**ZAMBIA MEDICINES REGULATORY AUTHORITY**

# GUIDELINES FOR DETECTING AND REPORTING ADVERSE DRUG OR VACCINE REACTIONS AND EVENTS IN ZAMBIA

**The safety of medicines in Zambia - why health workers need to take action**

**Produced by the National Pharmacovigilance Unit (NPVU)**
May, 2006

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## Glossary

| | |
|---|---|
| ACT | Artemisinin-based Combination Therapies |
| ADE | Adverse Drug Event |
| AEFI | Adverse Event Following Immunisation |
| ADR | Adverse Drug Reaction |
| AIDS | Acquired Immunodeficiency Syndrome |
| ARV | Antiretroviral Drugs |
| DHMT | District Health Management Team |
| HIV | Human Immunodeficiency Virus |
| MOH | Ministry of Health |
| NPVU | National Pharmacovigilance Unit |
| PHO | Provincial Health Office |
| PRA | Pharmaceutical Regulatory Authority |
| TDRC | Tropical Diseases Research Centre |
| UMC | Uppsala Monitoring Centre |
| UNZA | University of Zambia |
| WHO | World Health Organisation |
| TB | Tuberculosis |

# Acknowledgements

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These guidelines were compiled on behalf of the National Pharmacovigilance Unit (NPVU) by the Pharmacovigilance Technical Working Group, which comprised the following individuals: Ms. Esnat Mwape, Acting Director General, PRA; Dr Sindwa Kanyimba, Clinical Pharmacologist, University of Zambia; Dr. Oscar Simooya, Clinical Pharmacologist, Copperbelt University; Dr. Albert Mwango, Anti Retroviral Therapy Specialist and Coordinator, Ministry of Health; Dr. Ray Handema, Head of the Department of Biological Sciences, University of Zambia; Mrs. Bernice C. Mwale, Pharmacist, PRA; Mr. Pelekelo Mangisha, Pharmacist, PRA; Dr. Adiele Onyeze, Epidemiologist/EPI Team Leader, WHO/Zambia; Dr. Sansan Myint, 3 by 5 Country Officer, WHO/Zambia; Ms Leo Chivundu, EPI Desk Officer, UCI, Child Health Dept, MOH; Dr. Nathan Kapata, TB & Leprosy Specialist and Ms. Violet Kabwe, Logistics Drug Advisor, HSSP. Without their diligent commitment to the assignment these guidelines would not have been completed.

# Foreword

The objective of drug legislation and regulation in Zambia is, as provided in our National Drug Policy, to ensure that all drugs (medicines) and drug information conform to the required standards for quality, efficacy and safety throughout the chain of manufacture, importing, /exportation, distributioning/supply, storage and use.

It is however recognized that all medicines are potentially harmful. Therefore, mechanisms to continuously monitor the safety of medicines are necessary. The Zambian Government recognize this and enacted the Pharmaceutical Regulatory Authority Act No.14 of 2004. The Act establishes the Pharmaceutical Regulatory Authority (PRA), whose functions, among others, include post- marketing surveillance and monitoring of adverse reactions.

The National Pharmacovigilance Unit (NPVU) of the PRA will be responsible, on a day-to-day basis, for spearheading and coordinating a pharmacovigilance or drug safety-monitoring programme. The main goal of the programme will be to reduce of morbidity and mortality attributed to drug use through the early detection of drug safety problems.

These guidelines provide information on how to detect and report ADR/ADEs and facilitate your active participation in reporting suspected ADR/ADEs and providing information to those who need it. It is, therefore, my sincere hope that this handbook will be helpful in addressing and enhancing early detection of drug safety problems, in the interest of all the people of our country.

Hon. Sylvia T Masebo, MP

Minister of Health.
Lusaka, Zambia

# 1. Introduction

Although medicines are useful therapeutic agents, they are all potentially harmful. It is often said that a 'drug product without side effects is therapeutically ineffective'.

The thalidomide disaster, which struck in 1961 stimulated national and international action towards assuring the safety of medicinal products and reducing the risk of adverse reactions to them.

Various studies (Einnason 1993; Bates D W et al. 1995) have shown that up to 5% of all hospital admissions are due to the adverse effects of drug products, while other reports indicate that 10 to 20 % of the in-patients in hospitals experience a serious adverse drug reaction (Pirmohamed et al. 1999). It has further been estimated that adverse drug reactions (ADRs) are the $4^{th}$ to $6^{th}$ leading cause of death in USA (Lazarou et al. 1998). Providing services for the management of ADRs thus imposes a high financial burden on health care.

