied, the number of adverse events in the early phase are few and limited due to the select group studied. The long-term effects due to the pharmacological characteristics are not usually observed. Again, the real-life

factors including but not limited to interaction with other medicines, food, morbidity status, race as well as genetic disposition are yet to be studied.

The licensing of a drug for use is based on a favourable benefit-risk balance at the time of the approval for marketing and use. This balance is dynamic and needs to be monitored over time as the exposure of more persons to the drug increases. The continued presence of the medicines in the market depends on its maintenance of a positive benefit-risk balance. Perchance there is a change to the negative end of the spectrum, it is important to detect it early and handle the consequential issues in a timely manner. The process of pharmacovigilance ensures this, thus preventing the occurrence of harm to the patient and the population at large.

Regarding vaccines, the COVID–19 pandemic highlighted the beneficial effect of vaccines in preventing the occurrence of diseases. There are several vaccine-preventable diseases and whilst vaccines appear simple to administer to achieve the beneficial effects, adverse events may develop (Adverse Events Following Immunisation – AEFIs). For most patients, vaccines are safe but the occasional patient may develop serious adverse events. For the COVID vaccines these include Guillain-Barré Syndrome (development of ascending paralysis from the limbs), myocarditis (inflammation of the heart muscles), thrombotic thrombocytopenic syndrome (development of blood clots in vessels). The essence is to have in place an early detection strategy so as to manage these life-threatening risks while at the same time enjoy the beneficial effects of the vaccine.

3 Target Audience /Stakeholders (High level)

These include but not limited to the President and Members of the Executive Council (Ministers), Legislators and Judiciary, Head of Agencies, Vice Chancellors, Professors and other Academics and Administrative Professional Associations, Regulatory Councils, Non-Governmental Organizations, Faith Based Organizations. Chief Executive Officers (CEOs) of Establishments, Captains of various Industries

A schema of this target group is shown below (Figure 4). There are groups of stakeholders which should work concertedly to achieve this objective:

A. Those involved in the development and deployment of medicines into the healthcare system/population, such as universities and pharmaceutical companies.
B. Those that impact on Policies, Laws, Regulations as well as provide guidance regarding medicines and others that serve as Regulators or whose activities impact on the legal environment, determining the availability (controlling the entry into and maintenance) of drugs within the healthcare system, notably the Ministry of Health and the National Medicine Regulatory Agency.
C. Operators within the healthcare system determining the distribution of medicines, prescribing and use of medicines such as the Ministry of Health and Professional bodies.
D. Those whose function impact on the funding, support for use and monitoring of medicines such as governments, health insurance outfits, pharma consortium etc.

E. Major supranational bodies like WHO (HQ and UMC) and other UN organs (UNICEF, UNHCR etc.) as well as-international donors and NGOs such as the USAID, MSH and other partners supporting pharmacovigilance activities.

