

# DRUG INFORMATION BULLETIN

Vol 1: Medicines Control Authority of Zimbabwe May 2017

## In this issue

### 1. Increased Reporting from the Targeted Spontaneous Reporting (TSR) Programme

The Targeted Spontaneous Reporting (TSR) Program for ARVs, anti-TB and other Essential Medicines has been running successfully and has seen an increase in the number and quality of Adverse Drug Reports (ADR) that have been received by the Pharmacovigilance team. During analysis of the data from the reports, it was noted that there was an increase in the number of cases of adverse events reported from combination antiretroviral medication. For the period September 2012 to December 2016, the Medicines Control Authority of Zimbabwe (MCAZ), has received 1578 adverse drug reaction (ADR) reports, of these reports 79.1% were from ARVs. The analysis of the data has revealed a shift in the profile of the reported ADRs since the introduction of combination ARVs and Isoniazid Preventative Therapy. This shift has seen the ADRs being reported change from reactions such as Lipodystrophy, anaemia and Steven- Johnson Syndrome to gynaecomastia, renal malfunction and hepatotoxicity, in line with the change in ART guidelines. Figure 1, is a graph showing the increasing reporting trend from the TSR program:

1. Increase in serious reports from Targeted Spontaneous Reporting (TSR) of Anti-retrovirals and Anti-tuberculosis Programme.

2 New Kid on the block of Drug Interactions

3. WHO Pharmacovigilance Toolkit

4. Highlights for the year

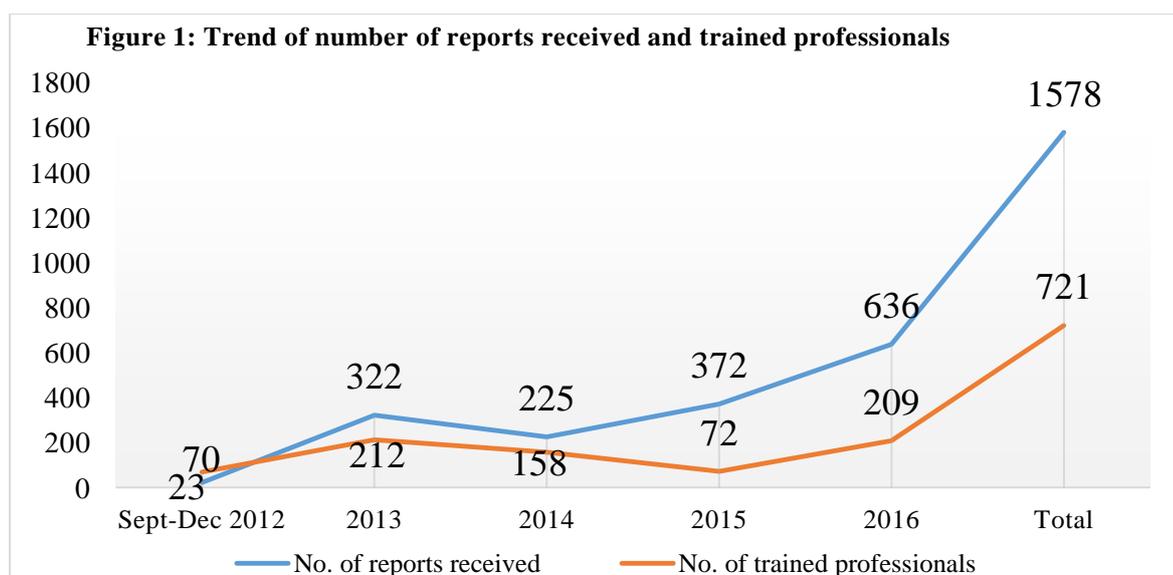


Fig 1: The graph shows that 2016 received the most number of reports since the program started.