Given the magnitude of this problem, it is recognised, that "*pharmacovigilance"*, which is defined as the activities related to the monitoring of adverse drug reactions and adverse drug events (ADEs) has a very important role in public health. Unfortunately, although the National Drug Policy acknowledges the widespread irrational drug use in the country, there is very limited information available about ADR or ADEs in Zambia. In this regard, it is likely that there is a higher incidence of ADRs or ADEs than is recorded.

The lack of a National Drug Quality Control Laboratory and lack of an efficient and effective post marketing surveillance system compound the likelihood of high incidences of counterfeit and substandard products circulating on the Zambian market. This is especially so in light of the high prevalence of HIV/AIDS, malaria, malnutrition and TB.

Pharmacovigilance is necessary in Zambia because of the differences noted in various countries with respect to the occurrences of ADRs or ADEs and other drug- related problems due to several factors including disease patterns, prescribing practices, treatment seeking behaviours, genetics, diet and drug manufacturing and distribution processes which influence quality, safety and efficacy of medicinal products.

It is recognised that ADRs and ADEs data generated from within Zambia will have greater relevance and educational value and can assist the Pharmaceutical Regulatory Authority to make evidence-based decisions. ADRs and ADEs monitoring will also help in promoting rational drug use and therefore reduce risks of adverse effects due to drugs in the country.

Additionally, in the recent past there has been an increase in the use of new drugs for the management of HIV/AIDS, malaria and TB for which there is insufficient safety data. It is therefore imperative that mechanisms are put in place to monitor the safety of these new drug products.

The purpose of these guidelines is to facilitate and stimulate your active participation in detecting and reporting ADRs and ADEs. These guidelines also provide answers about what, how and where drug safety problems should be reported.

## 2. Definitions

The terms listed below are defined specifically for the purposes of this Guide.

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

i. "A*dverse drug event (ADE)"* means 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'. The basic point in this case is the coincidence in time without any suspicion of a causal relationship;

ii. "A*dverse drug reaction (ADR)"* means 'a response to a medicine which is noxious (harmful) and unintended, and which occurs at doses normally used in man'. It is of important that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction);

iii. *"Counterfeit medicinal products" means* a medicinal product which is deliberately and fraudulently mislabeled with respect to identity and / or source. Counterfeit can apply to both branded and generic products and may include products with correct ingredients with the wrong ingredients with an insufficient quantity of active ingredient or with fake packaging;

iv. " D*rug* or *medicine" means* 'a pharmaceutical product, used in or on the human or animal body for the prevention, diagnosis or treatment of a disease, or for the modification of physiological function'.

v. *"Drug resistance"* means decreased susceptibility of a pathogen to a drug;

vi. *"Non adherence"* means the failure of a patient to take medication as prescribed by an attending health worker, such as where a medicine has been recommended to be taken twice daily for seven days and the patient only takes the medicine for two days;

vii. *"Product quality problems"* includes bioequivalence problems, expired products, poor storage or inadequate packaging information;

viii. " S*ide effect" means* 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug'. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose;

ix. "*serious adverse event" means* any event that is:

a) fatal

b) life-threatening
c) permanently/significantly disabling
d) Requires or prolongs hospitalisation
e) Causes a congenital anomaly
f) Requires intervention to prevent permanent impairment or damage

x. *"Treatment failure"* means the non achievement of an expected outcome achieved despite the patient taking the prescribed medications correctly; it may be caused by drug resistance, product failure, bioequivalence problems and the use of substandard or counterfeit products;

xi. " *unexpected adverse reaction"* is 'an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug'.

Note: *The terms adverse drug reaction (ADR) and adverse drug event (ADE) are used in tandem throughout this document for the sake of simplicity. Within the Zambian context, an ADE can also be non-adherence, non-response to a drug, either because the product was of a substandard quality or a counterfeit or because there is resistance.*

# 3. Organisation of the Pharmacovigilance System

The organization of the pharmacovigilance system in Zambia is set out in Appendix 1. The Pharmaceutical Regulatory Authority ( PRA) is mandated by law to undertake pharmacovigilance activities in Zambia. A National Pharmacovigilance Unit (NPVU) of the PRA will manage the day-to-day activities of the pharmacovigilance programme. The Unit will receive reports from health workers, the pharmaceutical industry as well as members of the public. In order for the Unit to operate efficiently, there is need for a well-established communication system among the players. The role and responsibilities of the key actors in the pharmacovigilance system will be as follows:

### 3.1. National Pharmacovigilance Unit (NPVU)

The NPVU of the PRA, is the hub of the pharmacovigilance system. It will receive and process all reports. Working closely with the Expert Review Panel, it will be responsible for the review, categorization and follow-up of reports. The NPVU through the Medicines Committee of the PRA will advise the Board of the PRA on matters related to pharmacovigilance. The NPVU will serve as a repository for any research findings relevant to pharmacovigilance. Other specific functions will include:

- recruiting and training staff for the Unit;
- providing [triplicate] ADR/ADE forms;
- developing manuals and guidelines for health facilities and laboratories;
- training health workers in the use of report forms;
- collecting data; and
- developing or /revising a coding and archive system for data entry and retrieval.

### 3.2. Health Centres and Hospitals:

The health centres and hospitals, including private health centres and hospitals, are on the frontline of patient care, and will provide basic building blocks of data from the source on ADR/ADEs based on observations of patients or laboratory results. The information, to be provided on multi-copy forms, will be fed in through the system as set out in Appendix 1. The white copies will be sent directly to the NPVU, the pink copy will be sent to the immediate next level of the health system and the last copy, green in colour will be retained at the local reporting facility.

The 3 referral hospitals (University Teaching Hospital, Kitwe Central Hospital and Ndola Central Hospital), defence hospitals and private hospitals or clinics will report directly to the NPVU. Other specific functions will include:-

- recording and reporting ADRs or ADEs;
- forwarding completed forms directly to NPVU and to the District Health Management Team; and
- providing feedback.

### 3.3. Laboratories

Laboratories are a source of information on drug resistance and other aspects of a patient's status. Information provided by them will be forwarded to the health centres, districts and hospitals, and then up the system along with other ADR and ADE information. The peripheral laboratories (i.e. at district and hospital levels) may feed samples and information to central reference laboratories or specific disease centres for further investigations. The reference laboratories or specific disease centres will provide feedback to the peripheral laboratories, and directly up the system to the NPVU. Their roles and responsibilities will include:

- sample collection, processing, recording, and reporting; storage and transportation where required and receiving feedback; and
- providing requested results to health centres, districts and hospitals; and directly to the NPVU or specific disease centre, if required.

### 3.4. District Health Management Team (DHMT)

The DHMT will provide technical and administrative support to the hospitals, health centres and laboratories. Roles and responsibilities will include:

- supervising the collection of data and specimens from sites within their jurisdiction;
- distributing blank ADRs and ADE forms; collect and forward completed forms;
- verifying or investigating ADR and ADEs whenever possible;
- providing administrative, technical and logistical support to health centres, laboratories, and (in some cases) hospitals; and
- providing feedback from PHO and/or NPVU.

### 3.5. Provincial Health Office (PHO)

The PHO will provide technical and administrative support to the DHMTs and provide a linkage with the NPVU. The role and responsibilities will include:

- collaborating and cooperating with DHMTs and their health facilities;
- providing administrative, technical and logistical support to DHMTs and hospitals;
- providing feedback to and from the NPVU;
- distributing blank ADR and ADE forms; collect and forward completed forms; and
- verifying or investigating ADRs and ADEs whenever possible.

Any clarification on the roles and responsibilities of these and other institutions in the flow chart as set out in Appendix 1 can be obtained from the NPVU.

### 3.6. Patients and other members of the public shall

The patients and other members of the public shall report ADR/ADEs either directly to the Unit or to the nearest health centres or hospitals

## 4. How to recognise ADRs

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs:

a) ensure that the medicine ordered is the medicine received and actually taken by the patient, at the dose prescribed;

b) verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation(s) made by the patient;

c) determine the interval between the commencement of the drug treatment and the onset of the event;

d) evaluate the suspected ADR after discontinuing the drug(s) or reducing the dose and monitor the patient's status;

e) analyse the alternative causes, other than the drug that could on their own have caused the reaction;

f) use relevant up-to-date literature and personal experience as a health worker on drugs and the ADRs of the drugs and verify if there are previous conclusive reports on such reactions. The NPVU is a very important source for purposes of obtaining information on ADRs. The manufacturer of a drug can also be consulted; and

g) report any suspected ADRs to the person nominated for ADRs reporting in the hospital or district or directly to the NPVU.