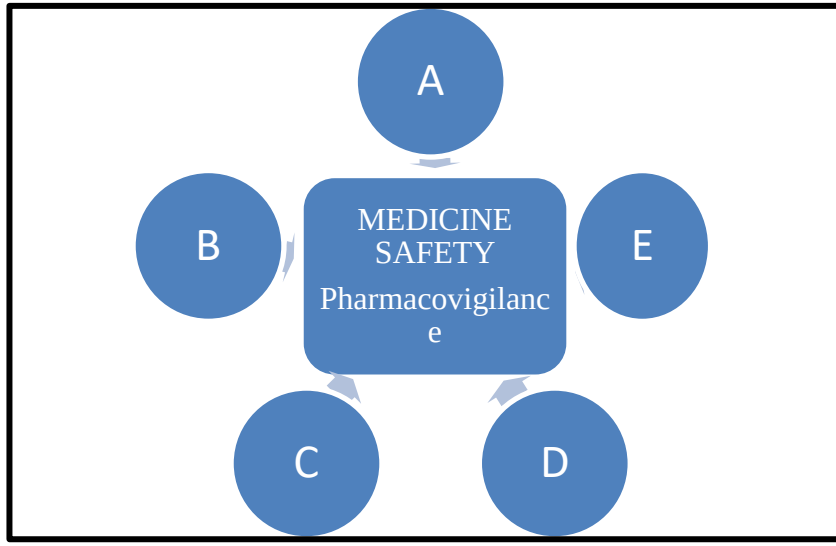

Figure 4: Schema of Stakeholders in Medicines Safety

3.1 Roles and Responsibilities

This is dependent on the position occupied by the user-stakeholder. It is pertinent to point out that reference should be made to the Pharmacovigilance Policy documents defining the roles and responsibilities of various stakeholders. However, for those not working within the health sector the areas to address include the following:

- Advocacy
- Creation of enabling environment
    - Administrative Issues /Executive Orders
    - Legal framework
    - Funding and Logistic Support

3.1.1 Advocacy

Considering the issues highlighted above, and the envisaged objective in supporting the safe use of medicines, top level executives should be able to advocate at various platforms and levels for the need to support pharmacovigilance (medicine safety) in all ramifications. They should also be receptive to overtures to promote medicine safety. In the public domain, some areas to address will include but not be limited to consumer reporting of adverse (harmful) effects of medicines, financial support for medicine safety issues including training and capacity building, as well as provision and utilisation of information regarding PV matters.

3.1.2 Creation of an Enabling Environment

The creation of an enabling environment for pharmacovigilance operation is usually determined by top level stakeholders outside the health sector. This includes notably those involved in making policies, laws and regulations. The politicians in executive positions, legislators, judicial officers and other officers responsible for legal issues should understand the intricacies in creating a legal framework for PV operations. In this regard, the various possible antagonistic interest groups who may lobby negatively to hinder the development of appropriate framework to facilitate the various interactions and activities in PV should be kept in view.

An example of an executive fiat /order facilitating the establishment of a medicine safety programme is that of the establishment of the WHO Programme of International Drug Monitoring facilitated by the US President Lyndon Johnson (Box 1**: Example of an Executive Order**). The prioritization of pharmacovigilance by Executive Officers will consequentially result in their establishments facilitating the allocation of resources for the setting up and operation of PV outfits.

3.1.2.1 Administrative Issues/ Executive Orders

Expected Roles and Responsibilities would depend on the position occupied and other activities in routine work. There is utmost need for persons to be fully aware of the need to monitor the intended benefits of medicines and be aware of the potential or unexpected adverse events, thus defining the changing balance of benefit and risks. This will ensure that there is an acceptable balance which guides its stay or exit from the pharmaceutical market. The expected intervention may be formal or informal, direct or indirect.

Box 1: Example of an Executive Order

THE WHITE HOUSE

Letter from the President to the Secretary of Health, Education and Welfare, John W. Gardner (Excerpts)

Dear Mr. Secretary:

I authorize you to perform the functions as may be required to provide Assistance by the United States in the World Health OrganizationInternational System to Monitor and Report Adverse Reactions to Drugs.

I am pleased that the grant made possible by this delegation of authority will enable the World Health Organization to develop a worldwide early warning system for drugs, similar to the system now in development in the Food and Drug Administration. The World Health Organization's international drug reactions monitoring system will help prevent widespread tragedy of the sort which resulted from the use of thalidomide.

Sincerely,
/s/ LYNDON B. JOHNSON

Source: Venulet J and Helling-Borda M Drug Safety 2010

3.1.3.2 Role of Legislature

The USA and UK, legislature acted promptly in response to adverse events to medicine -related mishaps (**Box 2**)

Box 2: Legislature supporting Medicines Safety

1. The **FDA Act 1935** which established the FDA following the use of an inappropriate vehicle diethylene glycol to prepare the antibacterial sulphanilamide resulting in the deaths of over 100 children.
2. **Kefauver-Harris Amendments Revolutionized Drug Development**
   President John F Kennedy on Oct. 10, 1962, signed into law the amendments which established a framework that required drug manufacturers to prove scientifically that a medication was not only safe, but effective before they go on the market, and afterwards report serious side effects
3. **The Medicines Act 1968** and subsequent Acts of Parliament of the United Kingdom addressed several aspects of drug use including those resulting from the use of thalidomide.

