DEMOCRATIC REPUBLIC OF CONGO

MINISTER OF PUBLIC HEALTH
SECRETARIAT GENERAL

DIRECTORATE OF PHARMACY AND MEDICINE

GUIDELINES ON THE PHARMACOVIGILANCE IN THE REPUBLIC DEMOCRATIC CONGO

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CONTENTS

ABBREVIATIONS AND ACRONYMS

AMM	: Marketing Authorization
NAPR	: National Pharmaceutical Regulatory Authority
CNPV	: Centre National de Pharmacovigilance
CPT	: Pharmaco Therapeutic Committee
DCI	: International Nonproprietary name
DAYS	: International Date of Birth
DPM	: Department of Pharmacy and Medicine
DSUR	: Development Update safety Report
NO	: Adverse event
EIG	: Serious Adverse Effect
EIM	: Undesirable Drug Effect
IN	: Medication Error
PIT	: Health training
I	: International Conference On Harmonisation
ICSR	: Individual case safety report
With DRA	: Medical Dictionnary for Regulatory Activities
OMS	: World Health Organization
PBRER	: Periodic Benefic-Risk Evaluation Report
PSMF	: Pharmacovigilance System Master File
PSUR	: Periodic Update Safety Report
PV	: Pharmacovigilance
QIF	: Inferior quality falsified
QPPV	: Qualified Person for Pharmacovigilance
RDC	: Democratic Republic of Congo
RPAS	: Periodic Safety Update Report
UMC	: Uppsala Monitoring Centre

INTRODUCTION

In the Democratic Republic of Congo, the National Pharmacovigilance System has been operational since 2009, the year of the creation of the National Pharmacovigilance Center by orders of the Minister of Public Health n°1250/CAB/MIN/SP/025/CJ/OMK/2009 of June 13, 2009 amended and supplemented by Ministerial Order No. 1250/CAB/MIN/SP/013/CPH/OBF/ 2015 of September 28, 2015 and Ministerial Order No. 1250/CAB/MIN/SP/AMM/033/CJ / OMK/2009 July 9, 2009 relating respectively to the organization of the National Pharmacovigilance System in the Democratic Republic of Congo and the installation of the National Pharmacovigilance Center (CNPV) within the Clinical Pharmacology and Pharmacovigilance Unit of the Faculties of Medicine and Pharmaceutical Sciences of the University of Kinsha

In DR Congo, the pharmacovigilance system is implemented by the Directorate of Pharmacy and Medicines of the Ministry of Health. It is a decentralized system with Regional Centers, but at the current stage, due to lack of funding, the implementation of the Regional Pharmacovigilance Centers has not yet been carried out, the National Pharmacovigilance Center is therefore the only functional technical structure in the routine of Pharmacovigilance activities. The National Pharmacovigilance Center has been an effective member of the Uppsala Monitoring Center (UMC) based in Sweden since 2010, as can be seen from this correspondence of June 17 from vigibase@who-umc.org of the UMC.

These guidelines are therefore drawn up by the DPM/ANRP in order to define the mechanisms for communicating and disseminating any information relating to the safety of use of the drug or other health product and the way in which the various stakeholders must fulfill the obligations as well as the mechanisms of collaboration between them.

They bring together general guidance on the requirements, procedures, roles and activities in this area, for stakeholders in the national pharmacovigilance system.

It should be noted, as with all guidance documents in rapidly evolving technical areas, that these guidelines are intended to be reviewed regularly.

The requirements explained in these guidelines are based on the ICH guidelines in which they exist, but may be clarified or contain additional requirements in accordance with DRC legislation.

I. GENERAL

I.1. GLOSSARY

- **Confidentiality:** any personal data (identity, element of privacy,
  etc.) or medical to identify the person for whom an adverse effect has
  been notified to a pharmacovigilance structure must be processed in such a way as to remain secret.
  Anyone working in a pharmacovigilance structure is required to respect
  medical secrecy (identity of persons, medical data, etc.), as well as respect
  professional secrecy for any information that it may come to learn in
  the framework of his work (expert report, industrial secrecy, etc.).
  The possible transmission of pharmacovigilance cases outside the structure having
  received the original notification (health authorities, etc.) must respect medical secrecy (including
  including the identity of the notifier) by any appropriate means.
- **Crisis:** a crisis is a situation in which urgent intervention is necessary
  to manage and control the situation given the associated risk. Date of birth
  international (DNI)This is the date on which the very first marketing authorization
  on the market for a product containing a given active ingredient, granted to any
  Pharmaceutical firm, in any country in the world.
- **Development safety update report (DSUR):** format and content for reports
  periodicals on drugs under development.
- **Source document:** any original document related to a file of
  pharmacovigilance, in particular:
  - Telephone conversation report, initial letter from the notifier, internal note in origin of the medical visitor
  - Pharmacovigilance form (completed by the notifier or a person responsible for pharmacovigilance), copies of additional examinations or hospital reports; • Letters (initial, follow-

  up[s], conclusion); • Transmission sheet,
  translations of the sheet; • Printing of computer
  entries (notices, summaries, tables) concerning the file.
- **Adverse event:** any medical event occurring after administration
  of a drug to a patient or clinical trial subject, without necessarily being
  caused by this medicine.

This means that any harmful and unsought-after reaction: clinical or paraclinical sign or symptom (abnormal laboratory results for example), or a disease associated with taking a drug, can be considered as an AE whether or not it is caused by this medicine.

- **Adverse effect:** a harmful and unwanted reaction to a drug or other
  health product, occurring at dosages normally used in humans for
  prophylaxis, diagnosis or treatment of disease or for recovery,
  the rectification or modification of a physiological function, or resulting from a
  misuse of the drug or product.
- **Serious adverse effect (SAE):** This is any adverse effect that leads to death,
  constitutes a life threat, requires hospitalization or extension
  hospitalization, results in significant or persistent incapacity or invalidity, or
  a congenital malformation.
  Life threatening means the patient was at risk of death at the time of occurrence
  of the EIM. Effects which, had they been more severe, would have been
  mortals.
  A suspicion of transmission of an infectious agent by a medicinal product is
  also considered a serious adverse effect.
- **Avoidable side effect:** This is the one that would not have occurred if the care had
  complied with the care considered satisfactory at the time.
  Example: anaphylactic shock after administration of penicillin in a patient with a history of allergy to this drug could have been avoided if the prescriber had taken into account this history (by prescribing another antibiotic). An effect side effects resulting from a medication error are preventable.
- **Unexpected adverse effect:** any adverse effect of its nature, severity or
  the issue does not correspond with the known authoritative information on this drug.
- **Adverse drug reaction (ADR) :** any response to the administration of a
  drug that is harmful and unsought.
  Response to drug administration means cause and effect
  between the drug and the ADR is at least possible.
  According to this definition, an ADR can result from the use of a drug at the doses therapy, overdose, misuse or medication error.
- **Minimum elements of notification:** with a view to effect notification
  suspected undesirable, the minimum elements are: an identifiable drug, a
  identifiable patient, an identifiable adverse reaction and an identifiable reporter.