## 5. What should be reported?

a) Report all suspected reactions, including minor ones, in the case of "new " drugs.

b) Report all serious or unexpected or unusual ADEs, in the case of established or well known drugs.

c) Report if an increased frequency of a given reaction is observed.

d) Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions

e) Report ADRs in special case or conditions such as drug abuse, and drug use in pregnancy and during lactation.

f) Report when suspected ADRs are associated with drug withdrawals.

g) Report ADRs attributed to an overdose or medication error.

h) Report when there is a non-response or when suspected pharmaceutical defects are observed.

i) Report all drug-related problems for example, problems associated with the quality of a product quality problems, suspected counterfeit products or treatment failure.

j) Report all adverse events following the ingestion of herbal or traditional medicines.

k) Report even if you are not certain whether the product caused the adverse reaction or adverse event and whether or not you have all the details.

The NPVU is particularly interested in the adverse events following treatment with artemisinin based combination therapies (ACTs) for malaria, antiretrovirals (ARVs) for HIV/AIDS, drugs for the treatment of tuberculosis, vaccines and other " new " drugs.

You are urged to report all suspected adverse events as soon as possible!

## 6. How and where to report ADEs?

Adverse Drug or Vaccine Reaction and Event Report Forms (ADVREF) may be obtained from Health Centres, District or Provincial Health Offices and the NPVU. A sample of an ADVREF is provided in Appendix 2. However, if report forms are not available, a copy may be made in triplicate as set out in Appendix 2. A health worker who will in turn transcribe the information on to an ADVREF may receive further, verbal reports from members of the public. The completed report form should be sent through the system, to the district or provincial pharmacovigilance coordinator AND directly to the NPVU.

In addition to reports received from health workers, all patients who experience an adverse event following the administering or application of a medication are advised to report directly to the NPVU by personal contact or at your nearest health facility. The NPVU has a 24-hour service and all reports received will be acknowledged.

Note: *All reports suggestive of resistance or other reactions to HIV therapies should be recorded on separate forms available from the local pharmacovigilance offices as set out in Appendix 3.*

## 7. Why health workers are in the best position to detect and report on ADEs

The effectiveness of a national post marketing surveillance programme is directly dependent on the active participation of health workers. Health workers are in the best position to report suspected ADEs observed in the course of providing every day patient care. All healthcare providers should report ADEs as part of their professional responsibility, even if they are doubtful about the precise link with the given medication.

*You can reduce the suffering of patients and save thousands of patient's lives by reporting all suspected adverse drug reactions of patients!*

## 8. Contacting the National Pharmacovigilance Unit

The NPVU will be grateful if you could submit your comments on your practical experience(s) in respect of ADRs or ADEs. Kindly advise whether this Guide is useful. For any queries or clarifications that you may have concerning pharmacovigilance please contact the NPVU with your comments/questions at:

National Pharmacovigilance Unit (NPVU)
Pharmaceutical Regulatory Authority
P O Box 31890
Plot No. 6903, Tuleteka Road
Light Industrial Area, Lusaka.

