Zimbabwe National Pharmacovigilance Policy and Guidelines Handbook

November 2013

106 Baines avenue
P.O Box 10559
Harare
Zimbabwe

Phone: +263-4-708255/792165
Fax: +263-4-736980
Email: mcaz@mcaz.co.zw

website: www.mcaz.co.zw
ACKNOWLEDGEMENTS

The Medicines Control Authority of Zimbabwe wishes to acknowledge all stakeholders in pharmacovigilance, especially the Ministry of Health and Child Care and all inter-governmental agencies such as the World Health Organisation, UNICEF and Global Fund in supporting pharmacovigilance activities in Zimbabwe, including the formulation of the Zimbabwe National Pharmacovigilance Policy and Guidelines Handbook. Special recognition goes to the MCAZ Pharmacovigilance and Clinical Trials Division for spearheading and organizing the development process. Development of this document was made possible by financial support from UNICEF. The enthusiasm, commitment and experience of the editorial team was commendable. A special acknowledgement is extended to the MCAZ secretariat for their hard work and time dedicated to this document.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Data Analysis &amp; Management of ADR/SAEs/AEFI Reports And Causality Assessment of a suspected ADR</td>
<td>21</td>
</tr>
<tr>
<td>6.1 Causality Assessment of Suspected ADR, SAE and AEFI</td>
<td>23</td>
</tr>
<tr>
<td>6.2 Difficult to Categorize Events</td>
<td>23</td>
</tr>
<tr>
<td>6.3 Summary Descriptive Analysis of a Case Series</td>
<td>24</td>
</tr>
<tr>
<td>6.4 Safety Signals That May Warrant Further Investigation</td>
<td>25</td>
</tr>
<tr>
<td>6.5 Signal Detection</td>
<td>25</td>
</tr>
<tr>
<td>6.6 Medication Errors</td>
<td>27</td>
</tr>
<tr>
<td>7. Product Defects</td>
<td>30</td>
</tr>
<tr>
<td>7.1 Product Defect Reporting and Recall Procedures</td>
<td>30</td>
</tr>
<tr>
<td>8. Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit Medical Products (SSFFCs)</td>
<td>31</td>
</tr>
<tr>
<td>8.1 Reporting of Suspected cases of Substandard and counterfeit Medicines and Other Related Products</td>
<td>31</td>
</tr>
<tr>
<td>9. Guidelines for Reporting SAES for Clinical Trials in Zimbabwe</td>
<td>32</td>
</tr>
<tr>
<td>9.1 Responsibilities of Sponsors, Investigators, Applicants &amp; Clinical Sites</td>
<td>32</td>
</tr>
<tr>
<td>9.2 General Information on SAE Reporting of Clinical Trials in Zimbabwe</td>
<td>32</td>
</tr>
<tr>
<td>10. Guidelines for Reporting Suspected Adverse Drug Reaction, Serious Adverse Event (SAE) and or Adverse Event Following Immunization (AEFI) by the Pharmaceutical Industry and MAHs</td>
<td>33</td>
</tr>
<tr>
<td>10.1 Scope</td>
<td>33</td>
</tr>
<tr>
<td>10.2 Legal Basis</td>
<td>33</td>
</tr>
<tr>
<td>10.3 Periodic Safety Update Report (PSUR)</td>
<td>33</td>
</tr>
<tr>
<td>10.4 Periodic Benefit Risk Evaluation Reports (PBRERs)</td>
<td>33</td>
</tr>
<tr>
<td>10.5 Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan</td>
<td>34</td>
</tr>
<tr>
<td>11. Integration of Pharmacovigilance in Public Health Programmes</td>
<td>36</td>
</tr>
<tr>
<td>12. Pharmacovigilance Training and Pharmacovigilance Toolkit</td>
<td>38</td>
</tr>
<tr>
<td>13. Effective Communication in Pharmacovigilance</td>
<td>39</td>
</tr>
<tr>
<td>13.1 The ERICE Declaration on Effective Communication in Pharmacovigilance</td>
<td>39</td>
</tr>
<tr>
<td>14. Reporting of Adverse Events Following Immunisation (AEFIs)</td>
<td>41</td>
</tr>
<tr>
<td>14.1 Immunisation Schedule For Children Under Five Years</td>
<td>42</td>
</tr>
<tr>
<td>14.2 Vitamin A Supplementation</td>
<td>43</td>
</tr>
<tr>
<td>14.3 Basics of AEFIs</td>
<td>44</td>
</tr>
<tr>
<td>14.4 Objectives of AEFI Surveillance</td>
<td>44</td>
</tr>
<tr>
<td>14.5 Roles and Responsibilities at Various Levels</td>
<td>45</td>
</tr>
<tr>
<td>14.6 Steps for AEFI Investigation</td>
<td>47</td>
</tr>
<tr>
<td>14.7 Procedures of Determining and Recording of an AEFI</td>
<td>47</td>
</tr>
<tr>
<td>15. References</td>
<td>49</td>
</tr>
<tr>
<td>16. Glossary</td>
<td>51</td>
</tr>
<tr>
<td>17. Annexes</td>
<td>55</td>
</tr>
<tr>
<td>Annex</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Annex 1</td>
<td>ADR Reporting Form</td>
</tr>
<tr>
<td>Annex 2</td>
<td>Product Defect Form</td>
</tr>
<tr>
<td>Annex 3</td>
<td>MCAZ Recall Procedure</td>
</tr>
<tr>
<td>Annex 4</td>
<td>Serious Adverse Effects (SAE) Reporting Form</td>
</tr>
<tr>
<td>Annex 5</td>
<td>CIOMS Reporting Form</td>
</tr>
<tr>
<td>Annex 6</td>
<td>WHO Minimum Requirements for a National Pharmacovigilance Centre</td>
</tr>
<tr>
<td>Annex 7</td>
<td>Strengthening National Surveillance of Adverse Events Following Immunization</td>
</tr>
<tr>
<td>Annex 8</td>
<td>Safety Monitoring of H1N1 Vaccine</td>
</tr>
<tr>
<td>Annex 9</td>
<td>Cohort Event Monitoring Of Artemisinin Combination Therapies (ACTs) In Zimbabwe</td>
</tr>
<tr>
<td>Annex 10</td>
<td>Targeted Spontaneous Reporting (TSR) Program of Antiretrovirals (ARVs) and Anti-Tuberculosis (Anti-TBs) and all Essential Medicines in Zimbabwe</td>
</tr>
<tr>
<td>Annex 11</td>
<td>AEFI Reporting Form</td>
</tr>
<tr>
<td>Annex 12</td>
<td>WHO Causality Classification of Adverse Events (AE) definitions Categories use by MCAZ and ADR &amp;MR Committee</td>
</tr>
<tr>
<td>Annex 13</td>
<td>Table of Useful Guidelines</td>
</tr>
</tbody>
</table>
### ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Auto Disabled Syringe</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Events Following Immunization</td>
</tr>
<tr>
<td>AFP</td>
<td>Acute Flaccid Paralysis</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immuno Deficiency Syndrome</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacilli Calmette Guerin</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria Tetanus and Pertussis</td>
</tr>
<tr>
<td>DTP-HepB-Hib</td>
<td>Diphtheria, Tetanus, Pertussis, Hepatitis B and Haemophilus Influenzae</td>
</tr>
<tr>
<td>DT</td>
<td>Diphtheria Tetanus</td>
</tr>
<tr>
<td>EDLIZ</td>
<td>Essential Medicines List of Zimbabwe</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunisation</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barre Syndrome</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
</tr>
<tr>
<td>Hep B</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>HIB</td>
<td>Haemophilus Influenza Type B</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immuno-deficiency Virus</td>
</tr>
<tr>
<td>MCAZ</td>
<td>Medicines Control Authority of Zimbabwe</td>
</tr>
<tr>
<td>MCHIP</td>
<td>Maternal and Child Health Integrated Programme</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>NIDs</td>
<td>National Immunisation Days</td>
</tr>
<tr>
<td>NNT</td>
<td>Neonatal Tetanus</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral Polio Vaccine</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal Conjugate Vaccine</td>
</tr>
<tr>
<td>TT</td>
<td>Tetanus Toxoid</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
<tr>
<td>WCBA</td>
<td>Women of Child Bearing Age</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>ZEPI</td>
<td>Zimbabwe Expanded Programme on Immunisation</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

The thalidomide tragedy, which occurred from the late 1950's to the early 1960's, raised concerns regarding the safety of medicines and the potential dangers to public health associated with unexpected adverse reactions to medicines. In response, the Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) that reaffirmed the need for early action in regard to the rapid dissemination of information on adverse drug reactions. The World Health Organization (WHO), following the World Health Assembly Resolution (WHA 20.51 of 1967), established an international drug monitoring scheme initially with 10 member countries in 1968 to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. The initial activities of the pilot project culminated in the current WHO Programme for International Drug Monitoring Programme and has grown to become a global network of national pharmacovigilance centres in over 140 countries in 2013 (see www.who-umc.org).

Zimbabwe, through the Medicines Control Authority of Zimbabwe (MCAZ), became a participating country to the WHO International Drug Monitoring programme in 1998. The mandate of the MCAZ as a National Drug Regulatory Agency (NDRA) is to ensure that medicines that can be accessed by the public are safe, effective, and of good quality. The MCAZ also serves as the national pharmacovigilance centre. The operations of the centre are based on the WHO guidelines for setting up and running a national pharmacovigilance centre.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO). It aims at getting the best outcome from treatment with medicines. Good pharmacovigilance will identify the risks within the shortest possible time after the medicine has been marketed and will help to establish or identify risk factors for adverse drug reactions. When communicated effectively, this information allows for intelligent, evidence-based prescribing with the potential for preventing many ADRs. Such information will ultimately help each patient to receive optimum therapy at a lower cost to the health system. Adverse drug events (ADEs) from poor product quality, adverse drug reactions (ADRs), and medication errors contribute significantly to morbidity and mortality. Although most cases go undetected, particularly in developing countries, data from the US shows that ADEs are the fourth to sixth leading cause of death. ADEs constitute a huge cost to the health system, estimated in the US at $177.4 billion in 2000. Economic consequences of adverse events that are not frequently reported include the impact of adverse events on patient adherence to treatment, drug resistance, and treatment outcomes. Besides the economic consequences, cases of adverse events affect the credibility of the health system leading to loss of confidence.
The Zimbabwe National Pharmacovigilance Policy and Guidelines serve as a handbook for pharmacovigilance activities in the country. The pharmacovigilance activities are coordinated by the MCAZ in collaboration with the Ministry of Health and Child Care (MoHCC) and all key stakeholders both in the public and private health sector including the pharmaceutical industry. The guidelines also serve as a tool for providing an enabling environment for effective planning, implementation, monitoring and evaluation of the pharmacovigilance system by all key stakeholders. The guidelines address issues related to the systems and structures required for pre- and post-authorization monitoring of safety and effectiveness of medicines in Zimbabwe.