- **Pharmacovigilance survey :** evaluation work, carried out at the request of competent authorities by a CRPV, in collaboration with the person responsible for the pharmacovigilance of the company or organization using the drug or product concerned, whenever there is reason to believe that a drug risk

should be evaluated or re-evaluated. There are two types of Pharmacovigilance investigations:

- *Pharmacovigilance monitoring, carried out with the aim of carrying out specific monitoring of the tolerance profile of the drug or product as soon as it is placed on the market, during the first years, or even throughout its marketing period;*
- *The pharmacovigilance survey, carried out with the aim of reassessing the risk of a drug or product following an alert.*

- **Medication error:** is the unintentional omission or performance of a act relating to a drug that may be the cause of a risk or an event undesirable for the patient.

  Example: wrong prescription, forgetting to administer the medication, wrong drug dilution, patient confusion…

- **Clinical trial:** is defined as a clinical trial any investigation on subjects human beings, aiming to discover or verify the effects, clinical, pharmacological or adverse effects of one or more investigational products, with the aim of establishing their efficacy and/or safety.

  A clinical trial can take place at one or more sites.

- **Safety study after marketing authorization (Post Authorization Safety Study (PASS):** pharmacoepidemiological study or trial clinic carried out in accordance with the provisions of the marketing authorization market, with the objective of identifying, characterizing or quantifying a risk or confirm the safety profile of the authorized medicinal product or to assess the efficacy risk management measures.

- **Generic:** Generic is any medicinal product with the same quantitative and qualitative composition of active ingredient and the same form pharmaceutical than a reference medicinal product and for which the bioequivalence to the reference pharmaceutical (medicinal) product a been established by appropriate bioavailability studies.

- **Incident:** an incident is any situation in which an event occurs or a new information in relation to an authorized medicinal product, and which may have an impact on public health.

  An incident may concern the efficacy, safety or quality of a product medicated. In most cases this will be a safety issue. or product quality. Any situation, at first sight without gravity, but which is in the public domain - mediated subject or not - and which could lead to concerns of the public about a drug product, should be considered an incident. Of even situations that could have a negative impact on the use of a drug (which would cause patients to interrupt their treatment, for example) should be considered incidents.

- **Missing information:** is called missing information, any gap in the knowledge about a drug in relation to its safety or use and which could have a clinically relevant impact.
- **Investigational drug:** this is an experimental product under study or experimentation. This more specific term excludes placebos and drugs used as a comparator in clinical trials, which are included in the definition investigational drug product.
- **Risk Minimization Measures:** activities aimed at preventing, limiting the probability of occurrence or reducing the severity in the event of occurrence of an adverse effect associated with exposure to a drug product.
- **Misuse of a medicinal product:** this is any situation in which a medicinal product is used intentionally and inappropriately, in disagree with the authorized information on this medicine.
- **Medication leaflet:** paper containing information on the medication intended to the user and which accompanies the medicine.
- **Notification of adverse effects or Individual Case Safety Report (ICSR) :** it is the format and content of the report of suspected adverse reactions after the intake of a medicinal product by a specific patient at a given time.
  The English name with its acronym (Individual Case Safety Report (ICSR), are retained in this guide for consistency with international literature.
- **Spontaneous notification:** this is a report made by a notifier (healthcare professional, or patient) to a Pharmaceutical Firm, to the authority of regulation or other relevant organization describing one or more endpoints side effects likely to be due to the administration of one or more products drugs that have occurred in a given patient at a given time and which does not come of a study or any other organized data collection system.
- **Overdose:** administration of a quantity of medication, per intake or cumulatively, which is higher than the maximum authorized doses according to the authorized information on this medicine.
- **Periodic Safety Update Report (PSUR)**
  Update on Safety (RPAS): format and content for the submission of the assessment of the risk-benefit ratio of a medicinal product, provided by a marketing authorization holder, at regular time intervals known to the regulatory authority in the post-authorisation period.

Its objective is:

1. To assess the follow-up of the safety profile of a drug or product, with regard to the knowledge acquired and information available;
2. To consider, if necessary, a modification of the information on the drug or product, or even a reassessment of the benefit/risk ratio.

This document contains an update of the pharmacovigilance data collected worldwide during the period under review. It is transmitted immediately at the request of the ANRP and/or according to a defined periodicity after the registration of the drug or product.

In practice, it includes a summary of all the pharmacovigilance data of which the company or organization using the medicinal product or product is aware, as well as any information useful for assessing the risks and benefits associated with the use. of this medicine or product. This summary is accompanied by a scientific assessment of these risks and benefits.

- **Pharmacovigilance:** science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions and any other problem related to the use of medicines and other health products.
- **Risk Management Plan:** is a detailed description of the Risk Management System. This plan must identify or characterize the profile of safety of the medicinal product concerned, as well as future characterizations in profile. He must also document the measures aimed at avoiding or minimizing the risk, including including the evaluation of the effectiveness of these measures. It must also contain the obligations post-marketing which have been imposed as a condition of the granting of the authorization to marketing.
- **Safety issue:** have included in this definition the potential risks important, the risks identified important and the missing information (see the definitions of these terms below).
- **Signal management process:** includes the following activities: signal detection signal, signal validation, signal confirmation, signal analysis and prioritization, signal evaluation and recommendations for action.

  These are therefore activities carried out to determine, on the basis of available information (ICSR, aggregate reporting, literature or other source), if there are new risks caused by a drug product or if the known risks have changed.
- **Drug product:** any substance or composition of substance presented as having preventive or curative properties with regard to human diseases as well as any product that can be administered to humans, in order to establish a diagnosis or to restore, correct or modify its organic functions, by its actions pharmacological, metabolic or immunological.
- **Investigational medicinal product:** a medicinal product of investigation is a Pharmaceutical form of an active principle under study or used as a reference in a clinical trial. This includes products already authorized but used or formulated and packaged in a manner different from that authorized, or used for an unauthorized indication or to obtain more information on the authorized form.
- **Immunological medicinal product:** Any medicinal product consisting of a vaccine, serum, toxin or allergenic product.

