RWANDA FDA
Rwanda Food and Drugs Authority

RWANDA FOOD AND DRUGS AUTHORITY

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Inside the Issue

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FOREWORD

Rwanda Food and Drugs Authority is mandated to conduct pharmacovigilance and post marketing surveillance for safety and quality of regulated products among other regulatory functions as per the Law establishing the Authority especially in its article 8, paragraph 9.

The Authority has made great strides in strengthening the national pharmacovigilance system through different initiatives including publishing medicine safety bulletin on a regular basis. Since 2021, Rwanda FDA has adopted an annual medicine safety bulletin to communicate all medicine safety information to the general public and healthcare professionals to highlight a vibrant pharmacovigilance regulatory system.

This 2nd issue of the medicine safety bulletin 2022, highlights key activities and achievements of the pharmacovigilance regulatory system through established technical committees including the National Pharmacovigilance Advisory Committee (NPAC) and the National Adverse Events Following Immunization (AEFI) Committee. The Authority trained 129 healthcare professionals from district and referral hospitals across the country on AEFI surveillance and investigation in order to establish a sustainable pharmacovigilance system.

Furthermore, the Authority received and analysed 556 adverse events following immunization (AEFI) reports on Covid-19 vaccines and 108 serious AEFI on Ebola vaccine regimen (Ad26 and MVA). Following that, four new medicines safety information and four safety signal communications were issued. To ensure the quality of pharmaceutical products on the Rwandan market, the Authority sampled around 613 samples of medicines for Laboratory quality control analysis. In addition, the Authority received and investigated 42 suspected poor quality products reports where 16 batches of pharmaceutical products were recalled from the market due to quality issues. A conducted post- marketing surveillance on antimalarial revealed that all 93 batches sampled and tested complied with the quality standards.

Rwanda FDA, as member of the Global Surveillance and Monitoring System for substandard and falsified (SF) medical products, is committed to preventing SF medical products on the Rwandan market and their consequences. This is achieved through registration of all medicines, GMP inspection; import and export control, laboratory quality control, pharmacovigilance and post-marketing surveillance activities. In light of this, many thanks are extended to Rwanda FDA staff and Development Partners whereby with their technical support, Rwanda FDA staff and stakeholders were trained on conducting a risk-based post-marketing surveillance (RB-PMS). Post Marketing Surveillance (PMS) technical committee was established to conveniently advise and guide the Authority in PMS-related matters especially in preventing, detecting and responding to any incidence of SF products on market.

Moreover, Rwanda FDA in collaboration with other partners is conducting an active surveillance on Dolutegravir to determine the safety profile of Dolutegravir-based regimens available on the Rwandan market.

It is through a strong collaboration and compliance to regulatory requirements that Rwanda FDA will continue protecting the public health and achieving its vision which is "To become a World-class Regulatory Authority".

Dr. Emile BIENVENU
Director General

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Date: 2022.10.08 19:41:08 +02'00'

EDITORIAL

Dear Colleagues, I would like to appreciate your continued interest in the Bulletin. Referring to this platform and providing your feedback brings growth and allows us to produce more relevant content in following issues of Medicine Safety Bulletin.

Mr. Lazare NTIRENGANYA

Chapter I. VIGILANCE

I.1. Vigilance system strengthening

1. National Pharmacovigilance system

The Pharmacovigilance (PV) system aims at protecting the public health from medicines-related harm. In Rwanda, the pharmacovigilance system is supported by regulatory framework, involves different stakeholders and structures such as Universities, health facilities, Drugs and Therapeutics committees, public health programs, marketing authorizations holders and advisory committees. Rwanda is the 113th member of the International program of Drug Monitoring. Additionally, the Authority has reporting tools and different databases for the reported adverse events.

i) Baseline assessment of the Pharmacovigilance system

A baseline assessment of the national pharmacovigilance system in Rwanda using a Standardised Assessment Tool was conducted in December 2018 through PROFORMA project supported by European and Developing Countries Clinical Trial Partnership (EDCTP). PROFORMA Project aims at strengthening the pharmacovigilance system and infrastructure in sub-Saharan Africa.