If successfully implemented, the pharmacovigilance system will lead to early detection of adverse reactions, interactions and other medicine-induced problems as well as the detection of previously unknown adverse reactions (signals). Furthermore, the system ensures communication of changes in risk/benefit balance to stakeholders with a view of promoting patient safety including rational and safe use of medicines, vaccines and complimentary medicines.
2. GUIDING PHILOSOPHY AND PRINCIPLES OF THE NATIONAL PHARMACOVIGILANCE POLICY AND GUIDELINES:

The policy and guidelines are based on the following guiding principles:

a. Good quality healthcare is assured through application of pharmacovigilance principles and practice in private and public healthcare systems at all levels in order to ensure patient safety.

b. Patients' access to safe and rational use of medicines.

c. Healthcare professionals are to consider pharmacovigilance practice as a professional responsibility.

d. Integration of pharmacovigilance into the overall health system both public and private.

e. Existence of consistent and effective partnerships and collaboration with all stakeholders.

f. Existence of financial commitment at all levels for sustained safety monitoring of medicines and other medicine related issues.

g. Use of current WHO and ICH guidelines for different types of methods of pharmacovigilance activities including causality assessment and pharmacovigilance training tools.

h. The National Pharmacovigilance Centre will work in close collaboration with the WHO International Drug Monitoring Programme including submitting ADRs, ICSRs and AEFIs to the Vigiflow database.

i. The National Pharmacovigilance Centre will collect patient ADRs in an ethical and confidential manner, analyse and communicate the information in a way that improves therapeutics and patient safety through the use of bulletins, alert notices and publications in international drug safety journals.

j. Inclusion of pharmacovigilance training curriculum and modules at academic institutions for both undergraduate and post graduate biomedical degrees, medicine, pharmacy, and nursing, physiotherapy and occupational health training programs using the WHO pharmacovigilance toolkit.

k. Recognition of national and international treatment guidelines.
3. FUNCTIONS OF THE ZIMBABWE NATIONAL PHARMACOVIGILANCE CENTRE

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 as follows:

a. To promote pharmacovigilance in the country, collect and manage ADR reports as well as reports of medication errors and suspected counterfeit/substandard drugs.

b. To collaborate and harmonize with other ADR collection activities within the country (e.g. national disease control programmes, poison control centres, etc.) and international ADR monitoring programmes.

c. To identify signals of drug safety such as unknown or poorly characterized adverse events in relation to a drug.

d. To undertake assessment of risk and options for risk management.

e. To identify if there are quality problems in medicines resulting in ADRs and more generally, support the identification of medicine quality issues.

f. To provide effective communication on aspects related to drug safety, including dispelling unfounded rumours of toxicity attributed to medicines and/or vaccines.

g. To apply information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines.

h. To encourage conduct of drug utilization studies.

i. To be an active participating member of the WHO International Drug Monitoring Programme WHO Collaborating Centres for Pharmacovigilance, the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden. The WHO headquarters is responsible for all policy issues relating to the WHO Drug Monitoring Programme whilst UMC focuses on technical issues and the day to day running of the WHO Programme.

j. Reporting ADRs, SAEs, AEFIs and Individual Case Safety Reports (ICSRs) to the WHO drug safety databases such as Vigiflow, Cemflow, Paniflow, Vigibase and Vigilyze and sharing of safety data for analysis and signal detection.
4. PHARMACOVIGILANCE 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). Brief highlights of the various pharmacovigilance methods are given below (adapted from the ICH E2E Guidelines. The full document can be downloaded from the ICH website using this link http://www.ich.org/products/guidelines/efficacy/efficacy- single/article/pharmacovigilance- planning.html

4.1 Spontaneous Reporting
Spontaneous reports are those adverse drug events/reactions that are voluntarily reported either to pharmaceutical manufacturers, to national or regional pharmacovigilance centers, or to national regulatory authorities by healthcare professionals, other professionals or consumers (ICH). Spontaneous reporting is sometimes referred to as passive reporting. A spontaneous report is an unsolicited communication by health-care professionals or consumers that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (WHO). It is designed to detect ADRs not previously observed in preclinical or clinical studies, to improve understanding of the potential risks, including reactions resulting from drug interactions or drug effects in particular populations, and to help provide a basis for effective drug regulation, education and consequent changes in practices by prescribers and consumers.

Spontaneous reporting is the most common method of surveillance worldwide. It has played a major role in the identification of safety signals throughout the marketed lifetime of medicines in general. It is the easiest system to establish and the cheapest to run. However, reporting is generally very low and subject to strong biases; and there is no database of all users or information on overall medicine utilization. These problems prevent the accurate assessment of risk and risk factors or making comparisons between medicines. A new term has been introduced that will replace “spontaneous reports”: this is individual case safety reports (ICSRs). ICSRs play a major role in the identification of signals of risk once a medicine is marketed. ICSRs can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs.

4.2 Case Series of Spontaneous Reports
Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events
known to be associated frequently with drug therapy, such as anaphylaxis, aplastic anaemia, toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore, when events such as these are spontaneously reported, it is important that pharmacovigilance centres place emphasis on these reports for detailed and rapid follow-up.

4.3 Stimulated Reporting
Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings), for new products or for limited time periods. Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed case definition. Although these methods have been shown to improve reporting, they are not devoid of the limitations of spontaneous reporting, especially selective reporting and incomplete information.

4.4 Targeted Spontaneous Reporting (TSR)
Targeted spontaneous reporting is a variant of spontaneous reporting. It focuses on detecting ADRs in a well-defined group of patients on treatment. Targeted spontaneous reporting (TSR) builds on the principles of both spontaneous reporting (described above) and cohort event monitoring (CEM, described below). Health professionals in charge of a well-defined group of patients would be sensitized to report specific safety concerns suspected to be medicine related. It provides a comprehensive monitoring method which is affordable, feasible and sustainable in settings with limited financial and human resources and promotes the role of pharmacovigilance as a best practice that improves quality of care. This focused approach has the same objectives and flow of information as spontaneous reporting. The reporting requires no active measures to look for particular syndromes.
TSR may be adapted either to measure all adverse reactions in the defined population or to focus only on specific reactions of particular concern. It is suitable for monitoring of patients on ARVs, anti-TBs and other essential medicines. The monitoring of ADRs can be integrated as a standard of care, to accompany the routine practice of monitoring success, death, default or failure of treatment within the cohort. One benefit of monitoring for safety within a treatment cohort is that the number and profiles of the exposed patients are known. To measure the burden of medicine-related problems accurately, recording and reporting of observed events needs to be as complete as possible.

4.5 Active Surveillance
Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is achieved by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records. It is best done prospectively. Active pharmacovigilance is sometimes very descriptively referred to as “hot pursuit”. The most comprehensive method is the cohort event monitoring (CEM). It is an adaptable and powerful method of getting good comprehensive data. Other methods of active monitoring include the use of registers, record linkage and screening of laboratory results in medical laboratories.
4.6 Cohort Event Monitoring
CEM is a prospective, observational, cohort study of adverse events associated with one or more medicines. An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment. CEM is sometimes referred to as prescription event monitoring (PEM), but this term is inappropriate when individual prescription with subsequent dispensing by pharmacists is not part of the process of supplying medicines to patients. In most resource-limited countries, the treatment of TB and other important diseases is not provided on a prescription basis. A CEM programme is essentially an observational study in normal clinical practice of a new medicine in the early post-marketing phase, but it can be used for older medicines. Its basic function is to act as an early warning system of problems with new medicines, although it will provide much more information.
CEM records all clinical events and not just suspected ADRs. It involves actively and systematically asking for reports of any and all events and provides a method that facilitates reporting. An event is any new clinical experience that occurs after commencing treatment with a medicine regardless of its severity or seriousness and without judgment on its causality. Favourable events may be recorded as an indication of an unexpected therapeutic effect.

4.7 Prescription Event Monitoring (PEM)
Prescription event monitoring is a method of active pharmacovigilance surveillance. In prescription event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events and reasons for discontinuation can be included in the questionnaire. Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals.
In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

4.8 Sentinel Sites
Active surveillance can also be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient sub-groups that would not be available in a spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs.
4.9 Registries
A patient registry is a list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry), a specific exposure (drug registry) and death (death registry). In each type of registry, information can be collected through a battery of standardised questionnaires in a prospective fashion.

4.10 Comparative Observational Studies
Traditional epidemiologic methods are a key component in the evaluation of adverse events. A number of observational study designs are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

4.11 Cross-Sectional Study
Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

4.12 Case-Control Study
In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups.

4.13 Cohort Study
In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated.
using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest or to study very rare outcomes.

### 4.14 Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

### 4.15 Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

### 4.16 Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

### 4.17 Drug Utilization Study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.
5. REPORTING OF ADVERSE DRUG REACTION /REPORTS BY HEALTHCARE PRACTITIONERS, PATIENTS AND CONSUMERS.

5.1 Reporters of Suspected Adverse Drug Reactions
All health care workers, including doctors, dentists, pharmacists, nurses, other health professionals and the patients are requested to report all suspected adverse reactions to drugs (including vaccines, X-ray contrast media, complementary medicines), especially when the reaction is unusual, potentially serious or clinically significant. It is vital to report an adverse drug reaction to the Medicines Control Authority of Zimbabwe pharmacovigilance programme even when all the facts are not available or there is uncertainty that the medicine definitely caused the reaction.

Adverse drug reaction reports do not constitute an admission that a health professional contributed to the event in any way. The outcome of the report, together with any important or relevant information relating to the reaction that has been reported, will be sent back to the reporter as appropriate. The details of the report will be stored in a confidential database. The name of the reporter or any other health professionals named on a report and the patient will be removed before any details about a specific adverse drug reaction are used or communicated to others. The information obtained from the report will not be used for commercial purposes. The information is only meant to improve understanding of the medicines used in Zimbabwe.

5.2 Reporting an ADR
5.2.1 Obtain Patient History and Do a Proper Examination

a. A full medicine and medical history should be done.
b. Determine if the adverse reaction can be explained by other causes e.g. patient's underlying disease, other medicine/s, over-the-counter medicines or complementary medicines; toxins or foods
c. The patient should be appropriately investigated to decide what the actual cause of any new medical problem is. A medicine-related cause should be considered, especially when other causes do not explain the patient's condition.
d. Few medicines produce distinctive physical signs. Exceptions include fixed medicine eruptions, steroid-induced dermal atrophy, acute extra pyramidal reactions
e. Lab tests are especially important if the medicine is considered essential in improving patient care or of the lab test results will improve management of the patient
f. Try to describe the reaction as clearly as possible and where possible provide an accurate diagnosis
5.2.2. Establish Time Relationships
   a. Some reactions occur immediately after being given a medicine while other reactions take time to develop.
   b. The time from the start of therapy to the time of onset of the suspected reaction must be logical.

5.2.3. Dechallenge and Rechallenge (when necessary)
   a. Resolution of suspected ADR when the medicine is withdrawn is a strong, although not conclusive, indication of medicine-induced disease.
   b. In cases where a withdrawal reaction is experienced, a rechallenge is when the medicine is again given to the patient. Rechallenge is only justifiable when the benefit of re-introducing the medicine to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases the reaction may be more severe on repeat exposure.
   c. “Positive” dechallenge is resolution of an ADR after withdrawing the medicine.

5.2.4 Check the Known Pharmacology of the Medicine.
   a. Is the reaction known to occur with the particular medicine as stated in the package insert or other reference?
   b. If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.

5.2.5 ADRs Reportable to the MCAZ
   a. All ADRs to newly marketed medicines or new medicines added to the Essential Medicines List
   b. All serious reactions and interactions
   c. ADRs which are not clearly stated in the package insert.
   d. Unusual or interesting adverse medicine reactions
   e. All adverse reactions or poisonings to traditional or herbal remedies

5.2.6 Reportable Product Quality Problems to MCAZ
   a. Suspected contamination
   b. Questionable stability
   c. Defective components
   d. Poor packaging or labeling
   e. Therapeutic failures
5.3 Characteristics of a Complete Case Report

Complete case reports include the following elements:

a. Description of the adverse events or disease experience, including time to onset of signs or symptoms;
b. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
c. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
d. Documentation of the diagnosis of the events, including methods used to make the diagnosis;
e. Clinical course of the event and patient outcomes (e.g., hospitalization or death);
f. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
g. Information about response to dechallenge and rechallenge; and
h. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, a complete case report also includes full descriptions of the following, when such information is available:

a. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);

b. Sequence of events leading up to the error;

c. Work environment in which the error occurred; and

d. Types of personnel involved with the error, type(s) of error, and contributing factors.

5.4 Prevention of ADRs

Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines that are described as follows:

a. Use few medicines, whenever possible

b. Use medicines that you know well

c. Do not change therapy from known medicines to unfamiliar one without good reasons.

d. Use text books and other reference material providing information on medicine reactions and interactions.

e. Take extra care when you prescribe medicines known to exhibit a large variety of interactions and adverse reactions (anticoagulants, hypoglycemic, and drug affecting the CNS) with careful monitoring of patients with such reactions.
f. Beware of the interaction of medicines with certain food stuffs, alcohol and even with household chemicals.
g. Review all the medicines being used by your patients regularly, taking special notice with those bought without prescription (over the counter, complementary).
h. Be particularly careful when prescribing to children, the elderly, pregnant and nursing women, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is also essential in these patients.
i. If the patient shows signs and/or symptoms not clearly explained by the course of their illness, think of adverse drug reaction.
j. If you suspect an adverse reaction, consider stopping the medicine or reduce the dosage as soon as possible and please report the adverse drug reaction to the Medicines Control Authority of Zimbabwe.