Many other countries including those in Africa have put in place Laws to guide the use of Medicines. The limitation of these statutes has been highlighted. This brief is intended to draw the attention of Legislators and Policy makers to the crucial role

they are meant to play in the creation of an enabling legal environment for Pharmacovigilance. The numerous encumbrances hindering the operation of Pharmacovigilance should be addressed positively and in a timely manner on the policy/legislative platforms. In effect, stakeholders including those in relevant Agencies handling Regulations should comprehensively address these provisions.

3.1.3.3 Funding and Logistic Support

Funding is a major issue in pharmacovigilance due to the cost-intensive nature of the several activities expected from the statutory outfit. A sustainable, vested interest-free financial mechanism should be in place to ensure that the operations are not hindered or influenced by some untoward interest detrimental to the set objectives.

The funding of Pharmacovigilance activities is quite unique. It is pertinent to ensure that the activities of operatives in the pharmacovigilance turf are fully insulated from vested interests in the course of their operations. This will to a large extent guarantee trust and acceptability of statements emanating from the pharmacovigilance outfits.

Chief Executive Officers (CEO) and other high-level stakeholders are usually in a position where they control resources or influence decisions regarding disbursement of funds. They are therefore in a position where they can provide funding or other logistic support to Pharmacovigilance facilities as a ***Corporate Social Responsibility (CSR)***

Furthermore, there is need to address the dire situation in RLS where issues of medicine safety is not prioritized in the national schemes. The psyche of the authorities and the generality of the people is that medicines are beneficial and useful and not a source of harm.

Donations from various multilateral and bilateral agencies have played useful roles in addressing the handling of medicine safety issues in many countries by supporting public health programmes.

Support for COVID Vaccine Safety underscored the importance of funding in ensuring safety in the development and use of medicines and vaccines. Grants from several corporate entities and individuals came into play. Some philanthropists supported the efforts in programmes monitoring the various adverse effects. The intensive efforts from government and private enterprises/persons were most salutary in the outcome of the COVID war.

The Executive and Legislative arms of Government can also collaborate to improve pharmacovigilance funding. This is illustrated in the case of the USA where the Prescription Drug User Fees (PDUF) Act was passed to support funding of the FDA in carrying out some of its duties and some proportion subsequently allotted to medicine safety. This funding mechanism backed by legal provision ensures sustainability of funding for pharmacovigilance activities. The important role of Governments and its agencies is paramount and should not be relegated or underprioritized in the scheme of its pharmaceutical operations.

4 Conclusion

In all, the safety of medications is the responsibility of all. It is not just the duty of those purportedly in the chain of healthcare situated in healthcare facilities. There is a vital role for policy makers, opinion leaders, executive officers, captain of industries, managers in non-health sectors of the polity. The need for persons at this level who have access to resources which can be used for the general good of mankind as corporate social responsibility. The role of such independent vested interest free bodies in the funding of pharmacovigilance will ensure transparency in the process of ensuring medicine safety. It is hoped that this brief provides the basic information on the need for medicine safety, the cost intensive processes involved, the importance of putting in place sustainable funding and the dire support required by all stakeholders with leadership by top level executives