Are considered as vaccines, serum and toxins, agents used to produce a active immunity (such as BCG, Polio Vaccine…), agents used to diagnose the immune status (tuberculin...) and the agents used to produce a passive immunity (diphtheria antitoxin, etc.).

Allergenic product means medicinal products intended to identify or induce an modification of the immunological response to an allergenic agent.

- **Risk-benefit ratio:** this is the evaluation of the positive therapeutic effects of a medicinal product in relation to its risks.
- **Identified risk:** An adverse effect for which there is strong evidence of association with a medicinal product.

  As an adverse effect adequately demonstrated by preclinical studies then confirmed by clinical observations. Or an adverse effect documented by well-conducted clinical trials or epidemiological studies, for which the difference between the control group and the control is such that it suggests a relation of cause and effect.
- **Significant Risk (Potential or Identified):** Whether potential or identified, a risk is said to be important if it can modify the risk/benefit ratio of a medicinal product or have an impact from a public health point of view.

  Several factors come into play to determine the significance of a risk: the effect on a patient, the severity, the impact on public health. A risk that could be included as a contraindication or in the precautions for use of a drug should be considered important.
- **Risk associated with the use of a medicinal product:** this is the probability occurrence of a harmful event, related to the quality, safety or efficacy of a medicinal product, with regard to the health of the patient or public health, or the likelihood of adverse environmental effects.
- **Potential risk:** a harmful effect for which there are elements that could suspect an association with a medicinal product, which association is not still proven.

  As a toxic effect observed by preclinical studies but not yet observed in clinical studies. Or an adverse effect documented by trials well-conducted clinical or epidemiological studies, for which the difference between the control and control group is not sufficient to suggest a causal relationship to effect.

- **Signal:** information from one or multiple sources suggesting a potential new causal association or a new aspect of a known causal association between a medicinal product and an adverse event, which is such that it justifies the setting en route to verification measures.

- **Risk Management System:** together Pharmacovigilance activities, and interventions aimed at identifying, characterize, prevent or minimize the risk associated with a drug product, including an evaluation of the effectiveness of these interventions.

- **Signal validation:** verification process of documents supporting the detection of a signal to check if they contain enough elements that can make suspect a new risk or a new aspect of a known risk and therefore justify in-depth analyses.

I.2. OBJECTIVES OF PHARMACOVIGILANCE

The main objectives of pharmacovigilance systems are to:

- Contribute to the evaluation and communication of the benefit/risk ratio of medicinal products placed on the market; - Work towards effective communication with professionals and the public on AEs and other drug-related issues;
- Promote education and clinical training in the field of AEs and other drug-related problems; - Promote the rational use of drugs; - Improve the quality of care and patient safety.

I.3. CHAMP D'APPLICATION

Pharmacovigilance applies to medicines and other health products for human use, in particular:

- Medicines within the meaning of the regulations in force;
- Homeopathic medicines;
- Vaccines and other biological products;
- Radiopharmaceuticals; • Cell therapy product; • Gene therapy product;
- Medical equipment; • Blood and its derivatives; • Insecticides and acaricides intended for application on humans; • Herbal products;

- Food supplements;
- Drugs in clinical trials;
- Cosmetic products.

Pharmacovigilance also deals with all other problems related to use such as medication errors, treatment failures, quality medicines inferior and falsified (QIF) and other health products.

I.4. PHARMACOVIGILANCE AND PHARMACEUTICAL POLICY NATIONAL

One of the major objectives of the National Pharmaceutical Policy of the Democratic Republic of Congo is to establish a pharmaceutical information and pharmacovigilance system. To this end, the Government of the Republic is committed to creating a National Pharmacovigilance System, the National Pharmacovigilance Center, the Regional Pharmacovigilance Centers, the Drug Dependency and Drug Addiction Center at the central, provincial and peripheral levels.

I.5. PHARMACOVIGILANCE IN SPECIALIZED PROGRAMS FROM THE MINISTRY OF PUBLIC HEALTH

The specialized programs of the Ministry of Public Health involved in the distribution of drugs as well as the health facilities are required to organize a pharmacovigilance service placed under the responsibility of a pharmacist or a doctor with proven knowledge of pharmacovigilance.

II. NATIONAL PHARMACOVIGILANCE SYSTEMS

The National Pharmacovigilance System is organized by the Ministry of Public Health and has the objectives of:

- Detect as early as possible all adverse effects of health products, especially those that are serious and unexpected and likely to be due to the use health products;
- Detect harmful effects resulting from misuse, medication errors, exposure to certain products, addiction, poor quality of health ;
- Provide training and information on the adverse effects of products of health with health professionals and the public;
- Give reasoned technical opinions to personalities and organizations having legal decision-making power on the authorization of use and regulation of products. health ;
- Carry out studies on the mechanisms and consequences of the adverse effects of health products.

The National Pharmacovigilance System is based on:

- A network responsible for collecting reports of adverse effects; • The recording, analysis, evaluation of the quality of the information collected and its ranking ;
- Centralization and evaluation of all risk information medicated;
- Communication on drug risks;
- Decision-making;
- The realization of studies concerning the safety of use of drugs and other health products.

The National Pharmacovigilance system is implemented by the Department of Pharmacy and Medicine (DPM)/National Pharmaceutical Regulatory Authority (ANRP) and includes the National Pharmacovigilance Commission, the Technical Committee, the National Pharmacovigilance Center, the Regional Pharmacovigilance Centers, the Pharmacovigilance Focal Points, pharmaceutical companies, specialized health programs, health professionals, the public, etc.

II.1. MAIN STAKEHOLDERS IN THE NATIONAL SYSTEM OF PHARMACOVIGILANCE

- National Pharmacovigilance Commission
- The Department of Pharmacy and Medicine (DPM/ANRP);
- The Pharmacovigilance Technical Committee;
- The National Pharmacovigilance Center;
- The Regional Pharmacovigilance Centers;
- Pharmacovigilance Focal Points in health structures;
- Pharmaceutical firms;
- Health professionals;
- The specialized programs of the Ministry of Public Health;
- The Audience

II.1.1. NATIONAL PHARMACOVIGILANCE COMMISSION The National Pharmacovigilance Commission sits with the DPM/ANRP and is responsible for:

- To define the orientations of Pharmacovigilance;
- Assess information on adverse effects of drugs and other health products;

- To advise the Director of the DPM/ANRP on the measures to be taken to ensure patient safety in the face of medication risks;
- To propose to the Director of the DPM/ANRP the surveys and work deemed useful for the exercise of Pharmacovigilance; • Giving advice to the Minister in charge of Health at the request of the latter on any question relating to the area of competence of the commission;
- Assess the risks incurred by the subjects participating in a clinical trial and give its opinion to the DPM/ANRP on its continuation or termination.