5.5 When to Report ADRs
An ADR reporting form (see Annex 1) should be completed as soon as possible after the reaction. It is better not to wait until final results and information such as hospital letters are received, because the report may be forgotten. These additional details can be sent to the MCAZ later.

5.6 Who Should Report
Reporters may be in the public or private health sector. They include physicians, pharmacists, and nurses. Other reporters include public health professionals, staff in medical laboratories and pathology departments, and pharmaceutical companies. Health and community workers (who are literate) should be encouraged to report, preferably to the clinician who prescribed the treatment, or directly to the MCAZ. Patients or patient representatives may also report.

5.7 Follow-Up
All reports of serious events should be followed up if details are incomplete. This may require the involvement of health professionals in a clinical setting who have been trained and appointed for this type of work. Occasionally follow-up information is required to fully assess reports of non-serious events. Follow-up requests should be kept to a minimum as they can discourage further reporting. Examples of follow-up information might be: essential missing details, information on the final outcome, the result of rechallenge, the results of laboratory tests, and post-mortem results from health facilities where autopsy is undertaken.

5.8 Feedback to Reporters
The pharmacovigilance centre will provide feedback to anyone who reports an ADR. Further feedback information will be provided to the reporter after causality assessment by the MCAZ PVCT Committee.
5.9 Patient and Consumer Reporting of ADRs, SAEs and AEFIs

Direct and spontaneous patient reporting offers added value for pharmacovigilance in that it can speed up the acquisition of knowledge about adverse effects. Patient reports are more direct and often more detailed and explicit than indirect reports through health professionals. Unlike reports from clinicians, they often describe how the adverse effects affect people’s lives. Spontaneous direct reporting also has important benefits beyond pharmacovigilance: the patient becomes an active participant instead of a largely passive recipient of treatment, and in the process learns how to manage one’s medicines and to communicate more effectively with health professionals. Lastly, public health estimates of disease burden in populations do not consider the effects on people’s everyday lives, and they should.

For these reasons direct patient and consumer reporting of ADRs, SAEs and/or AEFIs should be encouraged and routinely incorporated in pharmacovigilance activities. The WHO published a guideline which included patient reporting, the WHO Draft Guidelines for Adverse Event Reporting and Learning Systems (WHO, 2005).
6. DATA ANALYSIS & MANAGEMENT OF ADR/SAE/AEFI REPORTS AND THEIR CAUSALITY ASSESSMENT

Upon receipt of a completed ADR/SAE/AEFI form an MCAZ officer assigns an in-house report reference number on it and checks the information on the report form for completeness. The officer then requests for additional information or clarification from reporter when necessary and uploads the report into Vigiflow database.

The information on the suspected ADR/SAE/AEFI form is transferred to the MCAZ in-house report form and a case summary report is written which includes literature search and a recommendation of provisional causality.

The completed in-house report form is then tabled at the next Pharmacovigilance and Clinical Trials (PVCT) Committee meeting for expert causality assessment. During the PVCT Committee meeting, the Committee decision is endorsed on the MCAZ in house report from.

After the Committee meeting, the MCAZ secretariat then proceeds as decided by the Committee e.g. seek further information from ZEPI, inform other health care professionals of such adverse reaction if necessary as an alert notice or letter or article in the drug information bulletin. The MCAZ secretariat also writes acknowledgement and feedback letters to the reporter.
Assign in-house report reference number

Check information for completeness

Request for additional information or clarification from reporter and file report in ADR

Transfer the information on the suspected adverse drug reaction form or to the MCAZ in house report form.

The completed in-house report form should be tabled at the next Pharmacovigilance and clinical trials (PVCT) meeting for causality assessment.

During the PVCT committee meeting endorse the committee decision on the MCAZ in house report form

After the committee proceed as decided by the committee e.g seek further information from ZEPI, inform other health care professionals of such adverse reaction if necessary as an alert notice or letter or article in th drug information bulletin

Upload information into Vigiflow database including causality assessment outcome & case summary report into Vigiflow and commit report on second verification for data correctness
6.1 Causality Assessment of Suspected ADR, SAE and AEFI

6.1.1 The Bradford-Hill Criteria:
These are summarized below, with comments relating to pharmacovigilance.

a. **Strength**: A weak association does not mean that there is not causality but does weaken the case for common causality.

b. **Consistency**: Consistent findings observed by different persons in different places, with different samples, strengthen the likelihood of causality.

c. **Specificity**: Causality is more likely if the effect is observed in a very specific population at a specific geographic location and the disease has no other likely explanation.

d. **Temporality**: The effect has to occur after the cause and, if there is an expected delay between the cause and the effect, the effect must occur after that delay.

e. **Biological gradient**: A positive dose-response relationship strengthens the likelihood of a causal effect. With some interactions a negative dose response relationship may be suggestive.

f. **Plausibility**: A plausible mechanism between cause and effect is an indicator of causality, but not all drug-effect mechanisms are known.

g. **Coherence**: Evidence from clinical laboratory or clinical pathology increases the likelihood of causality, but the same issue applies as in point 6: such evidence may be unavailable.

h. **Experiment**: Other experimental evidence such as animal studies may be supportive.

i. **Analogy**: The effect of similar factors may be important, such as class effects of drugs.

6.2 Difficult to Categorize Events

6.2.2 Deaths
Relationships to death cannot be coded as probable or certain because there is no opportunity to see the effect of dechallenge or rechallenge. If there is a plausible time relationship and other causes can be excluded, a relationship to death should be coded as possible. If there is no plausible time to onset and other causes are evident, then the relationship should be coded as unlikely. If there is doubt, then they should be coded as unclassified and they can be reassessed as a group after an epidemiological analysis.

6.2.3 Developing a Case Series
MCAZ suggests that sponsors initially evaluate a signal generated from post-marketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as MCAZ's Adverse Drug Reporting System or AEFI's. As part of the case-level review, the FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as
necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

a. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
b. Absence of symptoms related to the event prior to exposure;
c. Evidence of positive de-challenge or positive re-challenge;
d. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
e. Consistency of the event with the known effects of other products in the class;
f. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and
g. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. MCAZ recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

MCAZ suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, MCAZ recommends that sponsors report all known contributing factors that led to the event.

6.3 Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, MCAZ recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

a. The clinical and laboratory manifestations and course of the event;
b. Demographic characteristics of patients with events (e.g., age, gender, race);
c. Exposure duration;
d. Time from initiation of product exposure to the adverse event;
e. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;

f. Use of concomitant medications;

g. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;

h. The route of administration (e.g., oral vs. parenteral);

I. Lot numbers, if available, for products used in patients with events; and

j. Changes in event reporting rate over calendar time or product life cycle

6.4 Safety Signals That May Warrant Further Investigation

It is not possible to characterize all events definitively because the actual risk to patients cannot be known and because there is invariably under-reporting of some extent and incomplete information about duration of therapy numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

a. New unlabeled adverse events, especially if serious;

b. An apparent increase in the severity of a labeled event;

c. Occurrence of serious events thought to be extremely rare in the general population;


e. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);

f. Confusion about a product's name, labeling, packaging, or use;

g. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);

h. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a Risk MAP goal) and

i. Other concerns identified by the sponsor or MCAZ.

6.5 Signal Detection

6.5.1 Signal Identification-General Approach

A signal is defined as “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously” (WHO definition).

Usually more than a single report is required. Alternatively, several similar events have been identified with a strong relationship to a medicine (“certain” or “probable”) and there does not seem to be good evidence anywhere of these events being recognized as a reaction. Events coded as “possible” can be used as supporting evidence. A group of unexpected deaths coded as “possible” forms an exception to this general rule and will need to be taken seriously. Occasionally a single event (certain or probable), notable for its severity, seriousness or distinctiveness, can be regarded as a signal. There may be one or two case-reports in the literature, but this is insufficient as validation and the signal needs to be strengthened.
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.

It is important to stress that new pharmacovigilance systems may have very few reports and may not be able to detect signals. It is therefore important for them to follow closely what is going on in other centres and also to rely on the WHO Pharmaceuticals Newsletter and UMC’s Signal document to keep abreast of signals that may be of importance to them. International collaboration is always key to both signal identification and signal strengthening and should be encouraged including use of the WHO Vigilyze and Vigibase databases.

The data in the report(s) need to be of good quality if a signal of a new ADR is to be considered. There should be sufficient data to fully assess the relationship of the drug to the event. Selecting only those reports with a certain or probable relationship ensures this. The strongest signals will have several reports with a certain or probable relationship. A signal may possibly be identified from one distinctive “certain” report. If there are no “certain” reports, at least three “probable” reports would be necessary for a signal. The first reports in a signal with a certain or “probable” relationship are called “index cases”. Cases coded as “unclassified” or “unassessable” should not be considered in the investigation of a signal.

The “unlikely” events should be scrutinized on a regular basis because they may contain hidden or unrecognized reactions. A cluster of similar events of significance may suggest an unexpected reaction that was not recognized at the time of clinical assessment. However, they should not be included in the assessment of a signal for which there are reports with certain, probable or possible relationships because differences could mask the characteristics of the signal being investigated.

6.5.1.2 Reviewing Other Experiences for Detection of Signals
Are there other similar reports in the database? Look for related clinical events for the suspected medicine and not simply a single event term. Also, look at related medicines in the same ATC classification grouping. Search the worldwide database of suspected adverse reactions of the WHO Collaborating Centre (UMC), available at: https://vigisearch.who-umc.org/. This search service requires login details from UMC (contact UMC at info@who-umc.org) The IC value for a drug–event combination can often be found in the combinations database provided to National Centres by UMC. If no reports can be found in VigiBase, ask for information held by other National Centres through the Vigimed e-mail network coordinated by UMC. Search the literature for similar reports, using search tools such as PubMed or Micromedex. Ask the pharmaceutical company if they have received similar reports and ask for details. Were similar
events identified in clinical trials? (Search the literature and/or ask the company for reports of clinical trials of the medicine)? Were similar events identified in preclinical studies? (Ask the pharmaceutical company.) Has this event, or have any similar events, been identified in post-marketing cohort event monitoring (prescription event monitoring or IMMP) studies?

6.5.2 Selection Criteria for Events to Investigate for Signal Detection.

   a. There are good data
   b. The event is clinically relevant
   c. There have been several reports of the event that show a credible and strong relationship with the drug (certain/possible)
   d. If validated, the event is of sufficient importance or interest to:
      - require regulatory action;
      - require advice to prescribers;
      - be of scientific importance

6.5.3 Methods of Signal Detection

The main methods of identifying signals are:

   a. Clinical assessment of individual events
   b. Clinical review of collated events
   c. Record linkage
   d. Automated signal detection.

Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. Caution should be exercised if using this tool for evaluating the magnitude of risk or for comparing safety risks between drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate between different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

6.6 Medication Errors

Medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.
Medication errors and drug-related adverse events have important implications – from increased length of hospitalization and costs to undue discomfort and disability or increased mortality. Thus minimizing of medication errors, through early detection and clinical audit, is of paramount importance in healthcare by promoting compliance, adherence, recovery and the general well being of patients.