The aim of the baseline assessment was to identify the missing pharmacovigilance systems' structural elements, strengths, deficiencies, and gaps. During the baseline assessment, the following components were assessed:

- Policies, laws, and regulations
- Systems, structures and stakeholder coordination
- Data Management and signal generation
- Risk assessment and evaluation
- Risk management and communication

The assessment involved different key players in pharmacovigilance system across the country including regulatory authority, public health programs, health facilities, marketing authorization holders and Academia. The baseline assessment was conducted using different approaches such as document reviews, data reviews and interviews. The following institutions were assessed:

1) Rwanda Food and Drugs Authority;
2) Public Health Programmes including Maternal and Child Community Health (MCCH) and Units(Malaria and Other Parasitic Diseases (MOPD's);
3) Marketing Authorization Holders (MAH) and distributors;
4) Healthcare facilities including Ruhengeri Referral Hospital, Remera-Rukoma District Hospital, Gisenyi District Hospital and Kibagabaga District Hospital;
5) University of Rwanda.

ii) Pharmacovigilance Implementation plan 2021-2026

Based on the findings from the baseline assessment of the pharmacovigilance system in Rwanda as well as the WHO Global Benchmarking Tool (WHO-GBT) requirements specifically on the Vigilance function, Rwanda FDA developed and approved a five-year Pharmacovilance Implementation plan (2021-2026) to strengthen the Pharmacovigilance system in Rwanda for public health protection.

The PV plan is intended to operationalize the Pharmacovigilance-related strategic objective of the Rwanda FDA strategic plan (2021–2025). This national PV plan is intended to guide the coordination

of Pharmacovigilance activities, especially when new and existing medical products are being granted with marketing authorization by Rwanda FDA.

The plan has set Pharmacovigilance priorities, key interventions, and indicators to promote and strengthen the Rwandan national PV system for a five-year period. Seven objectives were set by this plan as follow for the 2021-2026 period:

1) To strengthen pharmacovigilance regulatory compliance in Rwanda;
2) To strengthen Pharmacovigilance structure, governance, and stakeholder coordination;
3) To establish procedures, processes, and tools to perform PV activities;
4) To strengthen the data management, signal detection and risk management for medical products;
5) To develop human resource capacity for a sustainable PV system;
6) To reinforce transparency and set communication mechanism for PV regulatory decision;
7) To set and monitor pharmacovigilance indicators.

Several activities have been conducted to respond to the above objectives that were set in the national PV plan. The table below provides updates on the PV plan implementation until March, 2022.

Table 1: Update on the Pharmacovigilance Implementation Plan 2021-2026

Objectives	Intervention	Indicator	Updates
1.Strengthen pharmacovigilance regulatory compliance in Rwanda	Develop and disseminate the Pharmacovigilance regulatory documents	Pharmacovigilance regulation and guidelines disseminated	- Regulations governing Pharmacovigilance were developed and published accessible on Rwanda FDA website. - Guidelines on safety and vigilance were published and disseminated on Rwanda FDA website. - Guidelines on AEFI surveillance were published on Rwanda FDA website.
	Conduct PV inspections and supervisions	Number of Pharmacovigilance inspections and supervisions conducted	- Supervisions conducted in 50 Health facilities (both Private and Public Hospitals) - Pharmacovigilance inspection plan developed - Conducted Pharmacovigilance inspections for 3 marketing authorization holders (Cipla ltd, Jansen cilag International and Cadila ltd)
	Enforce the requirements for the QPPV	% of MAH that nominated QPPV	47 Marketing Authorization Holders nominated the Qualified personnel in Pharmacovigilance
	Requiring submission of PSURs/PBRERs	Number of PSURs/PBRERs submitted	57 PSURs/PBRERs reports were received by Rwanda FDA from marketing Authorization Holders (MAH)
2.Strengthen Pharmacovigilance structure, governance and stakeholders coordination	Establish National Pharmacovigilance Advisory Committee	PV advisory committee established and functional	National Pharmacovigilance Advisory Committee was established and functional and is Multidisciplinary with different medical expertise
	Plan regular stakeholders' meeting	Quarterly stakeholder's meeting	Stakeholder's meetings are conducted on quarterly basis
	Establish or reactivate DTCs in public and private hospitals	Number of DTC reactivated	- From the survey conducted, 75% of DTC are fully functional within hospitals -