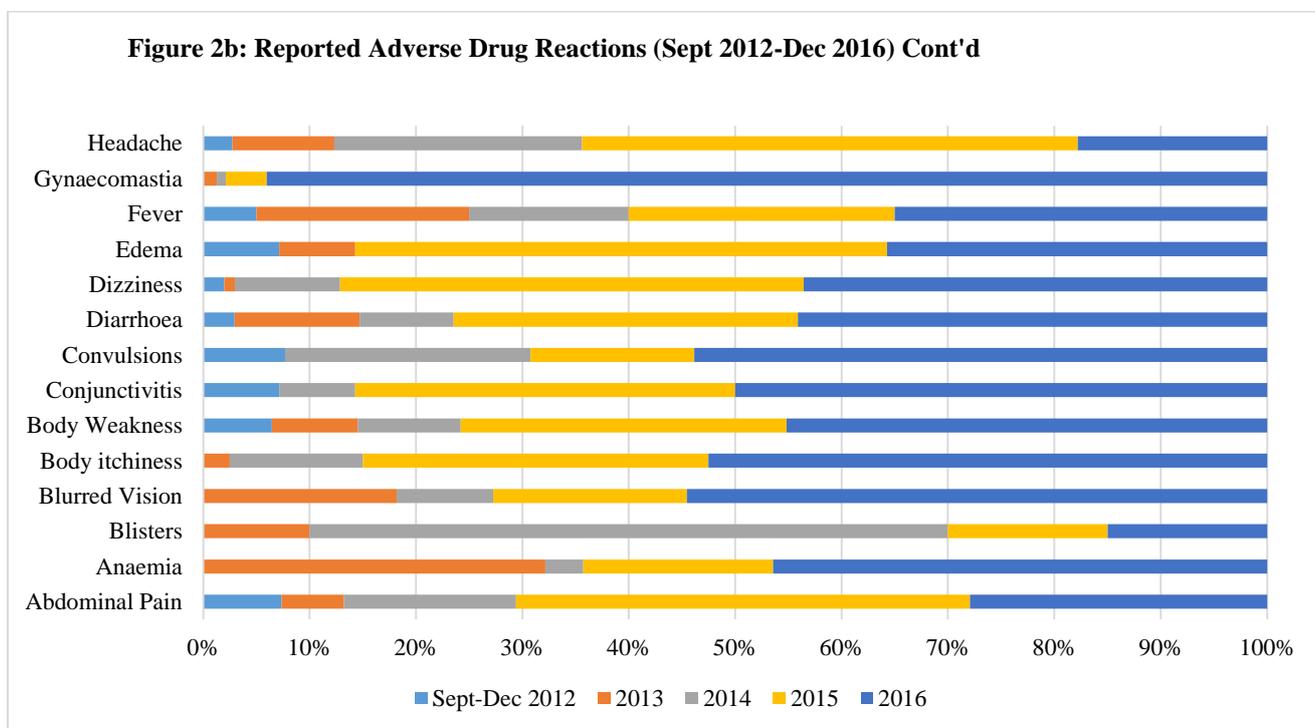
