RWANDA FOOD AND DRUGS AUTHORITY

RWANDA FDA

Medicines Safety

Bulletin

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Inside the Issue

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Director General Forward

Rwanda Food and Drugs Authority is a regulatory Authority established by the law No 003/2018 of 09/02/2018 with the mandate of protecting public health through ensuring safety, quality and efficacy of human and veterinary medicines, vaccines and other biological products, processed foods, poisons, medicated cosmtics, medical devices, household chemical substances, tobacco and tobacco products. The Authority has legal mandate to conduct pharmacovigilance and post-marketing surveillance for safety and quality of regulated products among other regulatory functions.

Rwanda is 113th full member of the WHO collaborating centre for International Drug Monitoring (Uppsala Monitoring Centre) and the current medicine safety bulletin is among the key pillars for medicine safety communication strategy as per WHO requirement for a functional Pharmacovigilance system.

Safety Monitoring activities for regulated products are currently well channelled through a coordinated mechanism that involve different stakeholders and aiming at early signal detection through the routine analysis and evaluation of spontaneous safety and quality reports from health facilities, public health programs, marketing authorization holders and World Health Organization. The Authority also conducts regular post-marketing surveillance activities by sampling at different level of supply chain and conduct Laboratory quality control analysis to inform regulatory decisions

The Medicine safety bulletin focuses on pharmacovigilance activities and continuous monitoring of drug safety before and after marketing authorization. It includes information on adverse drug reactions, adverse events following Immunization, falsified and substandard medicines, medication errors, lack of efficacy of medicines, drug-drug interactions, abuse and misuse of medicines.

During the execution of Rwanda FDA core mandate from November 2018 up to December 2020, the Authority has received 1427 adverse drug reactions reports (ADR); issued 11 new medicines Safety information; analysed 18 medication error reports. The Authority received 235 reports on suspected poor quality products and, recalled 75 batches after deep investigations including 59 batches of Human medicines and 16 batches of Veterinary medicines.

Rwanda FDA is committed to strengthening safety surveillance system and will continue to encourage all stakeholders, to create awareness, to conduct trainings and sensitizations to the public and health care workers on the importance of reporting of ADRs, AEs, AEFIs and poor quality products for public health protection.

Dr. Charles KARANGWA
Ag. Director General

0.1 EDITORIAL

In 2018, Rwanda FDA was established by the law N° 003/2018 where Authority is mandated to protect public health by ensuring Safety, Efficacy and Quality of human and veterinary medicines, vaccines and other regulated products. In its article 9, the Authority is mandated to conduct pharmacovigilance activities and post marketing surveillance for safety and quality of regulated products among other regulatory functions. The Authority has a dedicated division for Pharmacovigilance under the Department of Inspection and safety monitoring.

PHARMACOVIGILANCE is defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems". It is a very important medical discipline to prevent drug-related adverse effects in humans, ensure patient safety and promote the rational use of drugs. Pharmacovigilance aims at early detection of unknown safety problems, detection of increases in frequency, identification of risk factors, quantifying risks and preventing patients from being affected unnecessarily

Rwanda FDA being a newly established national medicines regulatory authority is in journey to fulfil all WHO minimum requirements for a functional National Pharmacovigilance System in the country, which include:

i) A national pharmacovigilance centre with designated staff (at least one full time) with clear. mandate, well defined structure and roles and collaborating with the WHO Programme for International Drug Monitoring.

ii) The existence of a national spontaneous reporting system with a national individual case safety report (ICSR) form i.e. an ADR reporting form.

iii) A national database or system for collating and managing ADR reports.

iv) 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 and

v) A clear communication strategy for routine communication and crises communication on medicine safety.

In 2008, the Ministry of Health initiated Pharmacovigilance system by establishing Drugs and Therapeutics committee that includes a sub-committee of Pharmacovigilance in the Hospitals and Rwanda FDA is strengthening these established committees through regular trainings of committee members, which include medical doctors, pharmacists, nurses and other allied health professionals. In 2013, Rwanda became the 113th full member of the WHO collaborating centres for International Drug Monitoring (Uppsala Monitoring Centre) and Rwanda FDA has reactivated the Vigiflow account and reports ADE/ADR reports to WHO-Uppsala Monitoring Centre to contribute to global medicines safety monitoring.

Scope of Pharmacovigilance

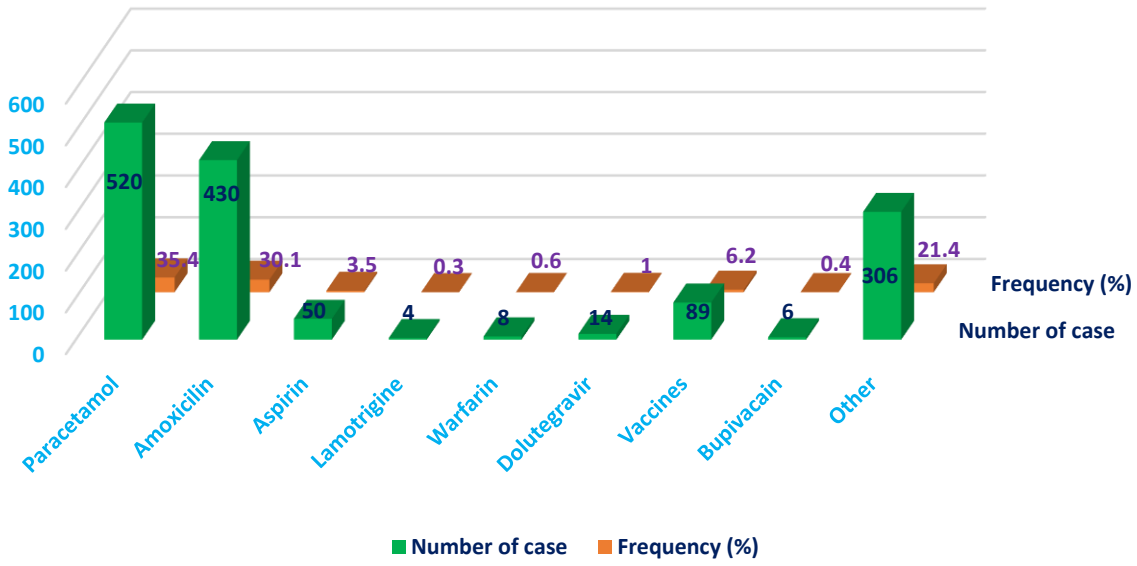
Pharmacovigilance has a broader scope which includes monitoring and surveillance of adverse drug reactions, adverse events following Immunization, Falsified and substandard medicines, medication errors, Lack of efficacy of medicines, drug-drug interactions, abuse and misuse of medicines.