Tel: 260 1 220098/220109/220088
Fax: 260 1238458
Email: pharmacy@coppernet.zm

## 9. References

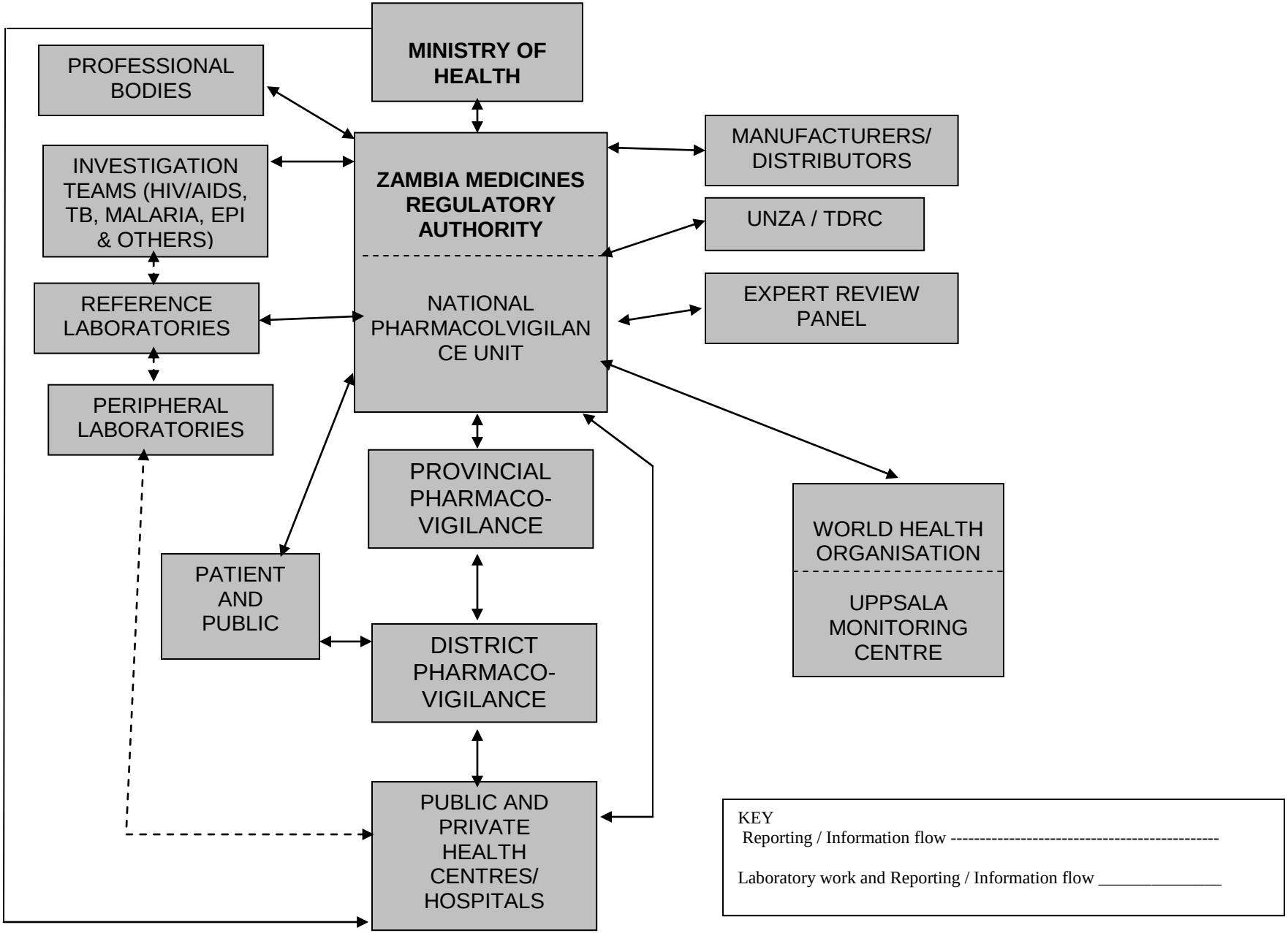

i. Bates DW, Cullen DJ, Laird N, et al. "Incidence of adverse drug events and potential adverse drug events, implications for prevention." *JAMA* 1995; 274: 29-34.

ii. Einarson TR. "Drug related hospital admissions." *Ann Pharmaco* 1993; 27: 832-840.

iii. Lazarou J, Pomeraz BH, Corey PN. "Incidence of adverse drug reactions in hospitalized patients, a meta analysis of prospective studies." *JAMA* 1998; 279: 1200-1205.

iv. Pirmohamed M, Breckenridge AM, Kitteringham NR, et al. "Adverse drug reactions." *BMJ* 1999; 316: 1295-1298.

## Appendix 1: Institutional Arrangements



# Appendix 2: The Adverse Drug or Vaccine Reaction/Event report form

Patient Initials: Sex: ○ Male ○ Female

Patient ID: ☐☐☐-☐☐☐-☐☐☐☐☐☐-☐

Patient NRC: ☐☐☐☐☐☐/☐☐/☐

Date of birth: ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

Weight (in kilograms): ☐☐☐.☐ Height (in centimeters): ☐☐☐

Patient is pregnant:(tick appropriate) ○ Yes ○ No ○ Maybe ○ Not applicable

## NPVU ADVERSE DRUG OR VACCINE REACTION/EVENT FORM

Date of Reporting: ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

Ministry of Health

**DESCRIPTION OF PROBLEM**
[Include drug/vaccine quality problem and side effects]

_____

_____

_____

_____

**OUTCOME** (tick appropriate)

☐ Recovered ☐ Hospitalized ☐ Life-threatening ☐ Disabled

☐ Death , Date of Death: ☐☐-☐☐☐-☐☐☐☐

☐ Other, _____ (SPECIFY)