The National Pharmacovigilance Commission is made up of the following members: • The Director of the DPM/ANRP or his representative

- The Director of the Department of Disease Control or his representative
- The Director of the Care Department or his representative
- The Director of the INRB or his representative
- The Representative of the Interministerial Committee for the Fight against Drugs • The Director of the National Poison Control Center or his representative
- The CNPV Director or his representative
- A representative of the Order of Physicians
- A representative of the Order of Pharmacists
- A representative of the National Association of Dental Surgeons
- A representative of the association of midwives
- A representative of all nursing associations
- A representative of the Association of Pharmacy Assistants
- A representative from each Regional Pharmacovigilance Center

The National Commission may not appoint any competent person if the agenda so requires.

The National Pharmacovigilance Commission is chaired by the Director of the DPM/ANRP or his representative.

The members of the National Pharmacovigilance Commission are bound by the obligation of confidentiality and are required to avoid conflicts of interest.

The National Pharmacovigilance Commission meets twice a year and decides on all questions proposed by the Technical Pharmacovigilance Committee. If necessary, it can request any outside expertise.

The Commission also decides in extraordinary session on measures or decisions taken urgently by the DPM /ANRP outside the sessions.

II.1.2. DIRECTION OF PHARMACIE ET DU MEDICAMENT: DPM/ANRP

Its mission is to:

- Establish the National Pharmacovigilance System and mobilize the necessary means for its operation;
- Manage national or international alerts on products and seize the Commission National if necessary;
- Coordinate the actions of the various stakeholders and ensure compliance with procedures good pharmacovigilance practices;
- Receive technical reports from the National Center for Pharmacovigilance; • Receive periodic reports from pharmaceutical companies (PBRERs and DSURs) and analyze them;
- Prepare and submit files to the National Pharmacovigilance Commission.

II.1.3. COMMIT TECHNIQUE OF PHARMACOVIGILANCE

The Pharmacovigilance Technical Committee is a scientific committee attached to the Center National Pharmacovigilance and is responsible for:

- Establish a permanent unit of pharmacology specialists and clinical experts who can, if necessary, assess the risks incurred by humans and propose the measures to be taken to the National Pharmacovigilance Commission; • Provide technical advice on all scientific issues arising at the Center National de Pharmacovigilance ;
- Prepare the work of the National Pharmacovigilance Commission;
- Respond to any request for technical advice presented by the DPM/ANRP;
- Plan the annual program of scientific and research activities to be undertaken.

The Technical Committee is chaired by the Director of the National Center for Pharmacovigilance. It is composed of :

- 6 medical specialists (general practitioner, internist, pediatrician, neuropsychiatrist, anesthetist-resuscitator and dermatologist);
- 1 dental surgeon;
- 3 pharmacists (community pharmacists, biologist and clinician);
- 3 Pharmacologues ;
- 3 Toxicologists and
- 1 Epidemiologist,

The latter are appointed by the National Pharmacovigilance Commission on the proposal of the National Pharmacovigilance Center.

The Technical Committee may call on any outside expertise if the agenda so requires.

It meets once a quarter under the direction of its chairman and whenever the urgency of the situation so requires.

II.1.4. CENTRE NATIONAL DE PHARMACOVIGILANCE (CNPV)

Created and implemented within the Clinical Pharmacology and Pharmacovigilance Unit (UPC PV) of the Faculties of Pharmaceutical Sciences and Medicine of the University of Kinshasa.

The National Center for Pharmacovigilance is responsible for:

- Apply good pharmacovigilance practice procedures;
- Manage the means necessary for its proper functioning.

The National Pharmacovigilance Center is responsible for:

- Receive from marketing authorization holders information on adverse effects of health products, assess the relative risk and establish attributability;
- Collect information from pharmaceutical establishments, health institutions, health professionals or any other person on the adverse effects of health products, assess the relative risk and establish accountability;
- Generate alerts in the field of pharmacovigilance and seize the Commission National Pharmacovigilance if necessary;
- Carry out and coordinate any survey and study aimed at better assessing the extent of a undesirable effect ;
- Transmit a quarterly technical report to the DPM/ANRP;
- Ensure contact with WHO collaborating centers for Pharmacovigilance and with other Pharmacovigilance Centers;
- Ensure the training of the personnel of the Regional Centers of Pharmacovigilance in the methods of collection of the collected data, validation, imputability and surveys in pharmacovigilance;
- Participate in the education and continuing education of health professionals relating to health products and adverse effects;
- Organize prevention campaigns aimed at the public to reduce morbidity and mortality linked to the irrational use of health products;

- Play the role of Regional Pharmacovigilance Center in the region where it is established;
- Receive activity reports from the Regional Pharmacovigilance Centers.

II.1.5. REGIONAL PHARMACOVIGILANCE CENTERS

The Regional Pharmacovigilance Centers are decentralized Units of the National Pharmacovigilance system. They ensure the collection and analysis of notifications from a province or a group of neighboring provinces. They are installed in Units or care structures within public university hospitals and, created by
via ministerial order, on the proposal of the National Pharmacovigilance Commission, after reasoned opinion from the National Pharmacovigilance Center.

The Regional Pharmacovigilance Centers constitute the expertise within the System National Pharmacovigilance in their area of activity and are responsible for:

- Collect declarations and information from professionals and/or structures ;
- Monitor, assess and prevent potential or proven drug risks and promote the rational use of medicines;
- Generate the signals; •

Conduct surveys and pharmacovigilance studies;

- Contribute to the training and information of health professionals on the pharmacovigilance ;
- Transmit to the National Pharmacovigilance Center the information collected on adverse effects and substandard and falsified medicines (QIFs);
- Transmit information relating to serious adverse effects expeditiously, ie as soon as the notifier becomes aware of them but in any case within a period not exceeding 7 calendar days.

II.1.6. PHARMACEUTICAL FIRMS HOLDING MARKETING AUTHORIZATIONS WALK

Any Pharmaceutical Firm holding a marketing authorization has the obligation to ensure the collection of information related to the adverse effects of its medicinal products, compliance with the declaration after registration and the transmission of periodic updated pharmacovigilance reports (PSUR) with up-to-date information collected from the internal and external market on the safety of the use of medicines.

They are required to set up a pharmacovigilance service under the permanent responsibility of a qualified person with experience in pharmacovigilance or Qualified Person for Pharmacovigilance (QPPV). The person in charge of pharmacovigilance must ensure compliance with the obligations of declaration of pharmacovigilance with his firm and the latter must collaborate for the smooth running of activities aimed at the safety of use of the drugs that it markets.