I. MEDICINES SAFETY IN RWANDA

Adverse drug events

Rwanda FDA receives reports on adverse drug events, adverse drug reaction (ADE/ADR), adverse events following Immunization (AEFI) and medication errors occurred in health facilities or reported by consumers/Patients. Moreover, the Authority receives also ADE/ADR reports from WHO, manufactures of medicines, public health programs and contracted research organizations (CRO) conducting clinical trials in Rwanda. From November 2018 up to December 2020, Rwanda FDA has received 1427 ADE/ADR reports from different pharmacovigilance stakeholders on different medicines as described on **Graph 1**:

Medicines reported with Adverse events (n=1427)



II. NEW SAFETY INFORMATION

Among key objectives of pharmacovigilance, there is early detection of unknown safety information on medicines; it is in that background Rwanda FDA has published new safety information on various medicines to be taken into consideration by prescribers and dispensers of medicines and precautions taken in patient's management. The following new safety information on medicines were published by the Authority and recommendations to healthcare professionals formulated in the following Table 1

Table 1: New medicine safety Information

Medicines	New Safety information	Recommendations to Healthcare Personnel
Direct-acting Antivirals (DAAs) for chronic hepatitis C such as Ledipasvir/sofosbuvir (Harvoni®), Daclatasvir (Daklinza®), Sofosbuvir/Velpatasvir (Epclusa®)	Risk of hypoglycaemia in patients with diabetes on Direct-acting antiviral medicines for hepatitis C	Monitor glucose levels closely in patients with diabetes during treatment with direct-acting antivirals medicines for hepatitis C, particularly within the first 3 months of treatment, and modify diabetes medication or doses when necessary
Promethazine Hydrochloride **injection**	Risk of severe tissue injury including gangrene which may require amputation following intravenous administration of promethazine **Hydrochloride injection**	Alert for signs and symptoms of potential tissue injury including burning or pain at the site of injection, phlebitis, swelling, and blistering The preferred route of administration is deep intramuscular injection and that subcutaneous
Paracetamol	✓ The risk of severe liver injury associated with overdose of Paracetamol/Acetaminophen ✓ Taking >100mg/kg or >4 g per day for a few days has been known to result in hepatotoxicity ✓ Large amounts overwhelm the body ability to process it and	✓ Prescribe the right dose of paracetamol in right duration of treatment. ✓ Don't prescribe two or more brands of medicine concomitantly with paracetamol as one of the active ingredient.

	safety can lead to build up of toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) which binds to liver which causes severe hepatic necrosis leading to acute liver failure	
Fluoroquinolones (levofloxacin , ciprofloxacin, ciprofloxacin extended-release tablets, moxifloxacin (Avelox), ofloxacin).	✓ Serious low blood sugar levels and mental health side effects associated with fluoroquinolone antibiotics and requires label changes ✓ Fluoroquinolones may be associated with mental effects including disturbances in attention, disorientation, agitation, nervousness, memory impairment, and serious disturbances in mental abilities called delirium	✓ Carefully monitor blood glucose levels in patients with symptoms of risk of hypoglycaemia or patients with diabetes while being treated with fluoroquinolones ✓ Inform patients about the risk of psychiatric adverse reaction ✓ Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances
Lamotrigine	Risk of Serious immune system reaction (hemophagocytic lymphohistiocytosis (HLH) associated with seizure and mental health medicine Lamotrigine (Lamictal**)**	✓ Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related

		adverse reaction is suspected ✓ Advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment
Amoxicillin	✓ Risk of drug reaction with Eosinophilia and systemic symptoms (DRESS) syndrome associated with Amoxicillin ✓ Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities	✓ Monitor patient on Amoxicillin and sensitise patients on reporting any suspected Eosinophilia and systemic symptoms (DRESS) syndrome
Hydrochlorothiazide	✓ Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)	✓ Patient under treatment with hydrochlorothiazide for long time should be examined potentially for any skin lesions including histological examinations ✓ The use of hydrochlorothiazide need to be carefully reconsidered in

		patients who had previous skin cancer
Levodopa	✓ Risk of dopamine dysregulation syndrome associated with Levodopa ✓ Dopamine dysregulation syndrome (DDS) is a relatively recently described iatrogenic disturbance that may complicate long-term symptomatic therapy of Parkinson's disease	✓ Prescribers should be aware of the occurrence of Dopamine dysregulation syndrome (DDS) for patient taking combinations of levodopa and dopamine receptors agonists ✓ Reducing the dose or discontinuing the medicine, or other appropriate measures should be taken if symptoms like Impulsive control disorder, compulsive sexual, buying and eating behaviors are developed when using Levodopa.
Ibuprofen	Risk of renal toxicity associated with the use of Ibuprofen	✓ Patients with high risk factors for renal toxicity should not be treated with Ibuprofen after careful consideration ✓ Healthcare providers should consider whether the patient is adequately hydrated before prescribing ibuprofen
Tramadol	✓ Risk of opioid effects in breastfeeding babies when mothers are being treated with Tramadol	✓ Healthcare providers should avoid prescribing tramadol to the mother during breastfeeding because of its safety in infants and new-borns

	✓ When used by breastfeeding women, tramadol and its metabolite are found in breast milk and may produce opioid effect in babies being breastfed	✓ Advise parents and caregivers to watch closely for signs of breathing problems in infants and new-borns exposed to tramadol through breast milk
Clarithromycin	Potential risk of heart problems in patients with heart disease treated with Clarithromycin	✓ Healthcare providers should be aware of significant risk and weight the benefits of prescribing clarithromycin to patient with heart disease because ✓ Patients with high risk factors for heart disease should not be treated with Clarithromycin

III. VACCINES SAFETY

Photo: Training on AEFI monitoring in Rwanda supported by APM Afrique

Vaccination is one of great public health success of planet history figure. Expended programs on immunization (EPI) use safe and effective vaccines. However, vaccines are not risk-free and Adverse Events Following Immunization may occasionally occur (World Health Organization, 2013). Vaccines safety is thoroughly ensured through extensive procedures including testing, safety, immunogenicity and efficacy review in laboratory, animals and three clinical trials phases in human before market approval (World Health Organization, 2013). Monitoring Adverse Event Following Immunizations is a major public health preoccupation to ensure safety of vaccines. Continuous post-market approval surveillance of vaccine safety is needed to identify and evaluate any eventual AEFI which might occur.

Adverse Event Following Immunization (AEFI) is defined as any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine(World Health Organization, 2020). Based on their causes, AEFIs are grouped into five categories (World Health Organization, 2020)**:** vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, immunization anxiety-related reaction, coincidental event.

AEFI surveillance systems exist at national and international levels to ensure effective monitoring and prompt actions in response to AEFIs (World Health Organization, 2013). There are many different organizations serving different purposes in vaccine safety and in the monitoring and support of national responses to adverse events such as Brighton collaboration, CIOMS/WHO work group, GAVCS, (World Health Organization, 2013):

Rwanda FDA as the national regulatory authority, through Pharmacovigilance and Food Safety Monitoring Division, in collaboration of National AEFI committee of experts and RBC Extended Program on Immunization ensures the national AEFI

surveillance, investigation and response. They effectively conduct AEFI investigation & Causality assessment procedures and Health care professionals training to detect clusters of AEFIs and all other events believed to be due to immunization.