6.6.1 Sources of Medication Errors
   a. Incomplete patient information
   b. Unavailable drug information (warnings)
   c. Miscommunication of medication order
   d. Confusion between drugs with similar names
   e. Lack of appropriate drug labeling
   f. Environmental conditions that distract health care providers
   g. Wrong diagnosis (inappropriate therapy)

6.6.2 Most Common Medication Errors
   a. Failure to adjust dosage in response to a change in hepatic/renal function
   b. History of allergy to the same or related medication
   c. Wrong drug name, dosage form or abbreviation on order
   d. Incorrect dosage calculation
   e. Atypical or unusual critical dosage consideration

6.6.3 Medication Error Monitoring and Reporting Program Features
   a. Evaluate the medication use process in collaboration with other health care professionals.
   b. Establish a process for identifying and tracking medication errors.
   c. Define categories of medication errors, e.g., prescribing, dispensing, administration, monitoring, compliance errors.
   d. Simplify process for documenting errors by developing a medication error reporting and evaluation form.
   e. Increase awareness of medication errors through education and the importance of reporting ALL medication errors, regardless of their suspected significance.
   f. Establish systems for detecting medication errors in the facility and pharmacy, e.g. med pass observation, random sampling, medication storage survey, etc.
   g. Involve health care practitioners, patients, and care givers in the medication error detection and reporting process.
   h. De-emphasize the focus on the punitive aspects to encourage medication error reporting and focus on the improvement of processes and systems.
   i. Respect the confidentiality of the patient, facility, and personnel involved with the medication error.
6.6.4 Role of the Pharmacist

6.6.4.1 Assessment
   a. Examine and evaluate causes of medication errors.
   b. Analyze aggregate data to determine trends, significance, frequency, and outcomes of medication errors.

6.6.4.2 Prevention Strategies
   a. Examine processes and develop interventions for reducing medication errors. Potential breakdown points are listed in Appendix A. Some examples of interventions are production changes, instituting bar coding, using different distribution systems, training personnel, standard prescription format, developing protocols for recording and transmission of prescription orders, and developing policies and procedures for proper storage and administration of medication.
   b. Establish goals and measurable standards.
   c. Monitor interventions and make necessary changes.

6.6.4.3 Reporting
   a. Communicate the results of the medication error program to healthcare practitioners, patients, and caregivers as appropriate.
   b. Promote reporting of medication errors to a national system for review and analysis, which will result in the development of recommendations to reduce and prevent medication errors and provide benchmarking data.
7. PRODUCT DEFECTS

7.1 Product Defect Reporting and Recall Procedures

The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization, including “Section 75” medicines, and do not place the patient at risk because of inadequate safety, quality or efficacy.

When products are suspected of being potentially harmful to users due to their defective quality, safety or efficacy, they may be subjected to a recall and all related information must be reported to the Pharmacovigilance and Clinical Trial Division at MCAZ.

Complaints must be handled positively and carefully reviewed, and corrective actions must be taken as necessary. This can mean amending a manufacturing process as well as implementing a recall of a defective product from all markets where it has been distributed. This is a very difficult area requiring professional judgement in coming to the correct decision. The company should have procedures to call into operation to decide whether a recall is required and how quickly it should be implemented.

A recall situation may result from customer complaint, detection of GMP failure after release, result from the ongoing stability testing, request by the national authorities, result of an inspection, known counterfeiting or tampering, adverse reaction reporting, or the result from the QC stability programme.

Please note that any person, MAH, health professional, applicant who comes across a product defect is required to complete a product defect form (Annex 2).

The classification and level of recall will depend on the potential hazard of the defective product and the extent of product distribution. These are determined after consultation between the applicant and MCAZ. For the approved recall procedure, please refer to the MCAZ recall procedure (Annex3).
Counterfeiting can apply to both branded and generic products; SSFFCs may include those with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging. Although the number of reported cases of SSFFCs – with their serious health repercussions, especially for the poor – continues to rise, the exact magnitude of the problem is unknown.

Counterfeiting relates to expensive hormones, steroids and anti cancer medicines, and pharmaceuticals related to lifestyle; in others, it may relate to inexpensive generic medicines. In developing countries, the most disturbing trend is the common availability of SSFFCs for the treatment of life-threatening conditions such as malaria, tuberculosis and HIV/AIDS. Experience has shown that vulnerable patient groups who pay for medicines out of their own pocket are often the most affected.

Counterfeiting is primarily motivated by its potentially huge profits. The success of counterfeiters is, at least in part, a function of their capacity both to adjust quickly to different contexts and products, and to change their focus of interest swiftly, according to where the most money can be made. Many factors facilitate the production or circulation of SSFFCs, including lack of equitable access to essential medicines; the presence of outlets for unregulated medicines; a lack of appropriate legislation; and weak penal sanctions.

The basic investigational elements of studies aimed at identifying the magnitude of the problem of counterfeiting in a national market are sound laboratory testing and verification of information available from national medicines regulatory authorities. Despite such measures, it is not always possible to trace the source of the problem. Close collaboration with the original manufacturers (which mostly use new technologies to identify their products unambiguously) and enforcement agencies (which use forensic means of analysis) has proved to be effective in tracing and fully identifying SSFFCs in recent years.

### 8.1 Reporting of Suspected Cases of Substandard and Counterfeit Medicines and Other Related Products

The MCAZ Licensing and Enforcement Division ensures good procurement practices and effective regulation of distribution chains, which closes opportunities for SSFFCs to enter the regular supply system.

MCAZ initiates programmes for the prevention and detection of export, import and smuggling of falsely-labelled, spurious, counterfeit or substandard pharmaceutical preparations.

Falsified medicines are more than simply substandard; combating falsified medicines is beyond the normal scope of regulatory control, as the manufacturer or distributor is usually difficult to trace. Combating falsified medicines is therefore a joint responsibility of the regulatory authority medical professional organizations, forensic investigation units, customs and other law enforcement agencies.
9. GUIDELINES FOR REPORTING SAEs FOR CLINICAL TRIALS IN ZIMBABWE

9.1 Responsibilities of Sponsors, Investigators, Applicants & Clinical Sites

In terms of Sections 23 and 24 of the Medicines and Allied Substances Control Act (Chapter 15:03), the applicant, sponsor and investigator of a clinical trial are responsible for proper reporting of Serious Adverse Events (SAEs) to MCAZ. The purpose of reporting SAEs is to ensure participant safety monitoring and to better understand the toxicity and safety of investigational products. Reporting and monitoring of SAEs is required to alert the MCAZ, sponsor, and clinical investigators of real and potential volunteer safety issues including safety information for the investigation product brochure. The MCAZ will carefully review the SAE Report and use this information to monitor the investigational product’s toxicity profile and volunteer safety.

Serious adverse events data provide the MCAZ and investigators with an early toxicity profile of an investigational product. The toxicity profile is an early warning system of potentially serious events that may occur with the use of an investigational product. This information might also be used during the application for registration of a new medicine review to determine if a product is safe for marketing. If a product is approved the safety information reported by the clinical sites during the clinical trial phase of product development will have contributed to the “adverse reaction” section of the Product Package Insert.

The MCAZ Serious Adverse Events (SAE) Form (Annex4) must be completed and submitted to MCAZ as soon as possible (within 24-48 hours) after the site becomes aware of an event. MCAZ may need to contact the clinical site for additional information regarding the SAE. MCAZ will maintain all SAE reports confidential on file and in a regulatory database and provide feedback to the reporter.

9.2 General Information on SAE Reporting of Clinical Trials in Zimbabwe

(Please refer to the Good Clinical Trial Practice Guidelines In Zimbabwe, GCP 2012, available on the MCAZ website www.mcaz.co.zw)
10. GUIDELINES FOR REPORTING SUSPECTED ADVERSE DRUG REACTION, SERIOUS ADVERSE EVENT (SAE) AND OR ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) BY THE PHARMACEUTICAL INDUSTRY AND MAHS

10.1 Scope
This guideline is intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with the use of registered medicines and in the management of safety data which arise during pre and post-marketing clinical trials.

For the purposes of this guideline, “Authority” refers to the Medicines Control Authority of Zimbabwe. The terms medicine and drug are used interchangeably. The definition of medicines in the Medicines and Allied Substances Control Act include medicines, vaccines and other biological products, complimentary medicines and investigational medicines for clinical trials including investigational new drugs (INDs).

10.2 Legal Basis
The MCAZ made a mandatory policy in an MCAZ dated 21st March 2000, circular 4/2000 Reference B/279/35/9/2000 requiring all MAHs to report suspected ADRs, SAEs and/or AEFI that occur in Zimbabwe only using the CIOMS reporting form for Pharmaceutical industry(See annex 5). MCAZ revised Statutory Instrument (SI) 150 of the Medicines and Allied Substance Control Act (Chapter 15:03) to include a mandatory requirement for MAHs to report suspected ADRs, SAEs and/or AEFI that occur in Zimbabwe using the CIOMs reporting form and Electronic E2B format. ADR and SAE reports that are compatible with the WHO Vigiflow database that MCAZ uploads the data for analysis and on the Vigibase and Vigilyze WHO databases for International Drug Monitoring Programme.

10.3 Periodic Safety Update Report (PSUR)
This is a periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined times post marketing authorization. PSUR to be submitted to the MCAZ as part of the new chemical entity application for registration, Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable. Routine PSURs should not be submitted to MCAZ unless the safety quality and effectiveness profile of the product has changed. The changes should be highlighted by the MAH to the MCAZ in writing including the appropriate regulatory action taken already by the country of origin or other countries, or to be taken.

10.4 Periodic Benefit Risk Evaluation Reports (PBRERs)
PBRERs to be submitted to the MCAZ as part of the new chemical entity application for registration, Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable.
PBRERs may however be required as justification for an application for a labeling amendment of Summary of product Characteristics (SPC) or package insert or a change of indication or a new safety alert or concern for the product or as supporting information for the application for registration of a dossier if necessary as per the CTD format requirements.

Routine PBRERs should not be submitted to MCAZ unless the safety quality and effectiveness profile of the product has changed. The changes should be highlighted by the MAH to the MCAZ in writing including the appropriate regulatory action taken already by the country of origin or other countries, or to be taken.

10.5 Beyond Routine Pharmacovigilance: Developing A Pharmacovigilance Plan

For most products, routine pharmacovigilance (i.e., compliance with applicable post market requirements) is sufficient for post-marketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information. The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. It is recommended that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

a. The likelihood that the adverse event represents a potential safety risk;
b. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
c. The severity of the event;
d. The nature of the population(s) at risk;
e. The range of patients for which the product is indicated (broad range or selected populations only); and
f. The method by which the product is dispensed (through pharmacies or performance linked systems only).

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (Risk MAP). Pharmacovigilance plans may be appropriate for products for which:

a. Serious safety risks have been identified pre- or post-approval, or
b. At-risk populations have not been adequately studied.

Sponsors may discuss with the Authority the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.
A pharmacovigilance plan could include one or more of the following elements:

a. Submission of specific serious adverse event reports in an expedited manner beyond
b. Routine required reporting (i.e., as 15-day reports);
c. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);
d. Active surveillance to identify adverse events that may or may not be reported through passive surveillance.
   Active surveillance can be
   - drug based: identifying adverse events in patients taking certain products,
   - setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or
   - event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure).

e. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs
f. Creation of registries or implementation of patient or health care provider surveys and
g. Additional controlled clinical trials.
11. INTEGRATION OF PHARMACOVIGILANCE IN PUBLIC HEALTH PROGRAMMES

The National Pharmacovigilance Centre was set up in 1994 by the MCAZ in collaboration with the University of Zimbabwe Medical School, Department of Pharmacy Drug and Toxicology Information Service (DaTIS) and the Ministry of Health and Child Care (MoHCC). The pharmacovigilance programme started with the system of spontaneous reporting as per the WHO minimum requirements (See Annex 6) for a National Pharmacovigilance Centre and then subsequently expanded to integrate pharmacovigilance in public health programmes. Since 2000 to date the Zimbabwe Expanded Programme on Immunization (ZEPI) - MoHCC joined the spontaneous reporting programme (see Annex 7) and also conducted targeted spontaneous reporting of H1NI vaccine in 2010 to 2011 in collaboration with the MCAZ. The TSR of H1N1 was sponsored by the WHO and data analyzed using the WHO Paniflow database (Annex 8).