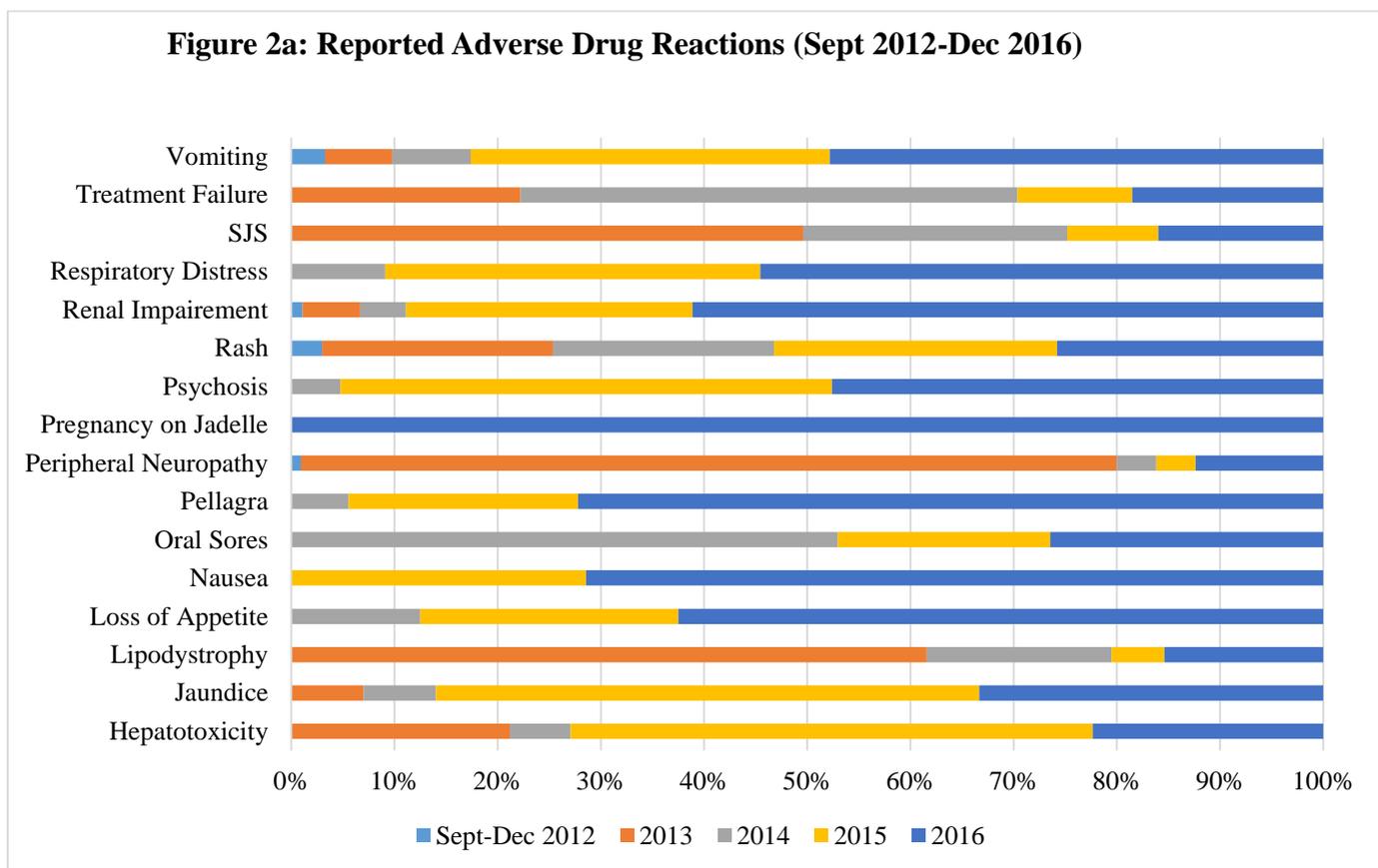