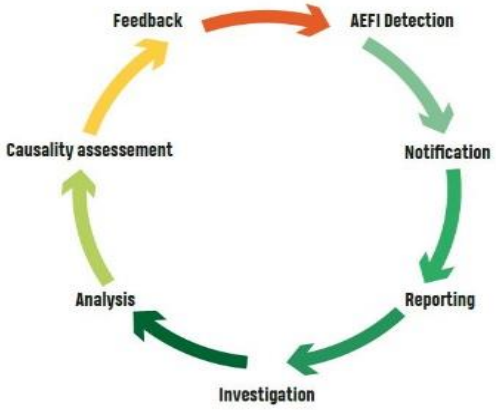
Rwanda FDA signed a collaborative agreement with AMP Afrique, The Agence de Médecine Préventive Afrique, a non-profit health organization based in Ivory Cost to support AEFI surveillance activities in Rwanda. AMP Project conducted SWOT analysis for the AEFI System in Rwanda which revealed the strengths such as functional system for AEFI in the country, existence of AEFI reporting tools, a greater number of trained professionals in vaccine safety, existence of the national AEFI committee, Adequate investigation of AEFIs serious cases

Rwanda Food and Drugs Authority in partnership with Agence de Médecine Préventive (AMP) Afrique organized three consecutives events which took place in Kigali City, Ubumwe Grande Hotel as follow: Stakeholders meeting (23/11/2020), Training of Trainers (23 – 27/11/2020) and Training of Health Care Providers (27/11/2020).

Vaccine Safety Surveillance Stakeholders Meeting with the aim of identifying gaps in AEFI surveillance and discussing strategies to improve and create a sustainable AEFI surveillance system across the country brought together health professionals from central and district levels: AEFI Committee members, Expanded Program for Immunization (EPI) staff, district vaccination officers who are AEFI focal points including those who have completed the online training course on vaccine safety basics, representatives of the Rwanda FDA involved in the pharmacovigilance / AEFI reporting; pharmacists and representatives of referral hospitals, private and public hospitals.

Training of Trainers workshop on Adverse Events Following Immunization surveillance with the aim to enhance the capacity to collect report and respond to AEFIs for effective surveillance and to cascade the knowledge gained to various regions/ organization brought together health professionals from central and district levels: AEFI Committee members, EPI staff, representatives of Rwanda FDA involved in the pharmacovigilance /AEFI reporting, district vaccination officers who are AEFI focal points, pharmacists, representatives of referral hospitals, private and public hospitals as well.

Fig 1: AEFI surveillance cycle



Training of Health Care Providers on Management of Serious AEFI-Rwanda with the overall aim of the training was to enhance the capacity of health care providers to collect report and respond to serious AEFIs at the health Centre and hospital and levels brought together 34 participants from district hospitals and health Centre levels and some participants from central level. This included the medical doctors, Pharmacists, EPI supervisors, heads of health Centres and nurses vaccinators. At central level there were AEFI Committee members, EPI staff, representatives of the Rwanda FDA involved in the pharmacovigilance / AEFI reporting.

IV. MEDICATION ERRORS

A 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 labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use[1].

Medication errors can occur in:

-Choosing a medicine: irrational, inappropriate, and ineffective prescribing, under prescribing and overprescribing;[2]

-Writing the prescription: prescription errors, including illegibility;[2]

-Manufacturing the formulation to be used: wrong strength, contaminants or adulterants, wrong or misleading packaging;[2]

-Dispensing the formulation: wrong drug, wrong formulation, wrong label;[2]

-Administering or taking the drug: wrong dose, wrong route, wrong frequency, wrong duration;[2]

-Monitoring therapy: failing to alter therapy when required, erroneous alteration[2]

Factors that may influence medication errors include:

-Factors associated with health care professionals: lack of therapeutic training, inadequate drug knowledge and experience, inadequate knowledge of the patient, Inadequate perception of risk, overworked or fatigued health care professionals, physical and emotional health issues, poor communication between health care professional and/ with patients;[3]

-Factors associated with patients: patient characteristics (e.g., personality, literacy and language barriers),complexity of clinical case, including multiple health conditions, polypharmacy and high-risk medications;[3]

-Factors associated with the work environment: workload and time pressures, distractions and interruptions (by both primary care staff and patients);[3]

-Lack of standardized protocols and procedures;[3]

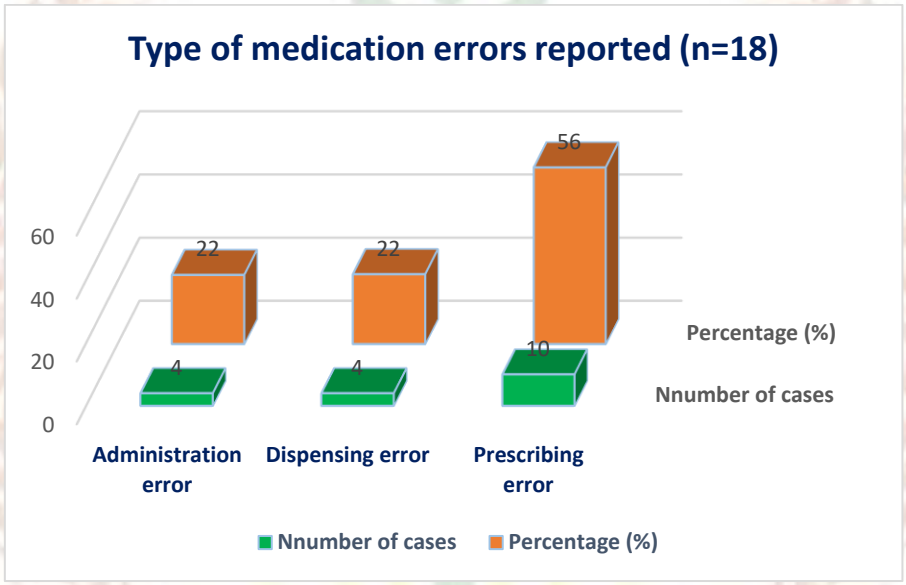
-Factors associated with computerized information systems: difficult processes for generating first prescriptions (e.g. drug pick lists, default dose regimens and missed

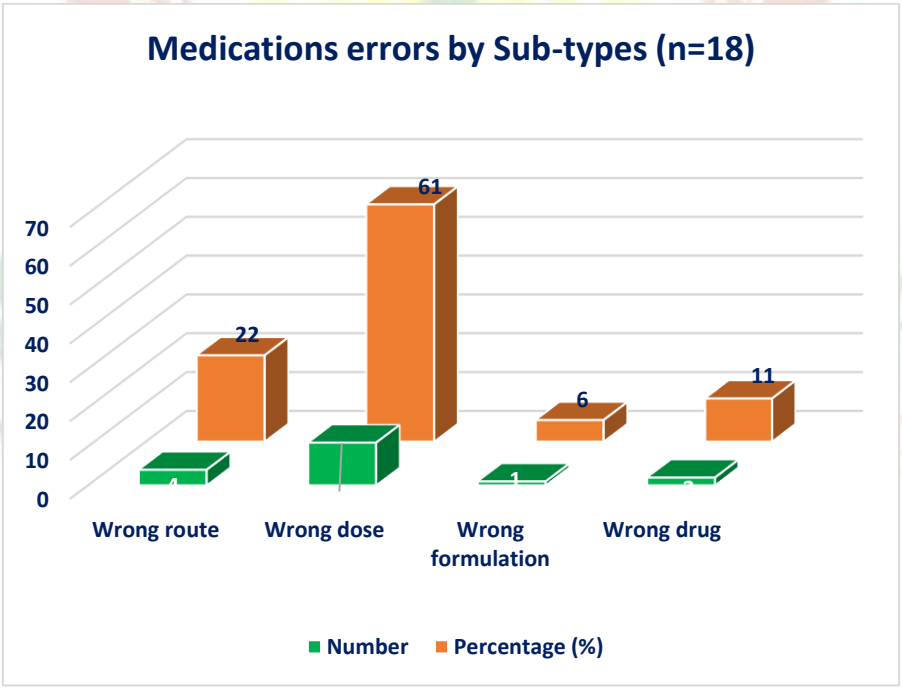
alerts),difficult processes for generating correct repeat prescriptions[3]

-Lack of accuracy of patient records[3].