The MCAZ in collaboration with the National Malaria Control Programme MoHCC conducted cohort event monitoring (CEM) of artemesinin combination therapies from 2008 to 2011 when Aretemether and Lumifantrine (Coarthermether) was introduced as the first line treatment for uncomplicated malaria after resistance to chloroquine. The study confirmed that Coarthermether was 96% effective in treatment of uncomplicated malaria and also showed a known adverse effect profile of the product as per product pack insert and summary of product characteristics labeling (See Annex 9). The Global Fund Round 5 sponsored the CEM of ACTs program. The results were presented at the 34th Annual Meeting of Representatives of the Pharmacovigilance National Centres Participating in the WHO Programme for International Drug Monitoring held in Dubrovinic, Croatia in November 2011. Results were also published in the MCAZ drug Information Bulletin December 2012. Following an invitation in October 2012 by the Secretary for Health and Child Care to strengthen pharmacovigilance of antiretroviral and anti-tuberculosis, the MCAZ is currently conducting a program of Targeted Spontaneous Reporting (TSR) of Anti-retrovirals and Anti-tuberculosis medicines in collaboration with the MoHCC, AIDS and TB Unit, and Directorate of Pharmacy Services.

The pilot phase was conducted from October 2012 to September 2013 in seven provinces of Zimbabwe and indicated that the method was feasible and successful and resulted in scale up to the main phase from October 2013 to 2015. The results of the pilot phase of TSR of anti-retrovirals and anti-tuberculosis medicines were presented at the 6th PVSF WHO-USAID meeting held in November 2013 in Accra, Ghana and at the First African Society of Pharmacovigilance held in December 2013 in Rabat, Morocco (See Annex 10) The TSR of anti-retrovirals and anti-tuberculosis was sponsored by the UNICEF, Health Trust Fund and Global Fund Round 8. Results of the Pilot phase of TSR of anti-retrovirals and anti-tuberculosis were also published in the MCAZ Drug Information bulletin and Drug Safety journal. These two active methods of pharmacovigilance have assisted greatly in the integration of pharmacovigilance in public health Programmes as per the WHO guidelines.
Regional or sentinels sites of pharmacovigilance are also being identified and set up countrywide for sustainable public health pharmacovigilance programs including use of Hospital Medicine Therapeutics Committees (HMTC) being established countrywide by the MoHCC since 2012. Zimbabwe's successful participation in the pharmacovigilance medicine safety initiatives in Africa was acknowledged when Zimbabwe hosted the 5th World Health Organization/USAID African Pharmacovigilance Consultants Meeting in Harare from 21st – 24th August 2012. The meeting was cosponsored by WHO and USAIDs and attended by Pharmacovigilance consultants from WHO, USAID and 15 African countries. The meeting recommended that for pharmacovigilance activities to continue to be successful in African countries, there was need for the countries through their national pharmacovigilance centres to improve the following:

a. **Collaboration with public health programmes.** There is increasing recognition that vertical programmes also need horizontal health systems for issues that are common to all disease programmes, including medicines safety. Disease control initiatives involving the administration of medicines to large communities need to be implemented with good knowledge of safety profile of the medicines and how these medicines could interact with each other. Pharmacovigilance should be a priority for every country with a public health disease control programme.

b. **Coordination and partnerships at country level.** The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the field of pharmacovigilance. Sustained commitment to such collaboration is vital for countries to meet the continually increasing demands and expectations of the public.

c. **Capacity building:** The third and possibly most important challenge was that new medicines are being introduced in a very rapid fashion into settings that have very little capacity to monitor the safety and safe use of these medicines. Not only is there need to build capacity in pharmacovigilance in these settings, but there is also need to explore ways in which capacity could be shared in the region.

d. **Submission of Individual Case Safety Reports (ICSRs) or ADRs to the WHO International Drug Monitoring Programme** Of note of concern was that African countries only contributed about 2% to this data of 8 million ICSRs reports and that there was need for all African countries to improve their pharmacovigilance systems and frequency of reporting (ICSRs) to the WHO Monitoring programme.
The safety of patients and the safe use of medicines are high priorities in the modern world. They are critical for the best health policy development and delivery of the best healthcare. They affect not only the welfare of patients but also the effective prevention and control of all kinds of diseases and the reduction of suffering and costs associated with them.

The 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 practiced. 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. This current toolkit is one example of this work. 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. The National Pharmacovigilance centre is to work closely with the academic institutions such as universities medical school, school pharmacy, biomedical sciences and school of nursing training programs in implementing relevant modules of pharmacovigilance trainings for all levels of education especially from high school upwards.
13. EFFECTIVE COMMUNICATION IN PHARMACOVIGILANCE

13.1 The ERICE Declaration on Effective Communication in Pharmacovigilance

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24-27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and International health organisations from 30 countries of the world.

Monitoring, evaluation and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties – consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organisations – working together. High scientific ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety and data may be hidden, withheld or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements a) - e) set forth the basic requirements for this to happen, and were agreed upon by all participants from 30 countries at Erice:

a. Drug safety information must save the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

b. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large as well as for the patients and health care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

c. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognised and overcome.
d. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and also made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

e. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

Health studies and reports are done to improve the quality, effectiveness and safety of healthcare in a country. Reports generated through pharmacovigilance plan/studies, provide evidence-based information for healthcare practitioners, policy makers and ultimately to patients, with the ultimate goal of providing quality, safe and efficacious medicines and care to patients. Findings from these studies/reports need to be communicated and disseminated effectively to influence optimal and timely practice and healthcare policies. Clear communication and active dissemination of evidence based information to all relevant audiences in easy-to-understand formats are critical to increasing awareness, consideration, adoption and use of evidence based information. Strategies for information dissemination include media coverage, press release, research summary document, flyers, posters, brochures, research briefs, policy briefs, study newsletters, community agency publications and websites, local events, seminars, conferences, community meetings and letter of thanks to study patients, amongst others.

The safety of patients worldwide is served by dedicated professionals doing their work well, but that work will never reach its considerable potential without excellent supporting communications. Excellent communications require a degree of expertise, creativity and skill which not all officials and scientists have as a matter of course. In every organization there is likely to be someone with a communications gift: look for them and use them if you can; otherwise put communications on your regular agenda as a high priority and give the activity of communicating as much attention as the content of what you wish to communicate. Failure to pay attention to the complexity and demands of effective communication lies at the heart of many of the most serious failures throughout health-care and regulation.
14. REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNISATION (AEFIs)

Immunization is a successful and cost-effective public health intervention that led to global eradication of diseases like smallpox and poliomyelitis in large areas of the world. It is estimated that immunization averts an estimated 2 to 3 million deaths from diphtheria, tetanus, pertussis (whooping cough), and measles every year in all age groups. Zimbabwe attained Universal Child Immunization in 1990 with considerable reduction in morbidity and mortality from vaccine preventable diseases and longer inter-epidemic periods of measles up to 2008. As Zimbabwe continues to adopt WHO recommended vaccination strategies in its population, it is becoming imperative that surveillance of AEFI be increased. The vaccine products and equipment used in immunization undergo intensive World Health Organization prequalification exercises to determine quality and approve their uses in countries. These precautionary measures do not necessarily eliminate the risk of adverse events that may arise from the use of products for immunization. Previous experiences have shown that determining causality of an event to a vaccine is a challenge that requires engagement of expert opinion and thorough investigation of the event. Events that occur after vaccinations are called Adverse Events Following Immunization (AEFIs); defined as a medical incident that takes place after immunization, cause concern and is believed to be caused by the immunization. Zimbabwe documented 80 AEFI cases in 2010, 14 in 2011, and 76 cases in 2012, most of which were known reactions. Documentation of AEFI cases is an essential part of their management when they occur in children to augment other safety precautions that will have been taken.

The safety of immunization programmes involves a wide spectrum of activities that include regulation, vaccine safety and quality, safe injections, waste disposals, and AEFI surveillance. Effective vaccines (i.e. vaccines inducing protective immunity) may produce some undesirable side effects which are mostly mild and clear up quickly. The majority of events thought to be related to the administration of a vaccine are actually not due to the vaccine itself - many are simply coincidental events or programmatic errors. It is not possible to predict every individual who might have a mild or serious reaction to a vaccine, although there are a few contraindications to some vaccines. Adherence to contraindications minimises the risk of serious adverse events. During mass immunization campaigns there usually is a general increase in adverse events following immunization. This can be attributed to two factors; the large number of vaccinations performed in a short period of time (from a few days to a few weeks) causes a temporary concentration of adverse events following immunization, and the pressure during the campaigns on vaccination teams means they may fail to observe safe injection practices. Public misconceptions may arise due to occurrence of AEFIs, and these may cause collective fear of vaccination. It is against this background that standardization and surveillance of adverse events following immunization is critical to enhance effective management of AEFIs. This document is a guide for health workers in the management of Adverse Events Following Immunisation (AEFIs), can be adapted to suit each level of health care, and is meant to cover issues of vaccine safety and quality, as well as communication of these events for management.
14.1 Immunisation Schedule For Children Under Five Years

Table 1: National Immunisation Schedule In Zimbabwe For Children Under Five Years as of November 2013

<table>
<thead>
<tr>
<th>Name of Vaccine</th>
<th>Age of administration</th>
<th>Route</th>
<th>Site</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>At birth or first contact before one year</td>
<td>Intradermal</td>
<td>Insertion of right deltoid muscle</td>
<td>0.05 ml</td>
</tr>
<tr>
<td>OPV1</td>
<td>6 weeks</td>
<td>Oral</td>
<td>Oral</td>
<td>2-3 drops</td>
</tr>
<tr>
<td>DTP-HepB-Hib1(Pentavalent)</td>
<td>6 weeks</td>
<td>Intramuscular</td>
<td>Right antero lateral aspect of mid-thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>PCV 1</td>
<td>6 weeks</td>
<td>Intramuscular</td>
<td>Left antero lateral aspect of mid - thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Rotavirus 1</td>
<td>6 weeks</td>
<td>Oral</td>
<td>Oral</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>OPV2</td>
<td>10 weeks</td>
<td>Oral</td>
<td>Oral</td>
<td>2-3 drops</td>
</tr>
<tr>
<td>DTP-HepB-Hib2(Pentavalent)</td>
<td>10 weeks</td>
<td>Intramuscular</td>
<td>Right antero lateral aspect of mid-thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>PCV 2</td>
<td>10 weeks</td>
<td>Intramuscular</td>
<td>Left antero lateral aspect of mid - thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Rotavirus 2</td>
<td>10 weeks</td>
<td>Oral</td>
<td>Oral</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>OPV3</td>
<td>14 weeks</td>
<td>Oral</td>
<td>Oral</td>
<td>2-3 drops</td>
</tr>
<tr>
<td>DTP-HepB-Hib3(Pentavalent)</td>
<td>14 weeks</td>
<td>Intramuscular</td>
<td>Right antero lateral aspect of mid-thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>PCV 3</td>
<td>14 weeks</td>
<td>Intramuscular</td>
<td>Left antero lateral aspect of mid - thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Measles</td>
<td>9 months</td>
<td>Subcutaneous</td>
<td>Left deltoid muscle</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>DTP Booster</td>
<td>18 months</td>
<td>Intramuscular</td>
<td>Antero lateral aspect of mid - thigh</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>OPV Booster</td>
<td>18 months</td>
<td>Oral</td>
<td>Oral</td>
<td>2-3 drops</td>
</tr>
</tbody>
</table>

Minimum ages for each antigen are given. Children should receive first doses at these stated ages or at first contact after reaching that age. Maximum age limits are: BCG 11 months, Rotavirus 32 weeks and Pentavalent 23 months (these antigens **should not** be given after these age limits).
14.2 Vitamin A Supplementation

Vitamin A supplementation has been integrated in the routine immunization since 2005. Any contact with a health worker is an opportunity to screen mothers and children for eligibility to receive Vitamin A supplementation. The optimal interval between doses for children is 6 months in Zimbabwe.