Fig 2a and 2b: The most frequently reported ADRs from the TSR program. The most reported cases are rash (434), followed by gynaecomastia (234) and Steven-Johnsons-Syndrome (125)

## ADVERSE DRUG REACTIONS OF INTEREST

### Gynaecomastia from patients on Efavirenz

There has been an increase in reports of gynaecomastia from January to October 2016 from patients on Efavirenz containing ARVs. From 618 reports of patients on Efavirenz- containing ARVs. . 196 (31.72%) were gynaecomastia cases. About 17.3% cases had the disorder for less than one month, 53% for one month to a year, 13.3% for more than one year, and the rest of the cases were of unknown duration. Most of the patients (54%) were between 21-45 years of age, 15.8% were below 20 years and the rest were above 46 years. The increase in the number of gynaecomastia reports could be attributed to Efavirenz which was introduced as a first line medication in antiretroviral therapy in 2013.

Some of the cases of gynaecomastia that have been received have been severe, disabling and in some instances requiring surgical intervention. Health care professionals (HCPs) and prescribers are encouraged to be attentive to the development of gynaecomastia in patients and encourage patients to be forthcoming and report the ADR. Early detection of the condition can result in reversal of the condition. Respond accordingly as the cost of a mastectomy is beyond the reach of most of the patients.

### Renal impairment from patients on Tenofovir

Tenofovir (TDF) based ART regimen(s) have been widely used, as they are more effective and less toxic than some regimens and recommended as part of preferred first line –regimen for initiation and maintenance including second line regimens. Tenofovir may however be associated with acute kidney injury or chronic kidney disease and/or reduced bone mineral density in some few patients. The main target of toxicity appears to be the proximal tubule,

and in severe cases, patients can develop Renal Fanconi syndrome which refers to the generalized dysfunction of the proximal tubule.

1202 reports received for ART and Anti-TBs, 806 (67.05%) were ART with TDF based combinations Analysis of the TSR programme reports indicates that there has been an increase in the number of reports of renal impairment that has been associated with TDF use, where a total of 21(29%) reports have been received from 2012-2015 and 51 (71%) reports been received in 2016 alone. 72 (8.93%) ADR reports, were renal impairment cases associated with TDF, which had causality assessment that was classified as possible, due to TDF. The majority of these cases (70.8%) were reported during the period January to August 2016. 50% of the cases were in the 20-45 year age group, followed by 36.11% in the 45-65 years age group. promote regular kidney functions tests to promote early detection of any kidney malfunction.

In light of the above, all HCPs and prescribers are encouraged to be pharmacovigilant in detecting and reporting the ADRs.

### ON-LINE REPORTING!!!!!!

MCAZ has launched an e-reporting platform for convenient ADR reporting at:

<http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting>.

Those who do not have access to internet should continue to use the ADR reporting forms that were provided by the MCAZ. HCPs and prescribers are encouraged to report all ADRs that they come across including those assumed to be known

## 2.0 Drug Interactions to watch

### Unintended Pregnancies in women on Efavirenz based regimens with Jadelle implants

In most low to medium income countries, subdermal hormone based birth control implants such as Levonorgestrel (LNG) are the preferred contraceptives with an expected failure rate of less than 1% over five years. However their use has been compromised in HIV positive women of child bearing age that are under Efavirenz based Anti-retroviral therapy (ART) due to potential cytochrome P450 3A and uridine-diphosphate glucuronosyl transferases (UGTs), mediated drug-drug interaction. Currently there has been very few pharmacokinetic studies and even worse clinical studies published, examining the interactions of the hormonal contraceptives and ART

#### Mechanism of Interaction

Levonorgestrel is metabolized as a substrate of CYP450 3A4 and undergoes glucuronidation to a minor extent. Efavirenz is metabolized as a substrate of CYP3A4 and CYP2B6, it also inhibits CYP2C9 and CYP2C19, while inducing CYP3A4. The active metabolite for LNG (norgestimate-NGM), decreases by 83% after taking efavirenz 600mg for 14 days. In a retrospective study of 570 HIV – infected women that was done in Swaziland using the Jadelle (Levonorgestrel) implant, 2.8% become pregnant while on the implant. For the women on nevirapine or lopinavir/ritonavir – based regimens none become pregnant while 15 of the 121 (12.4%) women on EFV – based regimen became pregnant. In another prospective pharmacokinetic study 60 HIV – positive women were assessed for levonorgestrel concentrations, the participants received sub – dermal levonorgestrel implant. Other studies done by Sivin L et al and Scarsi K K, et al have confirmed the interaction of EFV and LNG.

There has been an increase in reports involving LNG and Efavirenz from 1 report that was received in 2015 to 9 reports that have been reported in 2016. Of the total number of reports

received from patients on ART and Anti-TBs, 0.8% of the reports were for Pregnancy in Women on Efavirenz-based ART and LNG. Ten percent of the reports were reported in 2015 while 90% were between January to December 2016. The outcomes of the reports were 10% miscarriage while 90% were reported as unknown.