APPENDICES

Appendix 1: Stakeholders in Pharmacovigilance

Policy and Decision Makers: Collaborators and Implementing Institutions
Government (all arms) • Executive: Presidency and Head of Government • Legislature: Senate President, House Speaker and Members of the National Legislature • Government Officials: Ministers and Directors – Finance, Education, Commerce and Industry • The Judiciary • Policy Makers and Health Managers • Ministry of Health (Departments and Agencies), • Regional/International Organizations such as AMA, AMRH, EAC, ECOWAS, NEPAD and SADC • African Regional Economic Communities (RECs) as applicable • Development Partners, NGOs and FBOs • Healthcare Executives and Managers (Public and Private sectors) • International and Local Pharmaceutical Industry (with the Marketing Authorization Holders) • National Medicines Regulatory Authority (NMRA) • National Drug Safety Advisory Committees • Public Health Programs

ACADEMIA

Universities

- Heads of Department
- Deans
- Provost
- Vice Chancellor
- University Senate/Council

Professional Regulatory Bodies:

Education

- National Universities Commission

Health

- Medical and Dental Council
- Pharmacy Council
- Nurses and Midwifery Council
- Medical Laboratory Sciences Council

Undergraduate and Postgraduate Students

- Medicine, Dentistry, Pharmacy, Nursing, Laboratory Sciences, Social Sciences, etc.

Clinical and other Healthcare Providers
• Hospital Executives and Operatives – Medical Consultants • Doctors (including Traditional/Alternate Medicine Practitioners) • Pharmacists and Patent Medicine Dealers • Nurses and Midwives • Other healthcare workers • NGOs, FBOs, etc. **Professional (Clinical) Associations/Societies** • Medical • Dentistry • Pharmacy • Nursing/Midwifery • Laboratory Sciences **Public** • Patient and Consumer Organizations • Patient Advocacy Groups • Public and Consumer **Media Executives and Operatives** • Print and Electronic • Mainstream and Social **Other high-level executives** • Bank Executives • Health Insurance Executives • Legal Practitioners

Appendix 2: Adverse Drug Reactions

In the clinical setting, following the administration of a drug, beneficial and/or adverse effects may occur. It is pertinent to note that these effects may be mild, moderate or severe and involve one or more organs in the body. No organ is exempt from a possible adverse effect. Some reactions affecting the skin and visible aspects of the body is shown below:

Appendix 2.1: Thalidomide

Thalidomide is a drug used as a sleeping pill to alleviate the symptoms of pregnancy. It was called by some a 'miracle drug' being perceived to be so effective. It is an innocent-looking, small, white and tasteless pill. The harmful effects was observed within a few years of use e.g absence of limbs (Amelia), seal like limbs (Phocomelia) which are quite notable and many other defects in internal organs which are not quite obvious.

Lessons learnt

The harmful effects were seen in most countries where the regulatory provisions were inadequate to guide licensure and use. In the USA, the FDA under Dr Kelsey on the premise of initial findings in animals, denied licensing thus, preventing its use. This was a major decision which protected the American population from the devastating effect of the drug. This was not the same for Canada a contiguous State which allowed the use of the drug. Dr Kelsey was honored by President John Kennedy of the USA for due diligence This scenario is quite informative as it underscores the enormous consequence of a simple diligent action.

Appendix 2.2: Allergic Reactions

There are various forms of presentation of allergic reactions to medicines which may develop following the intake of medicines. Some of the obvious and life-threatening ones include the following:

Anaphylaxis characterized by rashes, sweating, breathlessness, wheezing, faintness which may progress to shock, loss of consciousness and at times death. This may occur with common medicines including antibiotics (notably penicillins). Other less severe presentations with swelling of the face, periorbital (around the eyes) and other areas can also occur (Figure **5**).

Angioedema which usually present following intake of medicines with swelling of the face, lips, tongue and throat, difficulty in breathing progressing to loss of consciousness and death (Figure **6**).