For this, pharmaceutical companies must have the permanent document of the pharmacovigilance system (Pharmacovigilance System Master File: PSMF) which is the document required in the event of an audit or inspection.
In addition, pharmaceutical companies must regularly make available to the DPM/ANRP:

- Periodic pharmacovigilance update reports (PBRERs and DSURs) which they must communicate regularly in accordance with good pharmacovigilance practices;
- Spontaneous adverse effects communicated to them;
- Data from post-marketing studies;
- The risk management plan if necessary;
- Any document and data required by the latter for the audit or inspection.

Pharmaceutical companies must notify the National PharmacoVigilance Center without delay of all serious and unexpected adverse effects.

II.1.7. PHARMACOTHERAPEUTIC COMMITTEE (CPT)

Established in hospitals, Pharmacotherapeutic Committees (CPT) have the role of promoting and ensuring the rational use of drugs.

In terms of Pharmacovigilance, they take care of collecting reports of adverse effects in their area of activity, and send them to the Pharmacovigilance Center within their jurisdiction. They are also responsible for the management and management of adverse effects, medication errors, treatment failures, detection of substandard and falsified medicines. As such, these Committees are relays between the Regional Centers and the health structures in their respective areas.

II.1.8. HEALTH PROFESSIONALS

Doctors, dental surgeons, pharmacists, pharmacy assistants, nurses and midwives working in FOSAs, health programs and pharmacies are the preferred source of information. This is how they must collaborate in the safety of use of Medicines. To this end, they are trained and made aware of Pharmacovigilance and notification; they are required to notify a Pharmacovigilance center within their jurisdiction of:

- any suspected adverse reactions in connection with the use of one or more drugs ;
- any observation of abuse or misuse and;
- any medication errors and treatment failures
- any suspicion of the SSFFC
- any fact that they deem relevant to declare.

They are bound by the confidentiality of the data and information appearing on the notification.

Upon receipt of the notification, the Center must provide an acknowledgment of receipt and assist them in the event of serious adverse effects when treatment proves necessary.

II.1.9. PHARMACOVIGILANCE FOCAL POINTS

The focal points are health professionals who promote pharmacovigilance in their respective structures. They must :

- Make the relay between their structure and the Regional Pharmacovigilance Center
- Collect and send ICSRs to the Regional Pharmacovigilance Center
- Coordinate pharmacovigilance activities in their respective institutions

A focal point must receive basic training in pharmacovigilance including: adverse drug reactions and their manifestations by system and organs, notification,
accountability, database, information, signal, …

II.1.10. PROGRAMMES SPECIALISES

Several national health programs are implemented in the Democratic Republic of Congo. They distribute large quantities of medicines and health products from multiple sources.

Also, the population treated with these products is exposed to AEs and treatment failures if a strategy aimed at early detection and evaluation of any problem related to the use of these drugs is not put in place.

Thus, the specialized programs of the Ministry of Public Health involved in the distribution of drugs as well as the health facilities are required to organize a pharmacovigilance service placed under the responsibility of a pharmacist or a doctor with proven knowledge of pharmacovigilance.

II.1.11. PROFESSIONAL ORDERS AND ASSOCIATIONS (PHARMACEUTICALS, MEDICAL AND PARAMEDICAL)

Representatives of socio-professional health orders are members of the National Pharmacovigilance Commission.

II.1.12. PUBLIC

Public notification should be encouraged. It makes it possible to fight against under-reporting, and to freely report adverse effects without influence from the nursing staff.

Patients or their representative and approved patient associations, requested or not by patients, can make statements on the adverse effects suspected by the patient or his entourage to be related to the use of a medicine.
To do this, the public can contact the center directly by SMS, telephone, e-mail, website, etc. and must receive feedback from the center. In case of adverse effects

serious, the centre, in conjunction with the nursing staff, must make arrangements for treatment.

II.1.13. SOCKS

The media must be used optimally and efficiently, but also with caution, to convey pharmacovigilance information to the general public, the pharmaceutical industry and healthcare professionals.

II.1.14. CONSUMER ASSOCIATIONS

It is important to have the list of approved consumer protection associations and to communicate with them on pharmacovigilance in order to provide them with the real information.

III. NOTIFICATION

Notification is the reporting of adverse events following the use of a medication or other health product.
It provides the information necessary for the operation of the Pharmacovigilance system to improve patient care.
It is obligatory to notify any adverse event even when it is the consequence of abuse or misuse.

All providers are required to systematically notify adverse events.
Regulatory or legislative provisions may determine the mandatory nature or not of the notification.

III.1. NOTIFICATEUR

Can notify:

- Health professionals: Doctor, Pharmacist, Pharmacy Assistant, Nurse, Dental Surgeon, Midwife;
- Community Relays;
- Pharmaceutical companies;
- Sponsors of clinical trials;
- The patient or his representative and patient associations.

Patients and their entourage can also notify the Regional Pharmacovigilance Center directly.

III.2. WHAT TO NOTIFY?

- any adverse event as defined in this document. The effects to be reported may be symptoms and clinical signs (headaches, drop in blood pressure, etc.);
- changes in biological values (raised transaminases, lower blood blood sugar, …) or medication errors
- treatment failures
- Drugs interactions
- any observation of overdose, abuse or misuse
- any problem related to exposure during pregnancy or breastfeeding
- any observation of loss of efficacy (in particular with vaccines, contraceptives or drugs or other pharmaceutical products intended for the treatment of diseases involving life-threatening, etc.);
- any effect deemed relevant to declare.

III.3. CONDITIONS FOR NOTIFYING

At least 4 elements must be present to notify:

- **An identifiable patient :** initials, age and gender are essential, medical and medication history are important
- **An identifiable drug :** at least the name of the drug (Trade name and INN) and the date of start of administration must be present. The dosage + route of administration, the end date and the batch number are very useful.
- **An adverse effect :** the description of the adverse event must be given (nature, location, seriousness, characteristic) as well as the results of the investigations and tests, the start and end dates and evolution.
- **An identifiable notifier :** the name and contact details of the notifier will make it possible to contact him to provide him with information or help him in handling the case.

III.4. INSTRUMENT OF COLLECTION

The National Center for Pharmacovigilance notification form described in the point below of this document constitutes the notification tool for any adverse effect.

III.5. NOTIFICATION TERMS

III.5.1. Expedited notification

All adverse reactions that are both serious and unexpected will need to follow the rapid reporting process. This applies to spontaneous reports, those resulting from clinical or epidemiological studies, whatever their structure or objective.

The primary source of notification must be specified in the notification form.