Health education on reduced efficacy of levonorgestrel, use of dual contraceptive method and alternative contraceptive methods with less drug interactions such as Intra – uterine devices (IUDs) is encouraged.

## 3.0 WHO PHARMACOVIGILANCE Toolkit

### About Pharmacovigilance (PV) Tool

This Pharmacovigilance (PV) Toolkit is a package of simple PV tools and a description of supporting processes for the conduct of pharmacovigilance. It is targeted primarily at PV professionals in low and middle income countries, but is relevant everywhere PV is practised. It provides the framework and support needed for the effective conduct of pharmacovigilance at local, regional, national and international levels.

One of the essential aims of WHO and its partners is to provide countries with the necessary support and tools to be able to carry out pharmacovigilance activities effectively and in a harmonised way to ensure that data collected in each setting can be used globally. It aims to provide countries with a complete guide, tools and assistance to undertake comprehensive pharmacovigilance according to WHO guidelines and recommendations and in line with contemporary best practice. It also provides a means of monitoring and evaluating activities using a novel pharmacovigilance indicator that all countries can use to measure performance. This is a much neglected area and deserves more attention if PV is to become more effective and continue to be funded.

The Toolkit contents are endorsed by the WHO Advisory Committee on the Safety of Medicinal Products after the original text has been written and reviewed by global experts.

## Introduction

Patient safety is the focal point for health care. Modern medicines have had a positive impact on the management and control of disease conditions. However, even with all their benefits, there is evidence to the fact that adverse reactions to medicines are very common, yet often preventable.

These reactions have been the cause of illness, disability and even death and in some countries adverse drug reactions are among the 10 leading causes of mortality. The safety of patients and the safe use of medicines are crucial for health policy development and delivery of the best healthcare. To prevent or reduce harm to patients thereby improving public health, the safety of medicines in clinical use must be monitored and evaluated through specialised systems. This means having a well-organised pharmacovigilance system.

## Functions of National PV System

The functions of a national pharmacovigilance system are numerous and varied. Through consultation between WHO, the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) and The Global Fund, the minimum functions of a national pharmacovigilance system have been defined to include the following:

1. To promote PV in the country, collect and manage ADR reports as well as reports of medication errors and suspected counterfeit/substandard drugs
2. To collaborate and harmonize with other ADR collection activities within the country (e.g. national disease control programmes, poison control centres, etc.) as well as international monitoring of ADRs in cohorts of defined patients
3. To identify signals of drug safety, i.e. unknown or poorly characterized adverse events in relation to a drug or drug combination and/or its use
4. To undertake assessment of risk and options for risk management
5. To identify if there are quality problems in medicines resulting in ADRs; and more generally, support the identification of medicine quality issues

6. To provide effective communication on aspects related to drug safety, including dispelling unfounded rumours of toxicity attributed to medicines and/or vaccines
7. To apply information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines
8. To develop and maintain drug utilization information
9. To identify issues associated with unregulated prescribing and dispensing of medicines.

## How to Setup a PV Center

The setting up of a national PV centre requires several considerations. The WHO and UMC have produced a manual titled: "Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre" which contains Basic steps in setting up a Pharmacovigilance Centre, i.e.

- Make contacts with the health authorities and with local, regional or national institutions and groups, working in clinical medicine, pharmacology and toxicology outlining the importance of the project and its purposes.
- Design a reporting form and start collecting data by distributing it to hospital departments, family practitioners, etc.
- Produce printed material to inform health professionals about definitions, aims and methods of the pharmacovigilance system.
- Create the centre: staff, accommodation, phone, word processor, database management capability, bibliography etc.
- Educate pharmacovigilance staff with regard, for example, to:
  1. data collection and verification
  2. interpreting and coding of adverse reaction descriptions
  3. coding of drugs
  4. case causality assessment
  5. signal detection
  6. Risk management.
- Establish a database (administrative system for the storage and retrieval of data).