Figure 5: Generalised Allergic Reactions

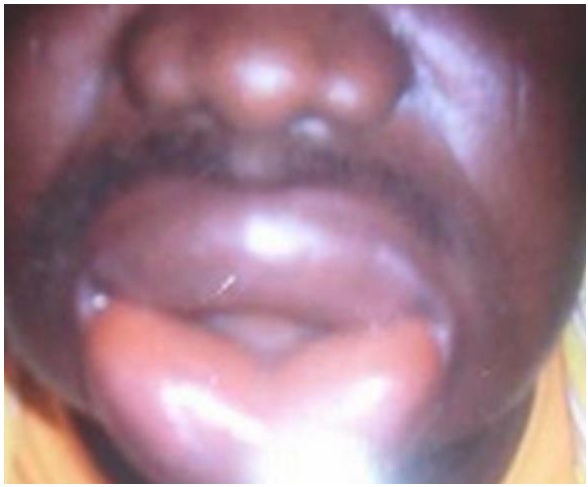

Figure 6: Angioedema in a patient on treatment with Lisinopril for hypertension

(Source: Departmental File)

Appendix 2.3: Steven Johnson Syndrome and Toxic Epidermal Necrolysis

Figure 7: Steven Johnson Syndrome

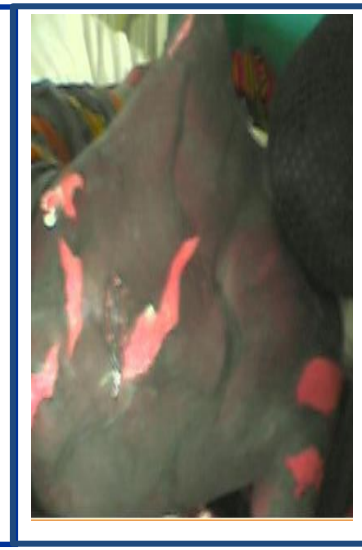

Figure 8: Toxic Epidermal Necrolysis

(Source: Departmental File)

Steven Johnson Syndrome and Toxic Epidermal Necrolysis

These conditions are severe skin lesions due to some drugs. They are characterized by development of body rashes which starts from the trunk, progresses to involve the face and became generalized. They are itchy, forms blisters that rupture forming ulcers after discharging clear fluids. These ulcers involve the

lips, mouth and eyes limiting patients' ability to eat or open eyes properly.

This type of adverse reaction follows the intake of some sulphonamide containing drugs used in healthcare settings such as the antibiotic cotrimoxazole, sulphadoxine in antimalarials and nevirapine (an antiretroviral used for the treatment of HIV/AIDS)

Appendix 2.4: Some other aspects addressed by Pharmacovigilance

2.4.1A: Medication Errors

MEDICATION ERRORS

In this instance, a medication is wrongly or inadvertently prescribed, dispensed or administered to a patient. For example,

Drug induced low blood sugar (*hypoglycaemia)* may result following inadvertent administration of a blood sugar lowering drug which will result in loss of consciousness (coma) and eventual death if not well managed. This state can also result from errors in dosage of this class of drugs or insulin. Drug induced low blood sugar is a common adverse reaction seen in practice

Medication errors do occur with a number of other drugs in various instances.

2.4.1B: Substandard and Falsified Medicines

SUBSTANDARD AND FALSIFIED MEDICINES

When medicines are developed, the process follows some set standards and the products meet some specifications and acceptable balance on a risk benefit scale.

Of interest, is the unfortunate development on a global scale where the set specifications are grossly undermined.

These activities result in 4% to over 20%of medicines in the market not meeting specified standards and are substandard.

The consequence of taking such medicines include failed treatment, harmful effect of treatment outright, toxicities and death

2.4.1C: Lack of Effectiveness

LACK OF EFFECTIVENESS

Medicines are administered to achieve some beneficial effect. In some instances, the desired effect does not occur. In fact, no effect or minimal effect may result.

It is important that the actions of drugs are monitored since lack of effect can have adverse consequences due to progression of disease and even death. The monitoring for this lack of effect comes under the purview of Pharmacovigilance
(Medicine Safety).