Table 2: Vitamin A Supplementation Schedule

<table>
<thead>
<tr>
<th>Target for Vitamin A</th>
<th>Immunisation Contact</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 6 – 11 months</td>
<td>Routine immunization/measles/polio NIDs/Campaigns</td>
<td>Oral</td>
<td>100 000 IU</td>
</tr>
<tr>
<td>Children 12 – 59 months</td>
<td>Routine immunization/measles/polio NIDs/Campaigns</td>
<td>Oral</td>
<td>200 000 IU</td>
</tr>
<tr>
<td>Lactating mothers</td>
<td>Within 4 weeks of delivery</td>
<td>Oral</td>
<td>200 000 IU</td>
</tr>
</tbody>
</table>
14.3 Basics of AEFIs

14.3.1 Definition
An Adverse Event Following Immunization (AEFI) is a medical incident that takes place after an immunization within 28 days, causes concern and is believed to be caused by an immunization. (WHO Aide Memoire: AEFI investigation 2004).

14.3.2 Types of AEFIs

14.3.2.1 Programme Error - An event caused by an error in the transportation, storage, handling, or administration of a vaccine. The errors may include the following:
   a. Injection Site Abscess
   b. Toxic Shock
   c. Ignored true contraindication

14.3.2.2 Coincidental – An event that occurs after immunisation that is not caused by the vaccine. This is due to chance or temporal association. Examples include:
   a. Seizures
   b. Meningitis
   c. Encephalopathy
   d. Encephalitis

14.3.2.3 Vaccine Related – It is an event caused by or precipitated by the active component or one of the other components of vaccine (e.g. adjuvant, preservative and stabilizer). This is due to the inherent properties of the vaccine. Examples include:
   a. Anaphylaxis
   b. Fever
   c. Severe Local Reaction
   d. Acute Flaccid Paralysis
   e. BCG Lymphadenitis
   f. Anaphylactic Shock
   g. Persistent Crying

14.3.2.4 Unknown – The cause of the event cannot be determined.

14.4 Objectives of AEFI Surveillance
   a. To ensure client safety
   b. To detect, investigate and report AEFIs
   c. To analyse AEFI reports and take corrective action
   d. To minimize AEFIs in routine immunization and mass campaigns
14.5 Roles And Responsibilities At Various Levels

14.5.1 Community
   a. Identification of AEFIs
   b. Reporting to nearest health worker/health centre

14.5.2 Service Delivery Level (hospitals/clinics - public and private)
   a. Identification and/or detection of AEFIs
   b. Management of AEFIs
   c. Reassure the care giver
   d. Investigation of AEFIs
   e. Completion of AEFIs forms (See annex 11)
   f. Notify district of any cases of AEFIs (NB. Use fastest means of communication in case of serious or fatal AEFIs)
   g. All fatal cases to be reported to the police for a post mortem
   h. Refer serious cases to district hospital with well completed investigation forms
   i. Keep the respective vaccine vial (clearly labeled) under cold chain in cases of severe reaction until investigations are complete
   j. In case of clustering of AEFIs (more than one case) from one batch number of vaccines, stop using that batch and report immediately
   k. Maintain line list of AEFIs
   l. Avoid answering to the media. Refer all questions to the DMO
   m. Write report and follow up
   n. Ensure all fields are completed

14.5.3 District Level
   a. Ensure all staff are trained on AEFI surveillance
   b. Provide AEFI SOPs to all facilities and ensure adherence
   c. Investigation of all AEFI cases
   d. Classify all the AEFIs
   e. Correct programme errors through on job training
   f. Facilitate management of cases
   g. Complete AEFI investigation summary
   h. Notify province of any cases of AEFIs (NB. Use fastest means of communication in case of serious or fatal AEFIs)
   i. Maintain district line list
   j. Ensure post mortems are done for deaths and reports are submitted timeously to next level
   k. Avoid answering to the media. Refer all questions to the DMO
14.5.4 Provincial Level

a. Contact National level focal person for severe and fatal AEFIs
b. Maintain provincial line list of AEFIs
c. Investigate or support investigation of serious AEFIs
d. Conduct regular supportive visits to districts
e. Ensure training of staff and provide resources for system
f. Ensure all reports are submitted to national level in duplicate
g. Reconcile provincial and national surveillance databases on a quarterly basis
h. Avoid answering to the media. Refer all questions to the PMD

14.5.5 National Level

a. Receive and review AEFI case reports from sub-national levels
b. Conduct investigations when necessary
c. Share all investigation forms and reports with Medicines Control Authority of Zimbabwe (MCAZ)
d. Give regular feedback to lower level and MCAZ
e. Ensure SOPs are compliant to requirements at all times
f. Provide training to all focal persons
g. Provide national guidelines on all vaccine management and surveillance issues
h. Avoid answering to the media. Refer all questions to the PRO

14.5.6 Medicines Control Authority of Zimbabwe

a. On receipt of a completed AEFIs form assign an in house report reference number.
b. Check information on the report form for completeness and clarity.
c. Request for any additional information or clarification from ZEPI where necessary and file the report form in the current AEFIs reports file.
d. Transfer the information from the AEFI form to the MCAZ in-house report form.
e. The completed in-house report form should be tabled at the next Pharmacovigilance and Clinical Trials (PVCT) Committee meeting for causality assessment. (See Annex 12)
f. During the PVCT Committee meeting endorse on the MCAZ in house report form the Committee decision.
g. After the Committee meeting proceed as decided by the Committee e.g. seek further information from ZEPI, inform other health care professionals of such AEFIs if necessary as an alert notice, letter or article in the drug information bulletin.
h. Code report and compute details into the Adverse Drug Reaction (ADR) Vigiflow database as per the SOP.
i. Complete the acknowledgement of receipt of report letter and send to ZEPI together with additional report forms.
14.6 Steps for AEFI Investigation
   a. Receive the report, conduct a quick assessment and inform the next level
   b. Take full socio-medical history
   c. Review available records which the patient might have brought and check any history of
      previous medication given
   d. Find out if the child had similar episodes prior to immunisation or any history of allergies,
      injury or any rituals done
   e. In case of an abscess refer the child to the next level for probable laboratory tests, incision
      and drainage
   f. Find out from care giver if anyone in the community had the same problem after being
      vaccinated
   g. Notify the next level and refer patient to next level when necessary
   h. Compile an incident report of what transpired and submit to the next level with copy of
      the completed AEFI forms
   i. After results are out dispel myths and misconceptions.
   j. In case of a suspected AEFI death offer bereavement counseling and inform the police
   k. Request for post mortem and parents to consent
   l. Avoid answering to the media. Refer all questions to the DMO/PMD/PRO.
   m. Have a fully equipped emergency tray
   n. Check the cold chain equipment and temperature records
   o. Keep the used vials under cold chain for investigation

14.7 Procedures of Determining and Recording an AEFI
14.7.1 History Taking
History taking should include the following:
   a. Vaccination history
   b. Chronic illnesses
   c. Acute infections
   d. Medications given before and after vaccination
   e. Allergies
   f. Feeding practices
   g. Growth and development of child
   h. Previous reactions to medicines
   i. Exposure to HIV

14.7.2 Examination
   a. Resuscitate the child and conduct a head to toe examination
   b. Note any abnormalities
   c. Take and record the child's temperature
   d. Confirm type of AEFI e.g. abscess and document findings
e. Counsel and reassure the care giver
f. Explain procedure to be followed and manage child appropriately

14.7.3 Completion of AEFI Forms
a. Fill in five (5) AEFI forms
b. Ensure complete documentation
c. Sign the forms
d. Date stamp all the AEFI forms
e. File 1 copy at clinic
f. Submit 4 copies to DNO for onward submission to Provincial/Chief Nursing Officer and then 2 copies to EPI Unit in MOH&CC Head Office

14.7.2 Communication
a. In case of fatal or severe AEFI use the fastest means of communication to inform the next level
b. The communication should follow the normal channel: District, Provincial and EPI Head office
c. Submit a comprehensive report and attach the AEFI forms

14.7.3 Investigation
Every case of AEFI should be investigated by a team and reported. The following should be checked:
   a. Cold chain maintenance
   b. Immunization technique
   c. Vaccine given
   d. Documentation practices
   e. Emergency tray
   f. Sharps disposal

14.7.6 Composition of Investigating Team
The investigation team to include:
   a. Programme Manager
   b. Health Promotion Officer
   c. Pharmacist
   d. Surveillance Officer
   e. Logistician
   f. Health Information Officer

Surveillance of AEFI is important in order to take corrective action and preserve public confidence in EPI.
15. REFERENCES

3. WHO. WHO’s role in the prevention and control of medical products of compromised quality, safety and efficacy such as substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Working group of member states on substandard /spurious /falsely-labelled /falsified /counterfeit medical products. Provisional agenda item 5 A/SSFFC/WG/3 Rev.1 17 February 2011
4. The World Medicines Situation-Pharmacovigilance and Safety of Medicines. WHO 2011
   http://apps.who.int/medicinedocs/en/d/Jh2992e/ # Jh2992e
   http://apps.who.int/medicinedocs/en/d/Js4893e/ # Js4893e
16. GLOSSARY

The definitions given below apply to the terms used in this policy. They may have different meanings in other contexts.

**Adverse Event:** Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

**Adverse Drug Reaction (ADR):** A response to a medicine which is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

**Applicant:** The person by, or on whose behalf, an application for registration is made.

**Causal Relationship:** A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance; a medicine causing an adverse reaction.

**Causality Assessment:** The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction.

**Cohort Event Monitoring (CEM):** A prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time.

**Counterfeit Medicine:** Medicines that are deliberately and fraudulently mislabeled with respect to identity and/or source.

**Data Mining:** A general term for computerized extraction of potentially interesting patterns from large data sets, often based on statistical algorithms.

**Dechallenge:** The withdrawal of a drug from a patient; the point at which the continuation, reduction or disappearance of adverse effects may be observed.

**Diary (patient):** A dated record of health events recorded by the patient.

**Event Dictionary:** A standard listing of terms which describe health events for use in event monitoring.

**Excipients:** All materials included to make a pharmaceutical formulation (e.g. a tablet) except the active drug substance(s).

**Health Practitioner:** Any person in respect of whose profession or calling a register is kept in terms of the Health Professions Act.

**Incident:** A health event which is believed to be incidental to the taking of a particular medicine.

**Index Case:** One of the first good descriptions of a specific adverse reaction to a medicine.
**Individual Case Safety Report (ICSR):** A report that contains information describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patient.

**Information Component (IC):** A measure of the disproportionality in the reporting of a medicine–ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected.

**Marketing Authorization Holders (MAHs):** The holder (an applicant, principal, individual, institute, manufacturer, company, importer, distributor, development partner/donor agency) of a marketing authorization to market a medicinal product. For the purpose of this policy document, the MAH's will have full responsibility and liability for their product on the market and full responsibility for ensuring that appropriate action can be taken when necessary as per the Medicines and Allied Substances Control Act (MASCA) Chapter 15:03and regulations. Medicines and vaccines distributed in Zimbabwe under section 75 provision of MASCA Chapter 15:03 including donated medicines, vaccines, and complementary medicines are subject to complying with pharmacovigilance requirements in Zimbabwe.

**Medical Dictionary for Regulatory Activities (MedDRA):** Medical terminology developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with an emphasis on ease of use for data entry, retrieval, analysis and display.

**Medication Error:** An error which occurs during the prescribing, dispensing and/or use of a medication.

**Medicine:** Any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in the diagnosis, treatment, mitigation or prevention of disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or restoring, correcting or modifying any physical, mental or organic function in man or in animals.

**Medicines Control Authority of Zimbabwe (MCAZ):** A statutory body established by an act of Parliament, The Medicines and Allied Substances Control Act (MASCA) [Chapter 15.03]. MCAZ is responsible for protecting public and animal health by ensuring that accessible medicines and allied substances and medical devices are safe, effective and of good quality through enforcement of adherence to standards by manufacturers and distributors.

**National Pharmacovigilance Centre (NPVC):** It is a centre of expertise for the art and science of monitoring and analysis of ADRs, and in use of the information analysed for the benefit of patients. The centre may function within the regulatory authority, a hospital, an academic institution or as an independent facility such as a trust or foundation.
**Periodic Safety Update Report (PSUR):** A periodic report produced by an applicant intended to provide an update of a worldwide safety experience of a medicinal product to the competent authorities at defined times post marketing authorization. applicable. PSUR to be submitted to the MCAZ as part of the new chemical entity application for registration Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable.