- Organize meetings in hospitals, academia and professional associations, explaining the principles and demands of pharmacovigilance and the importance of reporting.
- Promote the importance of reporting adverse drug reactions through medical journals, other professional publications, and communications activities.
- Further information on planning out these activities is provided in the manual, which is available free of charge from <http://apps.who.int/medicinedocs/en/d/Jh2934e/>.
- The following chapters are included in the document:
  1. Introduction
  2. Why pharmacovigilance?
  3. Definitions and aims
  4. How to start a pharmacovigilance centre
  5. Reporting of adverse drug reactions
  6. Special issues in reporting
  7. Practicalities in the organization of a pharmacovigilance centre
  8. Assessment of case reports
  9. Use of the data
  10. Relations with other parties
  11. Other sources of information
  12. Funding
  13. Glossary
  14. Causality categories
  15. WHO contacts

### WHO PV Indicators

The World Health Organisation Programme for International Drug Monitoring (PIDM) has published its Pharmacovigilance Indicators Manual for use in the assessment of pharmacovigilance systems. This manual is similar to the Indicator-Based Pharmaceutical Assessment Tool (IPAT).

At a meeting of the African Pharmacovigilance Consultants Network (PVSF) in Accra, Ghana in November 2015 and attended by the PIDM as well as the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program which is implemented by MSH, it was agreed that both WHO and SIAPS will work with PV experts including PVSF Consultants to come up with harmonised indicators.

This is because both indicators are very similar and countries will benefit from a harmonised system. This will also avoid duplication and redundancies.

### PV Methods

Several methods can be used to collect safety information in pharmacovigilance. In all national pharmacovigilance systems, *Spontaneous Reporting* forms the bedrock of the system despite its well-known limitation of under-reporting. It is relatively inexpensive and provides a life-time monitoring of all medicines in all patients in any healthcare system. There are other systems including active patient follow-up e.g. Cohort Event Monitoring (CEM). Detailed information of the various pharmacovigilance methods are available from the ICH website.

### Signal Identification General Approach

The identification of signals in the national pharmacovigilance centre's database, or another database, of adverse events or suspected adverse reactions requires careful review of individual reports and events. Careful, informed, routine, systematic and standardized clinical review of the Centre's reports with the recording and appropriate collation of good data provides the quickest and most satisfying way of identifying previously unsuspected adverse reactions. Following through the whole process from relationship assessment, to signal identification, to signal strengthening, to communicating the findings is essential.

### Crisis Management

Every day, somewhere in the world, there are crises in healthcare: serious or fatal unexpected adverse effects of drugs; allegations about damage from vaccines; outbreaks of infections in hospitals; the emergence of resistant strains of bacteria; the discovery of sub-standard drugs; evidence of failure to prevent harm to patients, and hundreds more.

No system of regulation, no hospital, public health programme, clinic, pharmaceutical company, Ministry, department or official is immune to the risk; crises will happen and usually when you least expect them.

### Organization, Resources and Society

### **WHO Headquarters**

A great deal of information is available here, including access to WHO publications.

[www.who.int/](http://www.who.int/)

### **EMP/QSM (the Pharmacovigilance “department” of WHO)**

<http://www.who.int/medicines/about/en/>

### **HIV Programme, WHO**

<http://www.who.int/hiv/aboutdept/en/>

### **Global Malaria Programme, WHO**

<http://www.who.int/malaria/en/>

### **Tuberculosis Programme, WHO**

[www.who.int/tb/en/](http://www.who.int/tb/en/)

[www.stoptb.org/](http://www.stoptb.org/)

### **Technical/Financial Assistance and Training Course Providers**

Several organisations are involved in providing technical assistance in pharmacovigilance to countries, donor organisations and the pharmaceutical industry. The list of these organisations is restricted to those whose activities are aimed primarily to providing technical assistance to governments, organisations and centres in resource-limited settings and excludes those whose activities are aimed solely at the pharmaceutical industry. They are divided into Collaborating Centres, Financing Entities, Technical Agencies, Academic/Research Institutions and Consultants though the distinctions may be arbitrary in that some financing entities may directly or indirectly also provide technical assistance.