Causes of medication errors include but are not limited to expired product, incorrect duration, incorrect preparation, incorrect strength, incorrect rate, incorrect timing, incorrect dose, incorrect dosage form, incorrect patient action, known allergen, known contraindication[1].

Rwanda FDA receives reports on medication errors that occur in hospital setting. The Authority has received around 18 medication errors categorized as follow in **Graph 2 and Graph3.**





Among strategies in place to prevent medication errors before drugs are approved for marketing, Rwanda FDA reviews the drug information, labelling, packaging, and product design to identify and revise information that may contribute to the occurrence of medication errors. For example, Rwanda FDA reviews:

- Proposed proprietary (brand) names to minimize confusion among drug names.

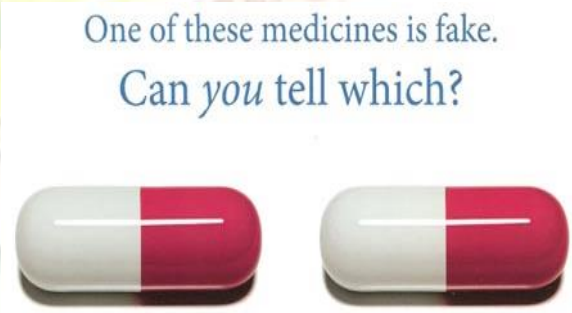
- Container labels to help healthcare providers and consumers select the right drug product. If a drug is made in multiple strengths – e.g., 5 mg, 10 mg, and 25 mg, – the labels of those three containers should be easy to differentiate.

• Prescribing and patient information to ensure the directions for prescribing, preparing, and use are clear and easy to read.

• Over the counter medicines labelling clearly lists active ingredients, inactive ingredients, uses, warnings, dosage, directions, and other information, such as how to store the medicine

Rwanda FDA may also issue communications alerting the public about a medication safety issue, which include ways to handle the medicines in order to minimize harm to patients or errors to occur. Rwanda FDA encourages healthcare professionals and public to report medications errors so that any aspect of health care practices, which may trigger medication error, and be addressed properly.

V. PREVENTION, DETECTION AND RESPONSE OF RWANDA FDA TO SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS



Substandard and falsified medicines can cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to the development of drug resistance. These poor-quality medicines also increase health care costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health[1].

Falsified medicines are medical products that deliberately/fraudulently misrepresent their identity, composition or source. Falsified medicines are fake medicines that pass themselves off as real, authorized medicines[2][3].

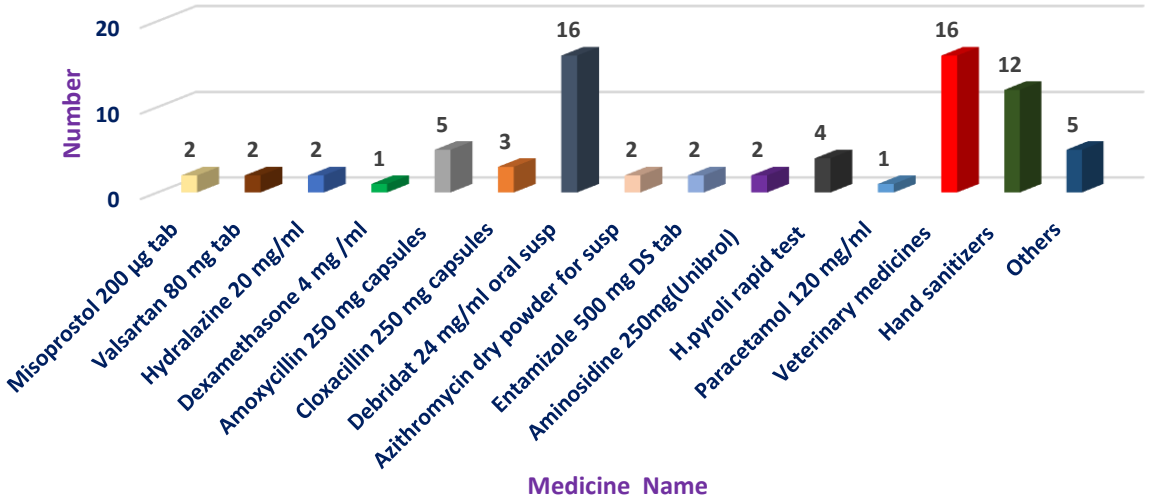
Substandard: Also called "out of specification", are authorized medical products that fail to meet either their quality

standards or specifications, or both. Medicines that met the correct specifications when they left the factory can be substandard by the time they reach patients, because they may have degraded during transport or storage. Medicines can lose their potency because they were not packaged properly, because they were not protected during transport or stored at temperatures or levels of humidity at which their active ingredients become unstable[2][3].

The magnitude of the falsified and substandard pharmaceutical problem has recently gained significant public attention due to a number of high profile incidents and greater media focus (1.2,3) The presence of sub-standard and falsified medical products (medicines and medical devices) on the market constitutes a very big concern to the public health and socio-economic aspects (2, 4). Actually, estimates put falsified medicines at around 1% of sales in developed countries, at more than 10% of the global medicines market, and around 25% to 50% in developing countries (3,5) where drug regulation, controls and enforcement are weak (6).

Routinely Rwanda FDA receives reports on suspected poor quality products from health facilities, retails pharmacies, manufacturers and other stakeholders. From November 2018 up now, the Authority has received 235 reports on suspected poor quality products and after deep investigation including sometimes Laboratory quality control analysis, the Authority has recalled 75 batches of medical products from the market as described in **Graph 4**:

Batches of substandard medical products recalled from the market November 2018 up to December 2020 (n=75)



VI. STRATEGIES TO COMBAT SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS IN RWANDA

Rwanda FDA has put in place measures to combat substandard and falsified medicines on Rwandan market that include;

- ✓ Registration of all medicines.
- ✓ Good manufacturing inspection (GMP) at Pharmaceutical Industries.
- ✓ Physical inspection at port of entry.
- ✓ Receive spontaneous reports on suspected poor quality products.
- ✓ Post-marketing surveillance activities, which consist of regular sampling of medicines.
- ✓ Laboratory quality control analysis of sampled medicines.
- ✓ Conduct customer complaint survey.
- ✓ Regional harmonization process e.g; East African Community Medicine regulatory harmonization.
- ✓ Information sharing with other regional and international regulatory bodies

VII. POST-MARKERTING SURVEILLANCE SAMPLING AND TESTING

Controlling the quality of all registered and authorized medicines through testing is extremely difficult and often unfeasible. Applying risk-based approaches to select medicines for sampling and testing as part of a post-marketing surveillance program is imperative.