**Periodic Benefit Risk Evaluation Reports (PBRERs):** PBRERs are to be submitted to the MCAZ as part of the new chemical entity application for registration Common Technical Document (CTD) pharmacovigilance plan for the product in line with its risk management plan where applicable.

**Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem.

**Post-Marketing Surveillance (PMS):** The practice of monitoring safety and effectiveness of pharmaceutical products or other consumable medical products after it has been released on the market with the objectives to decrease mortality and morbidity associated with adverse events and improving understanding of effectiveness in real-world situations.

**Re-Challenge:** To try a therapeutic pharmaceutical drug, suspected allergen, or medical treatment on a patient a second or subsequent time, to see if the suspected effects of the treatment occur again. This is typically performed to confirm allergic or adverse reactions to allergens or medications, but may also be used to confirm beneficial treatments or to retry a probable beneficial treatment which did not appear to be effective previously.

**Reporter:** Any person, patient or healthcare professional or institute who describes a suspected adverse effect on an ADR or ICSR form for submission to the National Pharmacovigilance Centre or any other relevant organisation for further consideration.

**Section 75 Medicines:** refers to exemptions which may apply to certain medicines, in line as stated in Section 75 of Medicines and Allied Substances Control Act [Chapter 15:03]. Such medicines require authorization for importation from the MCAZ.

**Serious Adverse Event:** A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is life-threatening.

**Side Effect:** Any unintended effect of a medicine occurring at normal dosage which is related to the pharmacological properties of the medicine.

**Signal:** Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.
**Spontaneous Reporting:** Unsolicited communication by healthcare professionals or consumers that describes one or more suspected adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

**Targeted Spontaneous Reporting (TSR):** A method that monitors and records all or a specific set of safety concerns in a defined population of treated patients, e.g. drug-resistant TB patients on treatment.

**Unexpected Adverse Reaction:** An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

**WHO Adverse Reactions Terminology (WHO-ART):** The WHO terminology for coding clinical information in relation to medicinal product therapy.

<table>
<thead>
<tr>
<th>MCAZ Reference Number (MCAZ use only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Details (to allow linkage with other reports)</td>
</tr>
<tr>
<td>Clinic/hospital Name:</td>
</tr>
<tr>
<td>Patient Initials:</td>
</tr>
<tr>
<td>Date of Birth:</td>
</tr>
<tr>
<td>Age:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction of Onset:</th>
<th>Duration:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than one hour</td>
</tr>
<tr>
<td></td>
<td>Hours</td>
</tr>
<tr>
<td></td>
<td>Days</td>
</tr>
<tr>
<td></td>
<td>Weeks</td>
</tr>
<tr>
<td></td>
<td>Months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of ADR</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
</tr>
<tr>
<td>Fatal</td>
</tr>
<tr>
<td>Not yet recovered</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant (Other) drugs taken &amp; Dates/period taken:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of drug:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspected drug(s), if known:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory tests results:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forename &amp; Surname:</td>
</tr>
<tr>
<td>Signature:</td>
</tr>
</tbody>
</table>

Send to: The Director-General, Medicines Control Authority of Zimbabwe
106 Baines Avenue, P O Box 10559, Harare
Tel: +263-4-708255 or 792165, E-mail: mcaz@mcaz.co.zw, Website: www.mcaz.co.zw

NB. This form may be completed for any ADR related to medicines or medical devices.

Rev 3 October 2013
Annex 2: Product Defect Form

REPORT ON MEDICINAL (PHARMACEUTICAL) PRODUCT DEFECT OR PROBLEM

To be completed by Pharmacists, Pharmacy Technicians, Medical Practitioners, Nurses, Veterinary Surgeons and other Distributors of Medicines.

1. Product Name (Brand and Generic)
2. Description of the Device
3. Intended Use
4. Size/Type of Container
5. Registration No.
6. Batch Number
7. Expiry Date
8. Name and Address of Manufacturer
9. Name and Title of Reporter
10. Your Practice Location and Address of Hospital, Clinic, Retail Surgery etc.
11. Phone Number
12. Date Problem Occurred or Observed
13. If requested will the actual product involved be available for examination by MCAZ.
   YES                                 NO
14. Signature of Reporter
15. Date
16. Defects/Problem Noted or Suspected (see a-j below)

NATURE OF DEFECT OR PROBLEM

a) Presence of foreign material
g) Wrong label, wrong packaging, wrong strength
b) Unusual odour
h) Lack of therapeutic response
c) Colour changes
i) Leakages
d) Fungal growth
j) Other (specify)
e) Suspected contamination

f) Parenteral solution - leaks, particulate matter, discoloration etc.

Return To: The Director-General
Medicines Control Authority of Zimbabwe
106 Baines Avenue
P.O. Box 10559
Harare
Fax: 736980  Tel: 736981-5
E-mail: mcaz@africaonline.co.zw

For Office Use Only
Report Number:
Date Received:
Annex 3: Product Recall Procedure

**MCAZ RECALL PROCEDURE**

WITHDRAWAL OR RECALL OF PHARMACEUTICAL PRODUCTS BY THE APPLICANT

The following is the approved procedure for the withdrawal or recall of pharmaceutical products:

1. **DEFINITIONS**

The procedure has already been in existence and all those handling pharmaceutical products are therefore being reminded to conform.

1.1 **Withdrawal**

Implies the total withdrawal of all batches of the product from the market.

1.2 **Recall**

Refers to removal from the market of a specific batch or batches of the product.

The recall of a particular batch or batches of a product from the market may be occasioned by the manufacturer or distributor, either following on reports of quality problems of a particular batch of a product, as a result of on-going stability studies or by the Medicines Control Authority of Zimbabwe (MCAZ) as a result of adverse reports or for other reasons.

The class of recall would be determined by the MCAZ or, in the event of greater urgency i.e. after hours or on a weekend, by the manufacturer or distributor concerned.

Levels of recall would be as follows:-

**Class Of Recall**

**Class A**

Recall from all suppliers and users i.e hospitals, wholesalers, retail outlets, doctors, nurses, dentists and customers or patients.

**Class B**

Recall from all suppliers.
2. PROCEDURES

A written procedure must be available and should include the following essential points.

2.1 The MCAZ must immediately, at least within 48 hours, be notified of the problem and must decide on the type of recall after discussion with the applicant.

2.2 Where the Authority cannot be contacted in case of urgency, the applicant or distributor must proceed immediately in terms of these provisions.

2.3 All collected stocks must be placed in quarantine or otherwise “frozen” and no further stocks of the relevant batch or batches distributed.

2.4 Methods of recalling products, depending upon the reason for doing so, must be clearly laid down. These methods could include some or all of the following:-

Class A

Where there is an immediate risk to the patient's health.

a) Wholesalers throughout the country and those in charge of hospital services in various provinces to be contacted in the first instance;

b) Telegraphic, facsimile or electronic mail (e-mail) communications with all members of the pharmaceutical and medical professions (for prescribed medicines).

c) A direct call to the patient or final customer through the radio, television, internet, local and national press.

Class B

Where no immediate risk to the patient's health exists.

a) Wholesalers throughout the country and the directors of hospital services in the various provinces to be contacted in the first instance;

b) Company representatives to call on all customers in order to arrange the return of unsatisfactory products.

c) Telephone calls to be made to all customers known to have received quantities of the batch being recalled requesting them to hold the batch for collection and/or return.

d) Notification through trade journals, internet, e-mail;

e) Expedited mail to all medical practitioners, dentists, veterinarians and pharmacists. In this regard, envelopes should be clearly labeled “URGENT MEDICAL RECALL” in a distinguishable color and of a size large enough to attract the attention of the recipient.
2.5. **After the Recall**

a) The quantities of the batch recovered must be reconciled with the quantities of the batch distributed.

b) The manufacturer concerned will advise all retailers, wholesalers and hospitals as well as other people in possession of the product, to return the products in question to their supplier for eventual return to the manufacturer who will report to the MCAZ on receipt, the number of products returned and consequently the number unaccounted for either through having been used or simply not returned.

c) A record of any ill effects (alleged or otherwise) caused by the faulty product must be kept.

d) The cause of the fault must be investigated and recorded.

e) At the conclusion of the recall operation, the MCAZ should be informed of the degree of success achieved and should be provided with a full report of the cause of the fault to remedy the situation to prevent a recurrence.

**Withdrawal of a product from the Market**

All procedures as for “recall”, except that the withdrawal will involve all batches of the product in question.
Annex 4: Serious Adverse Event Form

MEDICINES CONTROL AUTHORITY OF ZIMBABWE (MCAZ)
SERIOUS ADVERSE EVENT FORM

PVF03

MCAZ Office Phone: 263-4-736981-5 MCAZ Office Fax: 263-4-736980

<table>
<thead>
<tr>
<th>MCAZ Office Use Only</th>
<th>Report Number</th>
<th>Clinical Trial Ref Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Report Date: __ __ __ __</td>
<td>Site Awareness Date: __ __ __ __</td>
<td></td>
</tr>
<tr>
<td>Type of Report: ___Initial___Update</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event Previously Reported: __Yes__No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Site: ___________________ Telephone Number: (<strong>)</strong>__________________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed by: ____________________ Signature: __________________________________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Designation ______________________ Protocol Number</td>
<td>Volunteer ID Number</td>
<td></td>
</tr>
<tr>
<td>Age: ___ ___ Years/Months/Days (Circle) Weight (Kg) _____________ Sex: ___ Male__ Female</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMPLETE ONE SAE FORM FOR EACH REPORTABLE EVENT

1. PRIMARY REASON SAE IS BEING REPORTED (Check One Category)

   _Death__  __Overdose or error in administration__  _Grade 1 or 2 event__
   _Cancer__  _HIV Infection_  _Recurrent event__
   _Congenital anomaly/Birth defect__  _Immune dysfunction__  _Other__
   _Permanent disability/Incacity__  _Grade 3 or 4 event__  _Other__

2. REPORTABLE SAE (Use Key Word, Diagnosis, Cause of Death, Lab Parameter) TOXICITY

   GHAGE (1-5) defined as 1= mild, 2= moderate, 3= severe, 4= life-threatening, 5= death

   __________________     __________________

3. SAE ONSET DATE: __ __ __ __ __ __ __ STUDY WEEK: __Yes__No

4. VISIT NUMBER: __ __ __ IDENTIFIED POST-STUDY: __Yes__No

5. INVESTIGATIONAL PRODUCT
   A. VACCINE PRODUCTS (List ALL immunization date -DD/MM/YYYY)

   1. __ __ __ __ __ __ __  3. __ __ __ __ __ __ __  5. __ __ __ __ __ __ __  7. __ __ __ __ __ __ __
   2. __ __ __ __ __ __ __  4. __ __ __ __ __ __ __  6. __ __ __ __ __ __ __  8. __ __ __ __ __ __ __

   B. NON-VACCINE PRODUCTS
   Start Date: __ __ __ __ __ __ __ Date Last Administered or Tx End Date: __ __ __ __ __ __ __
   Dose, route, schedule at SAE onset: ____________________________________________

6. MANAGEMENT OF STUDY TREATMENT (Check One Response)

   _Continued__  _Temporarily withheld_  _Off Investigational Product at SAE onset_ or
Reduced dose or schedule  Permanently discontinued  treatment course completed

7. **EVENT SUMMARY**
Include clinical history of event, associated signs and symptoms, alternative aetiologies being considered, medical management, test results, and relevant past medical history below, or attach summary.

OUTCOME OF SAE:

8. **CONCOMITANT MEDICATIONS**
List ALL non-study Concomitant Medications being taken one month prior to SAE onset below, or attach a copy of the medication profile.