III.5.2. Reporting deadlines

All serious and unexpected adverse reactions which are fatal or constitute a life threat, including those occurring during clinical trials, must be notified to the National Pharmacovigilance Center expeditiously, i.e. as soon as the notifier becomes aware of them but in any case within a period not exceeding 7 calendar days.
Update notes may be provided within an additional period not exceeding 15 calendar days.

The count of days begins when a member of the notifying institution (member of the medical team, employee of a firm holding a marketing authorization) becomes aware of the suspected adverse reaction and that the minimum notification requirements are met.

All other serious and unexpected adverse effects must be reported immediately, but within a period not exceeding 15 calendar days.

Adverse, non-serious and non-unexpected effects may be notified within a period not exceeding 90 calendar days.

III.5.3. Filling in the notification form

The DRC notification sheet has 4 main parts corresponding to the 4 minimum notification elements:

The patient, the notifier, the drugs, the ADRs

a) First part: the patient

The following items will be collected for the patient:

PATIENT

Initiales :.....Date de naissance : ...../...../..... Poids :.....Kg Sexe : F / M N° dossier :.....

Enceinte? OUI /__/ NON/__/ ou DDR :.../.... /..... Adresse :.....

ANTECEDENTS :.....

.....

The patient's initials and not their full name will be recorded to ensure confidentiality.
The patient's age can be recorded instead of the date of birth.

b) The notifier:

LE NOTIFICATEUR

Nom et post-nom :.....

Médecin /__/ pharmacien /__/ Dentiste /__/ Infirmier /__/ Autre (préciser) :.....

Téléphone : ..... Email :.....

Institution de santé/service :.....

For the notifier on the other hand, we need to identify him as precisely as possible because we must be able to contact him, to communicate to him the information concerning his notification or to help him in taking charge of the effect. undesirable.

c) Medicines

LES MEDICAMENTS

	Nom Commercial	DCI	Voie	Posologie	Date de début	Date d'arrêt	indication	Fabricant	N° de lot
1									
2									
3									
4									

It is important to mention the drug responsible for the adverse effect but also the other drugs taken concomitantly by the patient. Because some side effects are the result of drug interactions rather than the action of a single drug in particular.

d) Adverse effects

In the current version of the notification form, this part is also presented in the form of a table to allow the recording of data relating to each AE separately.

EVENEMENTS INDESIRABLES

N°	EIM	Grave Oui/Non	Raison de gravité*	Date de début	Date de fin	Évolution à l'arrêt du traitement**	Évolution la réadministration***	Traitement correcteur
1								
2								
3								
4								
5								

*raison de gravité : 1= décès ; 2=hospitalisation/prolongation d'hospitalisation ; 3=Mise en jeu du pronostic vital ; 4=invalidité ; 5= effet sur le produit de conception ; 6=Effet cliniquement significatif
**Évolution à l'arrêt : 1=amendement ; 2=persistance ; 3=aggravation ; 4= inconnue
*** 1= réapparition ; 2=non réapparition ; 3=pas de réadministration

Résultats d'éventuels examens para cliniques (+ date de prélèvement) :
.....
Description (précisez le numéro de l'Evénement indésirable que vous voulez décrire) :
.....
.....

Some boxes must be filled in with numbers whose meanings are at the bottom of the table. You must be particularly careful when filling in these boxes.

In the “serious reason” column, 1 means death and 4 means invalidity.

III.5.4. Circular about notification

Reports of adverse reactions likely to be due to a drug can be made:

- Directly by mail in a closed envelope. The address is mentioned on the national file notification.
- By internet either by email or via the CNPV website
- By telephone via the specific notification software provided by the CNPV
- The forms can also be delivered by hand to CNPV or CRPV staff or to Pharmacovigilance focal points, particularly during Pharmacovigilance supervision visits.