Annually, Rwanda FDA develop post marketing surveillance plan which take into consideration the likelihood that poor-quality products exist and the potential health impact on patients. Sampling and testing activities target reported suspected poor quality drugs, newly introduced drugs on the market, drugs with limited safety and efficacy data, medicines with complex formulations, medicines known to have stability issues, medicines to which antimicrobial resistance is increasing, medicines in high demand, manufacturers or suppliers with previous quality issues, specific issues reported by prior inspections such as poor storage conditions, etc.

Sample collection sites includes point of entry to the market such as warehouses of importers or manufacturers, central medical stores such as Rwanda Medical Supply (RMS Ltd), BUFMAR, retail pharmacies, hospitals, health centres, health posts/ clinics, community health workers and informal outlets selling medicines outside the approved distribution system[4].

As per Rwanda FDA guidelines on Post-marketing surveillance of pharmaceutical products the Authority uses 3 level testing methodologies:

Level 1: Visual inspection which may reveal noncompliance without further testing only by verifying wrong labelling, Particulates, Crumbling tablets, Under fill, Glass particulates, Mould contamination, Discoloration, Wrong fill and Odor.

Level 2: Advanced screening: Once products pass the first level testing the next step is to use screening tools such MINILAB and TRUSCAN for identification test of the product

Level 3: Compendia testing: This step consists of complete monograph testing as detailed in the relevant Pharmacopeia, different tests can be performed such

Description, Friability, disintegration, Mass uniformity, Assay, Impurities, Microbiology test etc.

VI. LABORATORY QUALITY CONTROL

1. Introduction

Quality Control Laboratory Division is the stand-alone Division in Rwanda Food and Drugs Authority. The division is mandated to analyse different categories of food and food products, medicines, medical devices and Public health products, and samples are obtained from pre-market, post-shipment and Post-Market Surveillance. Test results generated are important in ensuring products comply with the set standards and enables the Authority to make evidence-based regulatory decisions. The Quality Control Division is established under the article 8 of the law establishing the Rwanda FDA that mandates the Authority to establish the quality assurance and quality control of regulated products and it has the following major goals:

- ✓ Conducting quality testing of food and drugs samples and provide accurate and precise results
- ✓ Carry out laboratory process and activities in accordance with World Health Organization (WHO) Good practices for pharmaceutical quality control laboratories (GPCL) and ISO/IEC 17025 General requirement for competence of testing and calibration laboratories:
- ✓ Meet the objectives of the Rwanda Food and drugs Authority
- ✓ Ensure customer satisfaction

The purpose of the testing is also to ensure that the assessment, registration and

inspection are conducted based on scientific data; the laboratory data also support the pharmacovigilance and clinical trial processes. The generated quality control results are also important in ensuring that the Authority makes evidence-based regulatory decisions during marketing authorization and enforcement of other requirements of the Rwanda Food and Drugs Authority Law.

1. Laboratory achievements (from 2018 to 2020)

i. From 2018 to 2020 the Laboratory has acquired two High Performance Liquid Chromatography (HPLCs) with Diode Array Detectors (DAD) and Fluorescent detector (FLD) in addition to one High Performance Liquid Chromatography (HPLC), disintegration apparatus, Friability, atomic Absorption Spectrophotometer (AAS) and dissolution system that were handed over from Rwanda Standards Board;

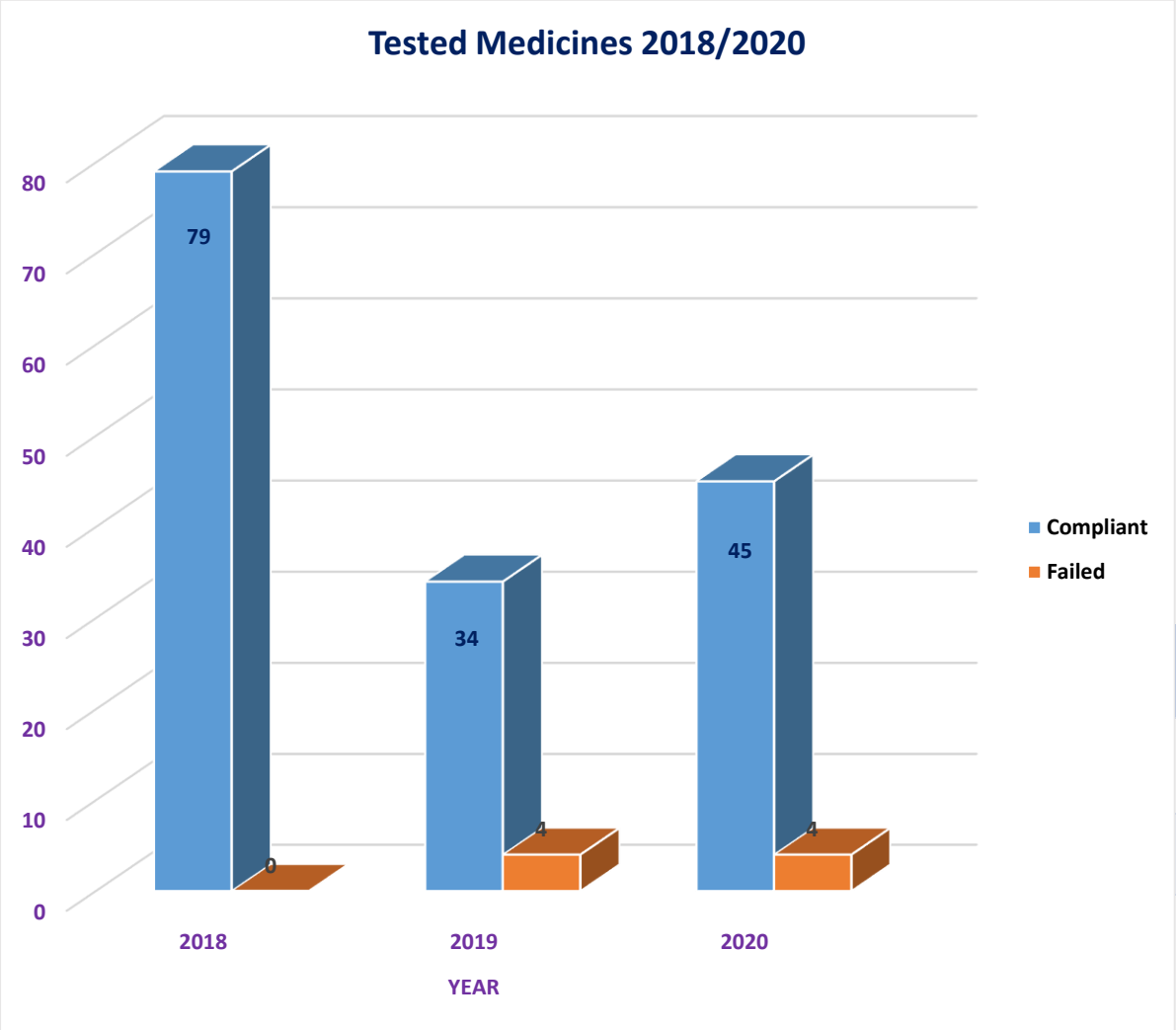
ii. Two laboratory officers attended six months training on Advanced Pharmaceutical Product Quality using Mass Spectrometry and other State of the Art Technique that was held in L.E.A.F. Pharmaceuticals LLC 216 West Cumming Park Woburn, Massachusetts 01801, USA

iii. The Division tested and reported 158 samples of medicines from pre market, post shipment and Post Market Surveillance where 8 of them failed to comply with the standards requirements

iv. The laboratory developed quality manual, 20 Standards Operating Procedures (SOPs) as per World Health Organization (WHO) Good practices for pharmaceutical quality control laboratories (GPCL) and ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories. The Five-year plan for operationalization of Quality Control Laboratory was also developed and submitted to Ministry of Finance and Economic planning for consideration.