9. **RELEVANT LABORATORY TESTS**
Complete the table below, or send copies of data forms or other laboratory slips with equivalent information.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Abnormal Result</th>
<th>Site Normal Range</th>
<th>Collection Date (DD/MM/YYYY)</th>
<th>Lab Value Previous or subsequent to this event</th>
<th>Collection Date (DD/MM/YYYY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. **PHYSICIAN ASSESSMENT AND SIGNATURE**

   Relationship of SAE to Investigational Product: (Check One Response)

   ___ Definitely  _____ Probably  ____ Possibly  ____ Not Related

   Physician Signature: ___________________________ Date: __ __/__ __/______

   Signature indicates review and approval of data provided

   Physician Name Printed: ____________________________

Rev 1 _October 2008
Annex 5: CIOMS Reporting Form for Pharmaceutical Industry

1. **PATIENT INITIALS** (first, last)
2. **COUNTRY**
3. **DATE OF BIRTH**
4. **AGE**
5. **SEX**
6. **REACTION ONSET**

7. **DESCRIBE REACTION(S)** (including relevant test/lab data)

8-12 **CHECK ALL APPROPRIATE TO ADVERSE REACTION**
- Patient Died
- Involved or Prolonged Inpatient Hospitalisation
- Involved Persistence or Significant Disability or Incapacity
- Life Threatening

13. **SUSPECT DRUG(S) INFORMATION**
14. **SUSPECT DRUG(S) (include generic name)**
15. **DAILY DOSE(S)**
16. **ROUTE(S) OF ADMINISTRATION**
17. **INDICATION(S) FOR USE**
18. **THERAPY DATES** (from/to)
19. **THERAPY DURATION**

20. **DID REACTION ABATE AFTER STOPPING DRUG?**
- Yes
- No
- NA

21. **DID REACTION REAPPEAR AFTER REINTRODUCTION?**
- Yes
- No
- NA

22. **CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION** (exclude those used to treat reaction)

23. **OTHER RELEVANT HISTORY** (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

24a. **NAME AND ADDRESS OF MANUFACTURER**
24b. **MFR CONTROL NO.**
24c. **DATE RECEIVED BY MANUFACTURER**
24d. **REPORT SOURCE**
   - Study
   - Literature
   - Health Professional
24e. **DATE OF THIS REPORT**
25a. **REPORT TYPE**
   - Initial
   - Followup
Annex 6: WHO Minimum Requirements for a Pharmacovigilance Centre

In 2010 WHO, the global Fund to Fight AIDS, TB and Malaria (GFATM) and other partners agreed on a set of minimum requirements that should be met in any national pharmacovigilance system:

1. A national Pharmacovigilance centre with designated staff (at least one full-time), staff basic funding, clear mandates, well-defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring.
2. The existence of a national spontaneous reporting system (see below) with a national individual case safety report (ICSR) form i.e. an ADR reporting form.
3. A national database or system for collating and managing ADR reports.
4. A national ADR or Pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management including crisis communication.
5. A clear strategy for routine communication and for communication about a crisis.

Countries applying for grants to support anti-TB treatment should include Pharmacovigilance as a core component of their prevention and treatment programmes. The minimum requirements are expected to become mandatory for countries benefiting from GFATM grants for HIV, tuberculosis and malaria treatment programmes.

In the absence of a functional PvC, the National TB Control programme (NTP) should include in its budget, funding for catalysing and facilitating the establishment of a PvC which fulfils as a minimum the conditions listed above, or for improving resources if an established PvC is incapable of coping with the demands of Pharmacovigilance of anti-TB medicines. This would be a legitimate and wise call of the funds of the programme because Pharmacovigilance should result in better therapeutic management, as well as more acceptable and safer treatment.

*World Health Organisation and GFATM Meeting to determine Minimum Requirements for Pharmacovigilance, Geneva, Switzerland, 14-15 January 2010 (www.who.int/medicines/areas/quality_safety_efficacy/).*
### Annex 7

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperlink 1</strong></td>
<td>Strengthening National Surveillance of Adverse Events Following Immunization</td>
<td><a href="www.mcaz.co.zw">MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013</a></td>
</tr>
</tbody>
</table>

### Annex 8

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperlink 2</strong></td>
<td>Safety Monitoring of H1N1 Vaccine (August 2010 to December 2011)</td>
<td><a href="www.mcaz.co.zw">MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013</a></td>
</tr>
</tbody>
</table>

### Annex 9

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperlink 3</strong></td>
<td>Cohort Event Monitoring Of Artemisinin Combination Therapies (ACTs) In Zimbabwe</td>
<td><a href="www.mcaz.co.zw">MCAZ Drug Information Bulletin Volume: 1 December 2012</a></td>
</tr>
</tbody>
</table>

### Annex 10

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperlink 4</strong></td>
<td>Targeted Spontaneous Reporting (TSR) Program of Antiretrovirals (ARVs) and Anti tuberculosis (Anti-TBs) and all essential medicines in Zimbabwe</td>
<td><a href="www.mcaz.co.zw">MCAZ Drug Information Bulletin Volume: 2 No:1 June 2013</a></td>
</tr>
</tbody>
</table>
Annex 11: Adverse Events Following Immunisation (AEFI) Case Investigation Form.

The health worker who detects AEFI should immediately complete this form.

| Identification | | |
|----------------|------------------|
| Surname        | Name of Immunisation facility |
| First Name     | Name of reporting facility |
| Next of Kin    | District |
| Sex            | Male [ ] Female [ ] |
| Date of Birth  | D D M M Y Y Y Y |
| Age (if no date of birth) | Years M M S S |
| Patient Physical Address | |
| Alternative Address | |
| | |
| Notification/Investigation | | |
| Date of onset of symptoms | Date of notification |
| Date of investigation | Investigated by |
| Duration of symptoms | Date of vaccination |
| | |
| Brief Medical history, Traditional medical history, any allergies and if on any treatment | | |
| | |
| Type of AEFI | | |
| Vaccine Related | Programme Error |
| Anaphylaxis | Yes No |
| Fever | Yes No |
| Severe Local Reaction | Yes No |
| Acute Flaccid Paralysis | Yes No |
| BCG Lymphadenitis | Yes No |
| Anaphylactic Shock | Yes No |
| Persistent Crying | Yes No |
| | |
| Coincidental | Unknown Yes No |
| Seizures | Yes No |
| Meningitis | Yes No |
| Encephalopathy | Yes No |
| Encephalitis | Yes No |
| | |
| Vaccine(s) given that day: | | |
| Details of vaccine | Details of diluent if used |
| Name of Vaccine | Dose | Lot/batch no. | Manufacturer | Expiry Date | Duration vaccine batch has been in use | Lot/batch No. | Manufacturer | Expiry Date | Duration diluent batch has been in use | History of previous reaction |
| BCG | | | | | | | | | | |
| OPV | | | | | | | | | | |
| DTP-HepB-Hib(Penta) | | | | | | | | | | |
| Rotavirus | | | | | | | | | | |
| PCV | | | | | | | | | | |
| Measles | | | | | | | | | | |
| Vitamin A | | | | | | | | | | |
| Treatment required | Yes No | |
| Death | Yes No | |
| If ‘Yes’ Date of Death | | |
| Post-mortem done | Yes No | |
| If ‘No’ Next of kin 1: Name……………….ID……………..Signature…………… |
| Next of kin 2: Name……………….ID……………..Signature…………… |
| Witness : Name……………….ID……………..Signature…………… |
### Specimen collection and dispatch (if any)

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Date collected</th>
<th>Dispatched to</th>
<th>Date of dispatch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Summary form following AEFI investigation

Completed by the District Level Manager and sent to Province then EPI HQ together with the AEFI Case Investigation form

- **Describe** trigger event
- **Clinic investigation carried out**
  - Yes
  - No
- **Reason likely to be due to immunization**
  - Yes
  - No
- **If ‘Yes’ then specify reason**

#### Reason likely to be due to:

<table>
<thead>
<tr>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Chain breakdown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstitution error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine manufacture error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsterile practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine associated but not manufacturer error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other error: Specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Corrective action taken**
  - Yes
  - No

- **Specify**

- **Investigator’s Name**
  - …………………………
- **Designation**
  - …………………………
- **Signature**
  - …………………………
- **Date**
  - …………………………

* A trigger is an agent that causes an event to happen.
* Cluster is two or more cases of same or similar events, which are related in time and have occurred within a specific geographical area or associated with the same vaccine, the same batch number the same vaccinator.
## Annex 12: WHO Causality Classification of Adverse Events (AE) Definition Categories

### Use by MCAZ and PVCT Committee

<table>
<thead>
<tr>
<th>WHO Causality classification of Adverse Events (AE) definitions categories used by MCAZ and ADR &amp; MR Committee</th>
<th>DAIDS Investigator causality classification of (AE) definition categories commonly used for clinical trials</th>
</tr>
</thead>
</table>
| CERTAIN | DEFINITELY RELATED  
The exposure to the study agent and adverse event are related in time, and a direct association can be demonstrated (e.g. the adverse experience has been identified as a known toxicity of the study agent product, and the study agent is clearly responsible for the event. |
| - event or laboratory test abnormality, with plausible time relationship to drug intake.  
- cannot be explained by disease or other drugs.  
- response to withdrawal clinically plausible.  
- event definitive pharmacologically or phenomenologically.  
- rechallenge if necessary. | |
| PROBABLE/LIKELY | PROBABLY RELATED  
The administration the study agent/procedures & adverse event are considered reasonably related in time and the event is more likely explained by the study agent than other causes. |
| - event or laboratory test abnormality, with reasonable time relationship to drug intake.  
- unlikely to be attributed to disease or other drugs.  
- response to withdrawal clinically reasonable. | |
| POSSIBLE | POSSIBLY RELATED  
The adverse event and the administration of the study agent/procedures are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent/procedures. |
| - event or laboratory test abnormality, with reasonable time relationship to drug intake.  
- could also be explained by disease or other drugs.  
- information on drug withdrawal lacking or unclear. | |
| UNLIKELY | PROBABLY NOT RELATED  
A potential relationship between the study agent/procedures and the adverse event could exist (i.e. the possibility cannot be excluded) but the adverse event is most likely explained by causes other than the study agent/procedures. |
| - event or laboratory test abnormality, with a time to drug intake which  
- makes relationship improbable.  
- disease or other drugs provide plausible explanations. | |
| CONDITIONAL/UNCLASSIFIED | NOT RELATED  
The adverse event is clearly explained by another cause not related to the study agent/procedures. |
| - event or laboratory test abnormality.  
- more data for proper assessment needed.  
- or additional data under examination. | |
| UNASSESSABLE/UNCLASSIFIED | PENDING  
*May be used as a temporary assessment only for death  
*Used only if data necessary to determine the relationship to study agent/procedures is being collected  
*A final assessment of relationship should be within 3 business days after reporting the death  
*If no final assessment is made within 3 business days by site, event will be assessed as possibly related to study agent/procedures  
*Any additional information received at a later time including an autopsy (post-mortem) report should be submitted as follow up report. |
| - a report suggesting an adverse reaction.  
- cannot be judged because of insufficient or contradictory information.  
- report cannot be supplements or verified. | |
<table>
<thead>
<tr>
<th>Number</th>
<th>Name of Document/Guideline</th>
<th>Source of document/ URL link</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6th Essential medicines List and Standard Treatment Guidelines for Zimbabwe. 2011.</td>
<td>NDTPAC, AIDS and TB Unit MOHCC</td>
</tr>
<tr>
<td>2</td>
<td>Guidelines for Antiretroviral Therapy in Zimbabwe. 2010.</td>
<td>NDTPAC, AIDS and TB Unit MOHCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wholesaling-practice-guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="http://www.fda.gov/cder/guidance/index.htm">http://www.fda.gov/cder/guidance/index.htm</a></td>
</tr>
<tr>
<td></td>
<td>Source</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>13</td>
<td>Royal Pharmaceutical Society of Great Britain</td>
<td>British National Formulary (BNF)</td>
</tr>
<tr>
<td>14</td>
<td>Royal Pharmaceutical Society of Great Britain</td>
<td>British National Formulary for children</td>
</tr>
</tbody>
</table>