### **Monitoring and Evaluation**

There is a need for a globally acceptable monitoring and evaluation format for pharmacovigilance including pharmacovigilance indicators to permit all stakeholders to be able to assess the capacity, functioning and progress of any pharmacovigilance system. The World Health Organization through its Advisory Committee on the Safety of Medicinal Products (ACSoMP) has been developing a new set of Pharmacovigilance Indicators as part of its normative work.

A comprehensive Indicator-based Pharmacovigilance Assessment Tool (IPAT) has been produced by the USAID-supported Strengthening Pharmaceutical Systems Programme implemented by Management Sciences for Health, USA.

## **4.0 Highlights for the year**

### **TSR Program**

A total of six training workshops were held under the TSR programme in 2016. Up to 210 healthcare professionals were trained on ADR reporting and completeness of the reports. The workshops were conducted in the following provinces, Manicaland, Masvingo, Midlands, Mashonaland East, Matebeleland South and Mashonaland Central. 2016 recorded the highest number of reports since the programme started. We thank everyone for reporting.

**KEEP ON WITH THE GOOD WORK!!!!!!**

### **2017 Trainings**

- **MCAZ will be conducting TSR trainings**
- **EPI/MCAZ AEFI data management trainings**

### **Stakeholders Meeting**

The annual stakeholders meeting was held on Monday 12<sup>th</sup> of December 2016. The Director General addressed various stakeholder members on the achievements MCAZ had achieved during the year.

### **AiBST Phase 1 Clinical Trial Unit**

The MCAZ attended the opening of the AiBST Phase 1 Clinical Trial Unit (CTU) at Chitungwiza General Hospital, the first of its kind in Zimbabwe. Novartis attended the ceremony, to accredit the CTU and hosted a week long training workshop on phase 1 clinical trials which was attended by officers from the Pharmacovigilance and Clinical Trials Unit. We congratulate AiBST on the achievement.

## Medical Research Council of Zimbabwe (MRCZ), Annual Health Research Forum 2016

The annual health research forum was held under the theme “**Promoting Health Research for Zimbabwe**”, as the MRCZ was providing an update on key matters regarding health research in Zimbabwe. MCAZ presented on regulatory updates in Clinical Trials and notified the forum that it was in the process of updating the Good Clinical Practice guidelines and development of systems that are efficient and reduce timelines for approval of clinical trial authorization application.

### EPI/MCAZ AEFI surveillance and case investigation trainings

Trainings on AEFI case investigation and surveillance were conducted in Mashonaland west, Masvingo, Midlands and Manica land.

The trainings were a follow up to recommendations from the November 2015 WHO training on the new AEFI causality assessment method. It had been recommended that AEFI surveillance guidelines should be revised and thereafter health care professional should be trained on AEFI case investigation and communication, as Zimbabwe had adopted the new causality assessment method.

### Inter-country study to assess the inter-rater reliability of the WHO AEFI causality assessment methodology and the utility of the new WHO AEFI causality assessment software.

In 2012, WHO developed a revised methodology for causality assessment of AEFI . The new method proposed by WHO uses a 4 step

#### UPDATES

- **Zimbabwe National Pharmacovigilance Policy and Guidelines Handbook, Second Edition, 2016**
- **Adverse Events Following Immunisation (AEFI) Surveillance Guidelines, 3<sup>rd</sup> Edition 2017**

process and allows the National Committees to review AEFI cases and guide the assessors on their causality. Recently electronic AEFI causality assessment software based on WHO methodology has been developed by WHO to assist the assessors in their evaluation of individual cases of AEFI

In this study, the reliability of the causality assessment classification using the methodology developed by WHO will be assessed by determining the agreement in final classification. Reliability assessment will be conducted within and between teams of assessors from 2 countries (India and Zimbabwe). The final results will be based on the overall proportion of cases with the same classification.