3. Establish procedures, processes, and tools to perform PV activities	Develop and use SOPs, reporting forms, and checklists that consider risk-based approaches in Pharmacovigilance	Number of procedures and tools developed and implemented	- 24 Procedures were developed and implemented - 5 reporting forms and one online reports system developed and used - 12 Formats and templates developed and used
	Distribute the Pharmacovigilance reporting tools	Number of facilities where tools where distributed	- Reporting Tools were distributed in hospitals, clinics and retail pharmacies - Online reporting system (PViMS) is also used for reporting ADR/AEFI and accessible on https://pvims.rwandafda.gov.rw/security/landing
	Conduct Public awareness campaign on Pharmacovigilance reporting	Number of Public awareness campaigns conducted	- One Public Awareness campaign was conducted - Presentation in seminars, conferences and meeting were conducted and PV awareness raised
4. Strengthen the data management, signal detection and Risk management for medical products	Establish and sustain a national database for ADRs and adverse events following immunization (AEFI)	Number of ADR and AEFI reports received	From November 2018 up to March 2022 - 3629 ADR reports were received by the Authority - 560 AEFI on covid-19 vaccine received - 108 serious AEFI on Ebola vaccine (Ad26 and MVA)
	Conduct active surveillance on medicines for signal generation and detection	Number of active surveillance conducted	-Active surveillance on Dolutegravir-based regimen currently unrolled 830 participants and target is 3000 participants
	Establish procedures for signal detection and investigation	Number of signal under investigation	- Database for signals was developed and 40 are under investigation - 4 Direct Healthcare letters were issued on signals under investigation

Reinforce transparency and set communication mechanism for PV regulatory decision	Develop safety communication strategy and plan to address routine safety communication and communication during crises	- Medicines safety communication published - Medicine safety bulletin published	- 19 Medicine safety information were published accessible on Rwanda FDA website - 2 Medicine safety Alerts were issued - 2 medicine safety bulletin was developed and published
	Develop/update and disseminate PV information, education, and communication materials	IEC materials developed and disseminated	Pharmacovigilance Information, Education and communication materials (IEC) were developed and distributed in 102 health facilities including Hospitals, Health centres and Retail Pharmacies
	Publish pharmacovigilance data in scientific journal	Number Publication of vigilance data in scientific journal	One Publication on Safety of co-administration of Praziquantel and Albendazole
Develop human resource capacity for a sustainable PV system	Train Rwanda FDA staff in different areas of pharmacovigilance	Number of Rwanda FDA staff trained	- 11 pharmacovigilance staff were trained in different areas of Pharmacovigilance - 3 Staff attended advanced training on pharmacovigilance provided by Uppsala Monitoring Centre (UMC)
	Train healthcare providers and stakeholders in Pharmacovigilance	Number of Health professionals trained in Pharmacovigilance	620 Health professionals were trained on Pharmacovigilance
Set and monitor pharmacovigilance indicators	Set and monitor indicators and targets for pharmacovigilance system performance	Number of indicators monitored	4 Pharmacovigilance Indictors are monitored

2. PV Advisory Committee

The National Pharmacovigilance Advisory Committee is one of the WHO's minimal requirements for a functional National Pharmacovigilance System. In this regard, Rwanda FDA has established the National Pharmacovigilance Advisory Committee which is a multidisciplinary team that provides technical expertise related to Pharmacovigilance and medicine safety monitoring.

The established National Pharmacovigilance Advisory Committee is composed of 13 experts in different medical fields such as dermatology, toxicology, cardiology/paediatrics, clinical Pharmacy, oncology, pharmacology, gynaecology and veterinary Medicine

In order to perform the advisory role in their relevant area of expertise to guide pharmacovigilance regulatory actions by Rwanda FDA, the committee is composed by the following members:

Table 2: Members of the National Pharmacovigilance Advisory Committee

S/No.	Profession	Names
1	Dermatologist	Dr. Alice U. AMANI
2	Internist	Dr. Osée Sebatunzi
3	Division Manager PV&SM	Mr. Lazare NTIRENGANYA
4	Clinical Pharmacist	Mr. Innocent MUHIRE
5	Pharmacist	Mr. Cyprien MUSAFIRI
6	Toxicologist	Dr. Innocent HAHIRWA
7	Surgeon	Prof. Martin NYUNDO
8	Cardiologist/Paediatrician	Dr. RUSINGIZA Emmanuel
9	Oncologist	Dr. Pacifique MUGENZI
10	Paediatrician	Dr. Claude KABAYIZA
11	Pharmacologist	Dr. Jean Baptiste NYANDWI
12	Veterinary Doctor	Dr. Francois Xavier RUSANGANWA
13	Gynaecologist	Dr. MUHORAKEYE Febronie

In Rwanda, the safety monitoring activities for medical products is currently well channelled through a coordinated mechanism that involves different stakeholders and aims at early signal detection. This is done through the routine analysis and evaluation of Individual Case Safety Report (ICSR) of and quality reports from health facilities, public health programs (PHP), marketing authorization holders (MAH) and World Health Organization.