v. Quality Control Division registered and successful participated in the 2019 AMQF (USP Ghana) inter laboratory comparisons (ILC) for paracetamol (assay and Dissolution and registered for 2020 AMQF (USP Ghana) inter laboratory comparisons (ILC) for Azithromycin (pH), Amodiaquine tablets (related substances) and Ibuprofen (assay)

2. Laboratory testing Scope



The laboratory has capacity to conduct assay on the active ingredients and Purity (e.g. Chromatography, Titration), Identity of product (e.g. Spectroscopy, Chromatograph), Uniformity of mass, friability, disintegration and dissolution and metals analysis and metals screening, water content (loss on drying by Oven), Appearance (e.g. Clarity, Opalescence), acidity and alkalinity of solution.

Samples of medicines analysed from November 2018 up to December 2020

Table 2: Recalls for Human Medicines and respective quality issues

RECALLED HUMAN MEDICINES					
1	Cynomax (misoprostol 200ug) MAXTAR	M8TAB1801	Exp: 4/2020	BIO-GENICS /India	Failed Assay test at 40%
2	C-STOL (Misoprostol 200 ug) CORONA	ERW-005	EXP: 2/2021	Remedies Pvt Ltd/India	Failed Assay test at 40%
3	Hydralazine 20mg/ml	SX-18275	Mfg date: 07/2018,EXP: 06/2020	SWISS PARANTERALS Ltd	The manufacturer declared that they have failed to on-going stabilitity studies and urged the recall
4	Hydralazine 20mg/ml	SX-18275	07/2018; 06/2020	SWISS PARANTERALS ltd	The manufacturer declared that they have failed to on-going stabilitity studies and urged the recall
5	Dexamethasone 4mg/ml	180468	Mfg date: 04/2018, Exp date: 03/2021	JIANGXI XIERKANGTAI PHARMACETICAL CO. LTD/CHINA	The route of administration was not mentioned
6	Albendazole 400 mg Tablets ,	370420	Exp date: 08/2022	GlaxoSmithKline South Africa (Pty) Ltd.	The product failed to dissolution test in Lab Quality control tests
7	Silver Sulfadiazine Cream USP 1% (Agoburn),	K82001	Exp date: 02/2021	Agog Pharma Ltd., India	Failed the Assay (82.2%) test in Lab Quality control tests
8	Biperiden.HCl Sterop Tablets 2 mg	18B05	Exp date: 01/2023	Lab. STEROP NV, Belgium	The medicine was found with higher rate of impurities in Laboratory quality control tests
9	Chloramphenicol 0.5% w/v Eye Drops B.P; BN: ,	131936	Exp date: 01/2021	Abacus Parenteral Drugs Ltd., Uganda	Failed the Assay test (77.1%) and the degradation product content.

10	Ranitidine	All batches		Not specified	The medicines were found with nitrosamine impurity called N-nitrosodimethylamine (NDMA) at low levels;
11	Helicobacter Pyroli rapid tests	HP18112602	EXP11/2020	SAFE CARE BIOTECH	The rapid test were giving false positive results
12	Cloxacillin 250 mg capsules	1831132401	Mfg date: 12/2018, Exp. Date: 12/2021	REYOUNG PHARMACEUTICAL. CO.LTD/CHINA	Capsules were reported self-opening when they are going to be dispensed
13	Cloxacillin BP 250 mg capsules	183132400	Mfg date: 12/2018, Exp date: 12/2021	REYOUNG PHARMACEUTICAL. CO.LTD/CHINA	Capsules were reported self-opening when they are going to be dispensed
14	Amoxycillin BP 250 mg capsules,	B.N: 767190217;	Mfg date: 02/2019; Exp date: 02/2022	CSPC ZHONGNUO PHARMACEUTICAL (SHIJIAZHUANG CO.LTD) / HEBEI /CHINA	Capsules were reported self-opening when they are going to be dispensed
15	Cloxacillin BP 250 mg capsules	B.N: 183132399 ,	Mfg date: 12/2018, Exp date: 12/2021	REYOUNG PHARMACEUTICAL. CO.LTD/CHINA	Capsules were reported self-opening when they are going to be dispensed
16	Helicobacter Pyroli rapid tests	BN: HPB11308,	EXP :03/2020	QINGDAO HIGHTOP BIOTECH CO. LT	There were many false positif
17	ANIOS SPECIAL DJP SF 4X5L,	B.N:A24104S		Laboratoires Anios	The product was reported to be contaminated by a bacteria
18	ANIOS SPECIAL DJP SF 4X5L,	B.N:B14316S		Laboratoires Anios	The product was reported to be contaminated by a bacteria

19	Amoxicilline 250 mg capsules	B.N 767190205,	Mfg date: 02/2019, Exp date: 02/2022	CSPC ZHONGNUO PHARMACEUTICAL (SHIJIAZHUANG CO.LTD) / HEBEI /CHINA	The medicines were reported self opening and powder leakage
20	Amoxycillin BP 250 mg capsules (AMOXIMED)/1000 capsules,	B.N: 767190207,	mfg date:02/2019, exp date: 02/2022	CSPC ZHONGNUO PHARMACEUTICAL (SHIJIAZHUANG CO.LTD) / HEBEI /CHINA	The medicines were reported self opening and powder leakage
21	Amoxycillin BP 250 mg capsules (AMOXIMED)/1000 capsules,	B.N: 767190208,	mfg date:02/2019, exp date: 02/2023	CSPC ZHONGNUO PHARMACEUTICAL (SHIJIAZHUANG CO.LTD) / HEBEI /CHINA	The medicines were reported to self opening and powder leakage
22	Amoxycillin BP 250 mg capsules (AMOXIMED)/1000 capsules,	B.N: 767190216,	mfg date:02/2019, exp date: 02/2024	CSPC ZHONGNUO PHARMACEUTICAL (SHIJIAZHUANG CO.LTD) / HEBEI /CHINA	The medicines were reported to self opening and powder leakage
23	Paracetamol suspension 120mg/5ml (Toto-moL®),	B.N: 73718	mfg date: 02/2019, exp date: 01/2022	Laboratory&Allied Ltd./kenya	The product was detected with particulate matter
24	Helicobacter Pylori Antibody test strip	B.N HPB11303B	mfd date: 14/3/2019, exp date: 03-2021	QINGDAO HIGHTOP BIOTECH CO.,LTD/CHINA	The rapid test were giving false positive results
25	Urinalysis reagents strips with 3Parameters	BN:UR3511906A	Exp:06/2021	Not mentioned	Manufacturing date,manufacturer's name and Manufacturer address