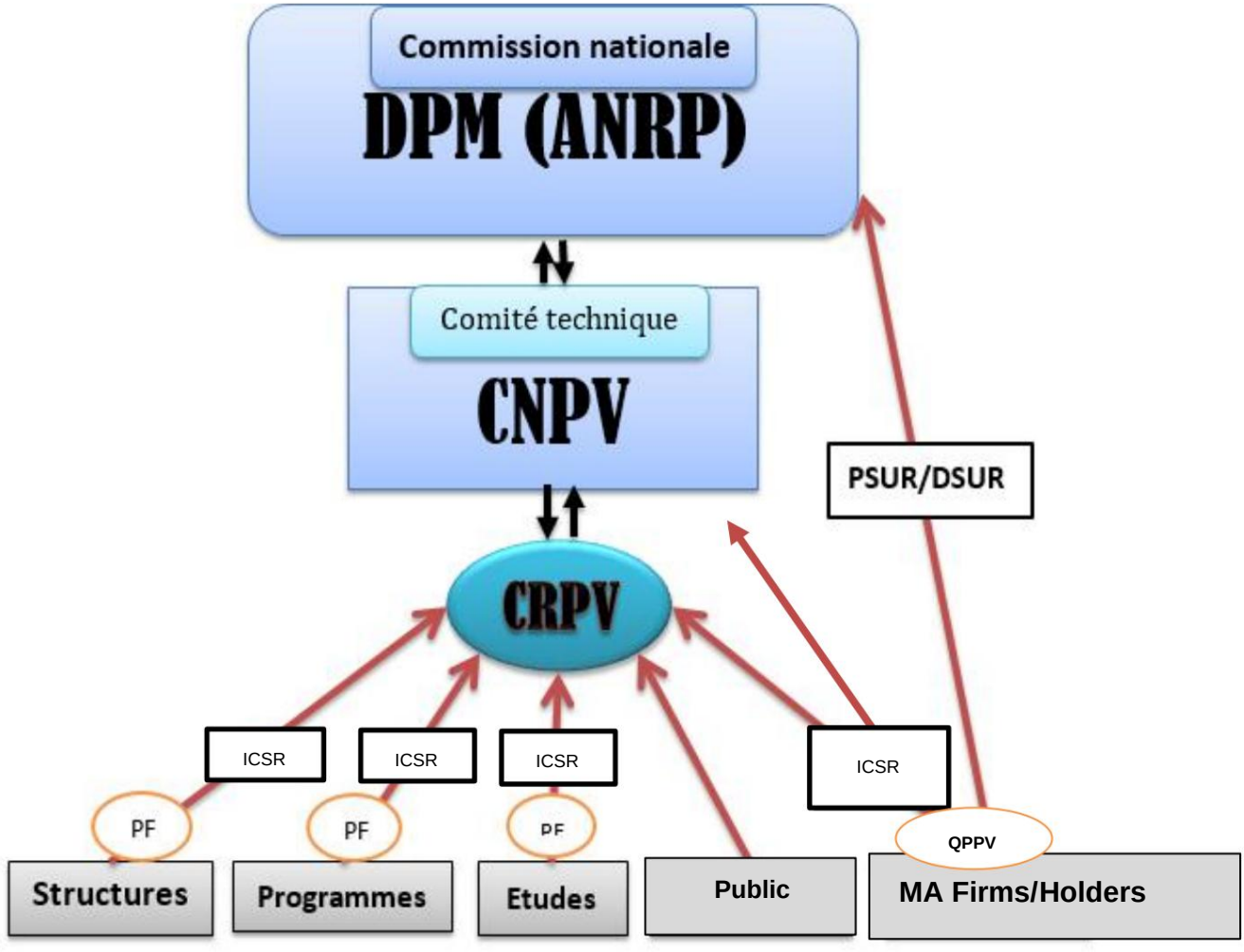

Figure 1. Notification circuit diagram

III.5.5. Evaluation of notified cases and Imputability of adverse events

The National PharmacoVigilance Center is responsible for evaluating cases. This evaluation must assess the following elements:

- **The quality of information:** completeness and integrity of data, quality of diagnosis (notification form);
- **Coding:** Drug names should be coded in a systematic way using for example the WHO Drug Dictionary. For coding of AEs, MedDRA terminology should be used.

- **Relevance:** relating to the detection of a new reaction, the regulation of the product, or the scientific or educational value of the observation;
- **Identification of duplicates:** certain characteristics of the observation such as sex, age, date of exposure to the drug, etc… can be used to identify cases that have been declared twice; • **Imputability**

or the determination of the causal link by the method of the center WHO collaborator

III.5.6. Actions to be taken following the evaluation of data on the pharmacovigilance

After evaluating pharmacovigilance data, the DPM/ANRP may decide to restrict the conditions of use, extend the precautions for use, suspend, withdraw or modify the marketing authorization. She must inform immediately the Regional Pharmacovigilance Centers and the other actors of the National Pharmacovigilance System.

IV. RESPONSIBILITIES IN THE MANAGEMENT OF A SIGNAL, A PHARMACOVIGILANCE CRISIS

IV.1. SIGNAL MANAGEMENT

The national pharmacovigilance system must enable the detection and management of national and international drug signals on drugs and other health products.

If a signal is confirmed after validation and verification, it triggers an alert.

Activities related to signal detection, signal validation, signal confirmation, signal analysis and prioritization and signal evaluation are entrusted to the National Center for PharmacoVigilance. This will formulate recommendations for action which will be proposed to the National Pharmacovigilance Commission for an opinion and the decisions will be taken by the DPM/ANRP.

The signals detected by the pharmaceutical companies holding MAs must be reported to the CNPV or the DPM/ANRP in accordance with good pharmacovigilance practices.

If the signal is triggered at the international level, an evaluation before its endorsement will be necessary. The National PharmacoVigilance Center will submit the results of the assessment and the proposals for action to the National Commission. Decisions will be made by the DPM/ANRP.

IV.2. CRISIS MANAGEMENT

Any crisis situation requires prompt intervention. It is therefore imperative that the intervention is not delayed by the administrative burden. Any crisis situation must be brought to the attention of the Director of the DPM/ANRP or his delegate. This will decide on the actions to be taken urgently. It entrusts the CNPV or the National Pharmacovigilance Commission with the task of carrying out investigations and quickly making proposals for action.

IV.3. ENQUETES ET SUIVI IN PHARMACOVIGILANCE

IV.3.1. Investigation

The pharmacovigilance survey is carried out with the aim of evaluating or reassessing the risk of a drug or health product. Following a national or international alert, the DPM/ANRP may decide to open an investigation on the proposal of the National Pharmacovigilance Commission with a view to possible preventive or corrective measures. In cases of emergency and flagrant an investigation can also be set up by an ad hoc commission including at least the DPM/ANRP.

In addition to alerts, other situations such as the presence of substandard and falsified medicine that has caused harm can also trigger an investigation.

As part of the pharmacovigilance survey, the DPM/ANRP requisition specifies:

- The location of the survey;
- The reasons for the investigation;
- The adverse effects concerned;
- The drugs/products concerned;
- The pharmaceutical forms concerned if necessary
- The name of the person(s) in charge of the survey.

The survey manager(s) develop(s) the survey protocol/approach and designate their rapporteur and the team manager.

The persons thus designated to conduct the investigation must sign the declaration of conflicts of interest and confidentiality.

When two different teams are designated, they should have different tasks to perform depending on the designated survey objectives. This will be justified by the different areas of intervention dictated by the need for the expected final results.

The investigation team contacts and then establishes contact with the MAH holder or his legal representative the elements which will constitute the investigation during the meetings, the minutes of which must be validated by both parties.

In the event that the investigation must take place outside the MA holder's facilities,
the investigators can operate directly without the intervention of the latter.

They carry out the investigation and gather the available data. Additional data can be requested if necessary.

In the event that additional laboratory analyzes must be undertaken, the rapporteur contacts the ANRP directly to carry them out.

During the evaluation of the data, each of the parties may enlist the assistance of a
expert ; analyzes and imputations are carried out concomitantly.

At the end of the investigation, the team sends its report to the DPM/ANRP after analysis of the investigation report, proposes measures to be taken to the DPM/ANRP before forwarding it to the national commission.

The national commission, after examining the proposals, proposes measures to be taken to the DPM/ANRP.

IV.3.2. Follow up

Pharmacovigilance monitoring relates to the monitoring of the benefit/risk profile of a medicinal product used in clinical trials, during the first years of post-authorisation use, then throughout its duration in circulation on the market.

Drugs used during mass treatments as well as vaccines during vaccination campaigns are also concerned by monitoring.

The procedure to follow is the same as that described for the survey!

IV.4. COMMUNICATION EN PHARMACOVIGILANCE

Information is an effective instrument to stimulate notifications. The firm pharmaceutical company or the marketing authorization holder, competent authorities and healthcare providers must communicate the risks of AEs effectively in order to gain public confidence.

A communication must be made in the following cases:

- when a regulatory decision is taken by the DPM/ANRP in connection with pharmacovigilance activities (suspension, withdrawal or non-renewal of the MA);
- when a modification of the Marketing Authorization requires specific information from healthcare professionals and other players in the National Pharmacovigilance System (for example: new contraindication or warning, modification of therapeutic indications or dosage, etc.);
- when there is a need to modify or recall the conditions of proper use of the drug or other health product (risks of misuse, medication error) or in the event of new recommendations for the management or prevention of a adverse effect (risk reduction).