## Product Defects and Recalls

A product defect is any medicine, vaccine or medical device product that is not of the correct quality, safety or efficacy as defined by its Marketing Authorisation which may pose risk to the users. A product recall is a process of withdrawing or removing a medicine, vaccine and/or medical device product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/ or concerns that the product is or may be counterfeit. The recall might be initiated by the manufacturer, wholesale dealer, applicant or the MCAZ.

There are three classes of recall, class I, class II and class III.

### Class I recall

Occur when products are potentially life-threatening or could cause a serious risk to health, eg microbial contamination of sterile injection or ophthalmic product.

### Class II recall

Occur when product defects could cause illness or mistreatment, but are not Class I, eg non-compliance with specifications

### Class III recall

Occur when product defects may not pose a significant hazard to health ie low risk to health but recall may be initiated for other reasons, due to quality, safety or efficacy concern, eg wrong or missing batch number or expiry date.

HCPs and Prescribers are encouraged to continue to report any product defects they come across. The following product defects were reported in 2016:

<b>Name of Product &amp; Batch No.</b>	<b>Manufacturer</b>	<b>Nature of defect or Problem</b>	<b>Type/Class of Recall Done</b>
Clotrimazole (Canesten) 1% Cream Batch Nos. BXPJLCR and BXPJLXG	Kern Pharma S.L., Spain	1% benzyl alcohol was used instead of the 2% benzyl alcohol as the preservative.	Class II recall
Paracetamol 500mg Tablets Batch 5MI 119	Medopharm, India	Colour change and suspected contamination.	Class II recall
Enalapril (Rennimed 20) 20mg Tablets Batch 0516276	Plus Five Pharmaceuticals, Bulawayo	Colour change of the product to off white and pale yellow.	Class II recall
Amoxicillin 125mg/5ml Suspension. All batches	Medicamen Biotech	Failure of the closure of the bottle	Class III recall.
Paracetamol/Codeine Phosphate (Novadol Co) 500/8mg Tablets Batch 16025 & 16075, 16026 and 16076.	Pharmanova (Pvt) Ltd, Zimbabwe	Colour change from white to brown/black	Class III recall.
Paracetamol/Codeine Phosphate (Panadene) 500/8mg Tablets Batch 150207	Datlabs (Pty) Ltd, Zimbabwe	The white caplets had grey spots.	Class II recall.
Sulfamethoxazole/Trimethoprim (Cotrimoxazole BP) 400/80mg Tablets	SM Pharmaceuticals, Malaysia	Mould and growth on tablets.	Class II Recall

**Editorial**

Dear Reader

We would like to thank you for taking interest in reading our bulletin and your continued support in reporting ADRs and AEFIs to the MCAZ National Pharmacovigilance Centre. In the coming year, the MCAZ will identify and set up sentinel or regional Pharmacovigilance Centres country-wide from the TSR programme sites that report to the MCAZ National Pharmacovigilance Centre.

**If you are interested in having your clinic, hospital or surgery as a regional or sentinel Pharmacovigilance Centre please express your interest in writing to the MCAZ Director General.**

We cherish your reports and will continue the publication of the Drug Information bulletin as one of the ways of disseminating Drug Safety information to Healthcare professionals. Please note that the reporting of a seemingly insignificant or common adverse reaction or side effect may help pinpoint a more widespread adverse effect or prescribing problem. If you have questions on any area of concern, please write to us on Medicines Control Authority of Zimbabwe, 106 Baines Avenue, Harare or call us on 708255/792165.

Thank you for Reading

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Medicines Control Authority of Zimbabwe