					were not mentionned on the products
26	Urinalysis reagents strips with 10Parameters	BN:UR105111906A	Exp date:06/2021	Not mentioned	Manufacturing date,manufacturer's name and Manufacturer address were not mentionned on the products
27	Debridat 24mg/ml granules for oral suspension,250ml	BN:3814, 3815,3816,3817,3818,3819,3820	Exp.date:06/2020	FARMEA10,RUE BOUCHE THOMAS ZAC SUD D'ORGEMONT 49000 Angers	Potential foreign materials in the products
28	Debridat 24mg/ml granules for oral suspension,250ml ,	BN:3851, 3852,3853	Exp.date:10/2020	FARMEA10,RUE BOUCHE THOMAS ZAC SUD D'ORGEMONT 49000 Angers	Potential foreign materials in the products
29	Debridat 24mg/ml granules for oral suspension,250ml ,	BN:3867	Exp.date:02/2021	FARMEA10,RUE BOUCHE THOMAS ZAC SUD D'ORGEMONT 49000 Angers	Potential foreign materials in the products
30	Debridat 4.8mg/ml granules for oral suspension,125ml ,	BN:3856, 3857, 3858	Exp.date:11/2020	FARMEA10,RUE BOUCHE THOMAS ZAC SUD D'ORGEMONT 49000 Angers	Potential foreign materials in the products

31	Debridat 4.8mg/ml granules for oral suspension,125ml	BN:3859, 3869	Exp.date:12/2020	FARMEA10,RUE BOUCHE THOMAS ZAC SUD D'ORGEMONT 49000 Angers	Potential foreign materials in the products
32	Azithromycine dry powder suspension(Zerocin)	BN:74261	Mfd:04/2019,Exp date:03/2021	Laboratory&Allied Ltd./kenya	Caking of the powder in the bottom of the bottles causing poor flowability
33	Azithromycine dry powder suspension(Zerocin)	BN:74346	Mfd:05/2019,Exp date:04/2021	Laboratory&Allied Ltd./kenya	Caking of the powder in the bottom of the bottles causing poor flowability
34	Entamizole DS 500mg	BN:94965XV(Box),95532XV (Blister)	Mfd:11/2018,Exp:11/2021,01/2022	ABBOTT LAB/PAKISTAN	Mislabelling,poor packaging,lack of patient leaflet,Discrepency of the information of BN and Exp date on primary packaging and Blister
35	Ketoconazole(Kenazole) 1%,	BN:1907205	Mfd:07/2019,Exp date:06/2022	DAWA Ltd	Lack of Seal integrity of packs and/or Leakage
36	Hand Sanitizers Manufactured by Oxalis Ltd	All batches		Oxalis Ltd	Failure to meet the quality standard where alcohol content was low
37	BEU Hand Sanitizers	All batches		Holly Trust Ltd/Kamonyi District	Failure to meet the quality standard where alcohol content was low
38	Huureka Disinfectant	All batches		KEWS CORPORATION/SOUTH KOREA	Suspected poor quality product
39	99%Methanol Alcohol	All batches		KVM	This hand sanitizer was manufactured based on Methanol

40	Guard Hand Sanitizer 30ml		Mfd:10/03/2020,Exp10/03/2021	KVMS Co. Ltd,Tel: 250788851252	Failure to meet the quality of standard
41	Aminosidine 250mg(Unibrol)	BN:5806898	Mfd:09/2019,Exp date:08/2022	Universal corporation/Kenya	Color change for some tablets on the blister
42	Aminosidine 250mg(Unibrol)	BN:5806675	Mfd:06/2019,Exp date:05/2022	Universal corporation/Kenya	Color change for some tablets on the blister
43	Purell-Instant Hand Sanitizer (60ML)		Mfd 18/03/2020,Exp 18/03/2021	BELLA LTD	Failure to meet the quality of standard
44	Lime Fresh Hand Sanitizer and disinfectants			Lime Fresh Family Ltd	The hand sanitiser do not contain Alcohol
45	NEMCHEM Terminal Hand Sanitizer(Ethanol based),	BN:0076	Mfd:20/03/2020,Exp:20/03/2022	NEM CHEM INTERNATIONAL	Failure to meet quality standard with low Alcohol content
46	Pure Skin Stay Safe Hand Sanitizer (Ethanol based) ,	BN:001	Mfd:May 2020,Exp:April 2022	Africana Buffalo Ltd/Kigali,Gasabo	Failure to meet quality standard with low Alcohol content

Source: Rwanda FDA databases

Table 3: Recalled Veterinary medicines

RECALLED VETERINARY MEDICINES					
NO	**Medecine incriminated**	**Batch No**	**Mfg and expirt date**	**Manufacturer**	**Safety/Quality issue**
1	Benzyl penicillin procaine+DHS	BN:MI12-06	Mfd:01/2019,Exp:01/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
2	Benzyl penicillin procaine+DHS	BN:MI12-07	Mfd:01/2019,Exp:06/2022	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
3	Benzyl penicillin procaine+DHS	BN:MI12-08,	Mfd:01/2019,Exp:01/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
4	Benzyl penicillin procaine+DHS	BN:MI12-09,	Mfd:01/2019,Exp:01/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
5	Benzyl penicillin procaine+DHS	BN:MI12-10,	Mfd:02/2019,Exp:02/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
6	Benzyl penicillin procaine+DHS	BN:MI12-11	,Mfd:02/2019,Exp:02/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
7	Benzyl penicillin procaine+DHS	BN:MI12-12,	Mfd:03/2019,Exp:03/2021	PUSHKIN LABORATORY LLC/Russia	Precipitation of the product with crystallization
8	Complex Multivitamine injection veterinary medicine	BN:190917	Mfd:09/2019 ,Exp:09/2022	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition on the labeling
9	Complex Multivitamine injection veterinary medicine	BN:190813	Mfd:08/2019,Exp:08/2022	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition on the labeling

10	Novalgine injection 50%	BN:190729 A	Mfd:07/2019,Exp:07/2022	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition on the labeling
11	Novalgine injection 50%	BN:180608	Mfd:180608,Exp:06/2021	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition on the labeling
12	Ivermectine injection 1%	BN:180617	Mfd:06/2018,Exp:06/2021	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition on the labeling
13	(Acaricide)Amitraz 12,5% EC	BN:GA20 1811 10	Mfd:11/2018,Exp:11/2021	HebeiChengSheng Tang Animal Pharmaceuticals Co Ltd	Lack of storage condition and evaporation of the products
14	Envit 100 ml,,	B.N: EEV1807	Exp date: 07/2020	Vitindia Pharmaceuticals Ltd A-6/1 India	The solution had issue of sedimentation
15	Envit 100 ml, ,	B.N: EEV1808	Exp date: 07/2020	Vitindia Pharmaceuticals Ltd A-6/1 India	The solution had issue of sedimentation
16	Envit 100 ml,,	B.N:EEV 1713	Exp date:10/2019	Vitindia Pharmaceuticals Ltd A-6/1 India	The solution had issue of sedimentation

Source :Rwanda FDA database

VIII. RATIONAL DRUG USE

Rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community[1].A sound rational drug use program has three elements[1]:

- Rational use of medicines strategy and monitoring
- Rational use of medicines by health professionals
- Rational use of medicines by consumers

Rwanda pharmaceutical services baseline assessment was conducted by Ministry of Health in collaboration with Rwanda FDA, Rwanda Biomedical Centre and the National Pharmacy Council and supported by USAID Medicines, Technologies and Pharmaceutical Services (MTaPS) program in February 2020. Data and information was obtained from Fifty-four health facilities (54) selected across all the five provinces of Rwanda. A total of 270 randomly sampled patients participated in a brief exit interview (5 per health facility) and only 250 fulfilled the inclusion criterion. A total of 540 randomly selected prescriptions (10 per health facility) were reviewed to understand the prescription patterns. The purpose was to identify key constraints and challenges and develop recommendations and strategies for improving pharmaceutical service delivery and rational use of medicines[2] .