**PLEASE LIST ALL DRUGS, VACCINES, AND HERBAL TREATMENTS**
*Include all drugs [including traditional medicines] taken in last 28 days*

| Name of Drug/ Vaccine/Herbal/ Traditional | Batch number (if available) | Daily dosage | Date started | Date stopped | Reason for Use | Source of Drug/Vaccine (TICK): Drug Store/ Pharmacy | Private health facility | Govt. health facility | Traditional |
|---|---|---|---|---|---|---|---|---|---|
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**Send to:**

National Pharmacovigilance Unit (NPVU)

Pharmaceutical Regulatory Authority (PRA)

P. O. Box 31890
Tuleteka Road

Plot No. 6903
LUSAKA

Tel: 260-1-220098/220109/220088
Fax: 260-1-238458

**HIV STATUS** (tick appropriate)

○ NEGATIVE ○ POSITIVE ○ NOT KNOWN

Latest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

2nd Oldest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐

3rd Oldest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐

**REPORTER'S DETAILS**

Full name:_____

(tick appropriate)

○ Doctor ○ Nurse ○ Pharmacist ○ Relative ○ Friend ○ Self ○ Other

Jan 2006 ver 1.0

## Appendix 3: HIV Drug Resistance Laboratory Request Form

# HIV DRUG RESISTANCE LABORATORY REQUEST FORM

Date of Reporting: ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

Patient ID: ☐☐☐-☐☐☐-☐☐☐☐☐☐-☐

Patient NRC: ☐☐☐☐☐☐/☐☐/☐

Facility ID: ☐☐☐☐-☐☐

**REQUESTING DOCTOR**

Full name: _____

Department: _____

Prescriber No: _____

(REMEMBER TO ALSO FILL OUT THE **ADR FORM**)

**PATIENT DETAILS**

Date of Birth: ☐☐-☐☐☐-☐☐☐☐

Weight (in kilos): ☐☐☐.☐

Height (in centimeters): ☐☐☐

**Marital Status:**

- ○ Never Married
- ○ Married
- ○ Divorced
- ○ Widowed

**Education Level:**

- ○ None
- ○ Highest grade, ☐☐
- ○ College/University

**Sex**

- ○ Male
- ○ Female

**Occupation**

- ☐ Miner
- ☐ Healthcare worker
- ☐ Agriculture/Farmer
- ☐ Teacher/Education
- ☐ Transport
- ☐ Police/Military
- ☐ Businessman/woman
- ☐ Other, _____ (SPECIFY)

**TYPE OF TREATMENT FAILURE**

**CLINICAL** ☐-Onset of new opportunistic infection ☐-Onset of new malignancy ☐-Recurrence of WHO Stage III conditions

**VIROLOGICAL**

Latest Viral Load: ☐☐☐☐☐☐☐☐ copies/mL ☐☐-☐☐☐-☐☐☐☐

2nd Oldest Viral Load: ☐☐☐☐☐☐☐☐ copies/mL ☐☐-☐☐☐-☐☐☐☐

3rd Oldest Viral Load: ☐☐☐☐☐☐☐☐ copies/mL ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

**IMMUNOLOGICAL**

Latest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐

2nd Oldest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐

3rd Oldest CD4 Count: ☐☐☐☐☐☐☐☐ cells/mm³ ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY)

**ANTIRETROVIRAL DRUGS HISTORY**

| Generic Name [AZT, d4 T, 3TC, NVP, EFV, ddI, ABC, TDF, NFV, LPV/r, FTC, others] | Class Type [NNRTI, NRTI, PI] | Date Started | Date Stopped |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**OFFICIAL USE ONLY**

CASE SERIAL NUMBER: |___|___|___|___|___|/|___|

Date sample received: ☐☐-☐☐☐-☐☐☐☐

Sample received Intact: ○ Yes ○ No

**SAMPLE DETAILS**

Date and time of collection: ☐☐-☐☐☐-☐☐☐☐ (DD MMM YYYY) ☐☐-☐☐ (HH MM)

**Sample Storage**

Frozen at -20 to -70°C ○ Yes ○ No

**Sample Types**

☐ Whole Blood ☐ Plasma (centrifuge) ☐ Plasma (standing)

**Sample Transportation**

○ PHO/DHMT transport ○ Public transport ○ Hired Courier

Date sample dispatched: ☐☐-☐☐☐-☐☐☐☐

Time sample dispached: ☐☐-☐☐

**Transportation Conditions**

○ Dry ice ○ Room temperature

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