IV.5. FUNDING OF PHARMACOVIGILANCE

The National Pharmacovigilance System must have regular financial resources to better achieve its objectives. Budget assessment should be based on notification rate, population size and drug consumption.

The sources of funding for the National Pharmacovigilance System are:

- the Congolese State subsidy;
- approval fees;
- mandatory pharmacovigilance costs (filing of PSURs);
- the participation of specialized programs of the Ministry of Public Health;
- subsidies other than those from the Congolese State;
- bodies or organizations involved in pharmacovigilance;
- any other source than those cited above.

NB Any funding from a pharmaceutical firm/MA holder must be done under conditions avoiding any conflict of interest.

ANNEXES

APPENDIX 1: Adverse Event Notification Form

République Démocratique du Congo

CNPV

Centre National de PharmacoVigilance

Fiche de Notification d'Evénement Indésirable

PATIENT

Initiales :.....Date de naissance : ...../...../..... Poids :.....Kg Sexe : F / M N° dossier :.....

Enceinte? OUI /__/ NON/__/ ou DDR :.../..../..... Adresse :.....

ANTECEDENTS :.....

.....

.....

LE NOTIFICATEUR

Nom et post-nom :.....

Médecin /__/ pharmacien /__/ Dentiste /__/ Infirmier /__/ Autre (préciser) :.....

Téléphone : ..... Email :.....

Institution de santé/service :.....

LES MEDICAMENTS

	Nom Commercial	DCI	Voie	Posologie	Date de début	Date d'arrêt	indication	Fabricant	N° de lot
1									
2									
3									
4									

Si plante médicinale : Nom scientifique		Nom vernaculaire	Voie d'administr. + quantité	Date de début	Date d'arrêt	Mode de préparation	Parties utilisés
1							

L'EVENEMENT INDESIRABLE

N°	EIM	Grave Oui/Non	Raison de gravité*	Date de début	Date de fin	Évolution à l'arrêt du traitement**	Évolution la réadministration***	Traitement correcteur
1								
2								
3								
4								
5								

*raison de gravité : 1= décès ; 2=hospitalisation/prolongation d'hospitalisation ; 3=Mise en jeu du pronostic vital ; 4=invalidité ; effet sur le produit de conception ; 5=Effet cliniquement significatif

**Évolution à l'arrêt : 1=amendement ; 2=persistance ; 3=aggravation ; 4= inconnue

*** 1= réapparition ; 2=non réapparition ; 3=pas de réadministration

Résultats d'éventuels examens para cliniques (+ date de prélèvement) :

.....

Description (précisez le numéro de l'Evénement indésirable que vous voulez décrire) :

.....

.....

.....

Fait à..... le ..... /...../.....

Signature :.....

NB : Avant de remplir cette fiche, veuillez lire attentivement les notes au verso !!!

Important

The patient's identity must be kept strictly **confidential.** She will only understand her initials. Example: For KASONGO Ngoma Jean, note “KNJ”). In the **date of birth range,** you can note the age if the complete date of birth is not available.

History : please note all the patient's medical history as well as certain risk factors such as smoking, alcohol, etc.

Drug in question.

Give the drug's INN (example: ibuprofen, nifedipine, etc.) and the trade name.
(Brufen, adalat…)

For traditional herbal products: specify the name of the plant, the part used (root, leaf, etc.) and the method of preparation (decoction, infusion, etc.)

Description of the Adverse Event : in the table, note the adverse events observed. It is important to describe them if necessary. Example: in the table you have notified number 2 of ***Lyell's syndrome.*** You can in the description range bring, for example, the following elements: " ***appearance of bubbles on an erythematous background, which peel off on contact, similar to burn lesions + Fever*** ".

Results of paraclinical examinations : this range concerns the results of paraclinical examinations carried out in relation to the observed adverse event (example: for a patient who had jaundice after taking antibiotics, give the results of the bilirubinemia (in relation to jaundice) and not the complete blood count (related to the diagnosis of bacterial infection)

Please note

- Please report all adverse events related to drugs [Medicine understood as any product used for the treatment, prevention, (including vaccines), or diagnosis (contrast agents etc.) of human diseases. Also report effects related to other health products (cosmetics, food supplements, traditional remedies and medicinal plants)] • It is useful to report adverse events even if you are not sure of the

relationship
cause and effect between them and the drug in question.

- Please send this notification in a sealed envelope or by internet to the National Center for Pharmacovigilance
    - o Address: Clinical Pharmacology Unit, Faculties of Medicine and Pharmaceutical Sciences, University of Kinshasa.
    - o Phone: cnpvrdc@yahoo.fr/pharmacoclinique@unikin.ac.cd

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The National Center for Pharmacovigilance remains at your disposal every working day for any information concerning the use of medicines and other health products.

ANNEX 2: Accountability algorithm used by pharmacovigilance structures in the DRC

(Assessment algorithm used by the WHO Collaborating Center for International Drug Monitoring, Uppsala, Sweden). This method is based on the following considerations:

has. The chronological relationship between the administration of the product and the event; b. Pharmacological data; vs. Medical or pharmacological probability d. Presence or absence of other causes.

Certain: A clinical event, including an abnormality in a laboratory test, that occurs within a plausible time frame following administration of a drug and cannot be explained by concomitant disease or other drugs or chemicals . The reaction to drug withdrawal (termination of treatment) must be clinically plausible. The event must be definitive pharmacologically or phenomenologically, and a satisfactory method of resuming treatment must be employed, if necessary.

Probable: A clinical event, including a laboratory abnormality, that occurs within a reasonable time following drug administration and is not likely to be attributable to concomitant disease or other medications or chemicals. The response to drug withdrawal (treatment cessation) must be clinically reasonable. It is not necessary to have information on the resumption of treatment for the event to meet this definition.

Possible: A clinical event, including an abnormality in a laboratory test, which occurs within a reasonable time following drug administration, but which could also be explained by concurrent disease or another drug or chemical. Information on drug withdrawal may be absent or unclear.

Unlikely: A clinical event, including an abnormality in a laboratory test, that occurs after drug administration within a time frame that makes a causal relationship unlikely. Other drugs, chemicals, or underlying illnesses may be plausible explanations.

Conditional/Unclassified: A clinical event, in particular an abnormality in a laboratory test, declared as an adverse effect and on which it is essential to have more information in order to be able to carry out a good evaluation or for which other data are under study.

Not Assessable/Not Classifiable: A report suggesting an adverse event that cannot be determined because there is insufficient or contradictory information that cannot be completed or verified.