The baseline assessment revealed an average of 2.6 number of medicines prescribed per patient encounter (WHO optimal value 1.6–1.8)[3], 5% prescriptions have polypharmacy (5 to 6 medicines per prescription), 68.2% of medicines prescribed are in generic name (WHO optimal value 100%)[3], whereas 24.3% are antibiotics (WHO optimal value 20.0–26.8%)[3] and medicines prescribed in injection form are representing 6.5% (WHO optimal value 13.4–24.1%)[3]. The percentage of medicines prescribed from an essential medicine list (EML) or formulary, which was high at 92.9%[2] (WHO optimal value 100%)[3].

Table 4: Prescribing Indicators

Prescribing indicators (n=540)	Mean or %	WHO optimal value
Average number of medicines prescribed per patient encounter	2,6	1.6–1.8
Percentage of medicines prescribed by generic name	68,2%	100%
Percentage of encounters with an antibiotic prescribed	24,3%	20.0–26.8%)
Percentage of encounters with an injection prescribed	6,5%	13.4–24.1%
Percentage of medicines prescribed from an EML or formulary.	92,9%	100%

In terms of prescribing indicators, the findings are not a lot divergent with the expected norms[3]. The practices are at a promising level and with sustained push for improvement; better results can be expected in the future.[2] Among consequences of irrational drug use we can mention Reduction in the quality of drug therapy leading to increased morbidity and mortality; waste of resources leading to reduced availability of other vital drugs and increased costs; increased risk of unwanted effects such as adverse drug reactions and the emergence of drug resistance[4].

Assessment of pharmacovigilance systems involves a set of indicators[5]. Pharmacovigilance indicators establish indices to delineate the baseline status and allow for the measurement of growth and level of performance of pharmacovigilance activities[6].

Rwanda pharmaceutical services baseline assessment results shows Drug Therapeutic Committees (DTC) are functional in most hospitals at 74.1%. Nevertheless, some notable results of indicators related to medicines safety were at a low percentage at health facilities. Hospitals reporting adverse drug event to Rwanda FDA in last six months (18.5%); hospitals with adverse drug events notified at the level of the facility in last six months, and hospitals reporting medications errors at the facility level in the last six months, each at 14.8%.[2]

IX. CAPACITY BUILDING

PROFORMA PROJECT

All Institutions involved in pharmacovigilance activities shall ensure availability of a sufficient number of competent and appropriately qualified and trained personnel to perform Pharmacovigilance activities and establish a training system on vigilance with adequate documentation such as training plans, training records, etc.

On 3rd December 2018, PROFORMA project had kick-off meeting in Kigali gathering all partners and stakeholders in Pharmacovigilance in Rwanda including Ministry of Health, University of Rwanda, Public health programs at Rwanda Biomedical centre and health facilities.

From 13-24 May 2019, PROFROMA Project held its' second annual meeting in Kigali and conducted a training of Pharmacovigilance for health professionals and partners from Rwanda, Kenya, Tanzania, Kenya and Ethiopia

PROFORM Project firstly conducted a comprehensive assessment of the current pharmacovigilance systems and practices in Rwanda. The aim was to identify the missing pharmacovigilance systems' structural elements, strengths, deficiencies, and gaps. Based on the identified gaps, comprehensive national pharmacovigilance plans and interventional measures aligned with local needs and priorities are developed and introduced in Rwanda.

PROFORMA is engaged in generating a cohort of pharmacovigilance-trained professionals from all stakeholder groups in East Africa, including healthcare providers and regulatory staff engaged in pharmacovigilance data collection, analysis, interpretation, and data sharing. Currently, a total of 10 postgraduates (seven PhDs and three MScs) are being trained to serve as part of the future pharmacovigilance expert regional task force.

In February 2020, during the 3rd PROFORMA Annual meeting in Nairobi, Kenya, PROFORMA launched an undergraduate pharmacovigilance curriculum for healthcare programmes to be

implemented in medical universities. The Pharmacovigilance curriculum was already integrated in the academic curriculum of Pharmacy department in the University of Rwanda.

PROFORMA Project also developed online in-service professional pharmacovigilance training curriculum that was integrated into the UR e-learning platform under the College of Medicine and Health Sciences (https://elearning.ur.ac.rw/course/view.php?id=6834)

In 2019, PROFORMA Project in collaboration with Rwanda FDA and RBC/NTD conducted active safety and efficacy surveillance on drugs used in mass drug administration (MDA) where 8300 children aged from 5-15 years old in 4 districts of the western Province of Rwanda ((Rusizi, Nyamasheke, Rutsiro and Rubavu) participated in the active surveillance while taking Praziquantel and Albendazole for the treatment and prevention of schistomiasis and soil Transmited Helminths (STH).

PHARMACOVIGILANCE TRAINING FOR HEALTHCARE PROVIDERS

Rwanda FDA on support of USAID/MTaPS have developed capacity building plan for members of Drugs and Therapeutics committees (DTCs) within health facilities. It is in that background that a pharmacovigilance training was organized and conducted in Bugesera district from 20 January 2020 up 23 January 2020. The training included clinical directors, pharmacists and nurses from both public and private Hospitals (district, provincial and referral hospitals), some participants were from wholesale pharmacies, retail pharmacies, Rwanda FDA staff and one staff from Expanded program for Immunization at Rwanda Biomedical Centre. The meeting focused on Pharmacovigilance system, Processes, roles& responsibilities, ADR/AEFI reporting, Pharmacovigilance methods, introduction to causality assessment, signal detection and management and functionality of Drugs and Thera5peutics committees within Hospitals.

REPORTING CHANNELS

Stakeholders such Medical doctors, Pharmacists, allied health professionals form hospitals and clinics, Patients and Public report to Rwanda FDA ADR/ AEFI to Rwanda FDA by completing the online reporting form in PViMS system accessible online on https://pvims.rwandafda.gov.rw/public/spontaneous. Reporter can also completing ADR/AEFI reporting form available at http://www.rwandafda.gov.rw/web/fileadmin/adr_aefi__reporting_form.pdf and sending it to E-mail: pv-sm@rwandafda.gov.rw

Pharmacovigilance Information Management System (PViMS) accessible on the link: https://pvims.rwandafda.gov.rw/security/landing