The roles and responsibilities of the National Pharmacovigilance Advisory Committee include the following:

a) Provide guidance on risk identification/management on the use of medical products including the detection, assessment, minimization and communication relating to the risk of adverse reactions and guidance on set up risk management plan (RMP);

b) Provide technical assistance on causality assessment for the reported adverse drug reactions;

c) Provide advice on the design of post-authorization safety studies (PASS) and pharmacovigilance audit/inspections;

d) Provide recommendations for urgent safety issues related to medicines and advice on the timing and message content for individual safety cases;

e) Provide advice for updating medical products list with safety concerns requiring additional monitoring;
f) Assess and advise on potential signals/alerts of adverse drug reactions and Suspected Poor-Quality products;
g) Advise on signal detection, investigation, analysis and management on medical products;
h) Provide guidance on medicine safety communication required especially in case of crisis,
i) Advise on medicine registration, renewal/variation of medicine taking into consideration their safety, efficacy and quality.

3. National AEFI Committee

The National AEFI committee is a multidisciplinary committee established in 2017 and members were appointed by the Ministry of Health as per WHO recommendation. The committee provides technical support in the following:

- Review individual serious, unusual AEFIs and other AEFIs referred to it by expert groups;
- Assess potential causal links between AEFIs and a vaccine (or vaccine lot);
- Monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events;
- Provide recommendations for further investigation, education, corrective action and communication with interested parties, including the media.

Areas of expertise for the committee members include paediatrics, neurology, forensic physician, pathology, and epidemiology, Microbiology, immunology and internal medicine and plans are underway to include more specialities. The current AEFI committee members are indicated in Table 3.

Table 3: Members of the National AEFI committee

Specialties/field of work	Officially nominated members
Paediatrician	Prof. Lisine Tuyisenge
Neurology	Dr. François Xavier Nshimiyimana
General Medicine	Dr. MUTAGANZWA Avite
Forensic Medicine	Dr. Hakizimana Francois Xavier
Pathology	Dr. Emile Musoni
Cold chain officer	MUDAHERANWA Evodie
Public Health Expert	Dr. RUGAMBWA Celse

I.2 Safety Surveillance Plan for Covid-19 Vaccine

Rwanda FDA has developed a specific safety surveillance plan for COVID-19 vaccines. This includes the capacity building for early detection, investigation and analysis of adverse events following immunization (AEFI), adverse events of special interest (AESIs) and vaccine-associated enhanced disease (VAED). The plan aimed at generating data on the safety profile of the COVID-19 vaccines in use, and ensure an appropriate and rapid response during COVID-19 vaccines introduction. Below activities were conducted in line with the safety surveillance plan for COVID-19 vaccines:

1.Training on Investigation of serious AEFI

Training of Hospital Focal Persons on Investigation of Serious Adverse Events following Immunization (Public and Private Hospitals)

Rwanda FDA and Rwanda Biomedical Centre/Expanded Program for Immunization (RBC/EPI) supported by the WHO country office has conducted a training of trainers for healthcare providers. One hundred and twenty nine (129) health professionals including medical doctors and nurses from all public hospitals and some private hospitals in Rwanda were trained. The training was also attended by Rwanda FDA staff involved in AEFI surveillance. The trainers were mainly members of the National AEFI committee, staff from Expanded Program for Immunization at Rwanda Biomedical Centre and staff from Rwanda FDA. The training focused on pharmacovigilance system, vaccine safety, adverse event following Immunization (AEFI) reporting, Investigation of serious AEFI and Vaccine safety communication.

March 2022: Training of Healthcare Professionals from District Hospitals on investigation of serious AEFI in Musanze District. (Photo/Rwanda FDA)

Effective vaccine safety surveillance systems allow timely detection, notification, and the response of identified event(s). A timely response is a crucial step in the context of the COVID-19 pandemic, as introduced vaccines are novel, they have been developed using new technologies and have never been used in humans at a large scale. These vaccines may be associated with safety features and potential risks, which were not documented during the clinical trial phases, hence close safety monitoring post-authorization should be carefully conducted to continue the assessment the safety profile of each vaccine, and respond to adverse events following immunization.

The gathered information during the investigation will contribute to the available knowledge on the vaccines but also a great opportunity to improve communication with communities to address public concerns on the COVID-19 vaccine towards increasing and maintaining trust in the immunization program.

The general objective of the training on investigation of serious AEFI was to capacitate the district teams on investigation of serious AEFI and address the community concerns arising following immunization.

Specifically, the training contributed to strengthening the capacity of district and referral hospitals to identify, report and investigate serious AEFIs and provide detailed information to allow recognition of a valid diagnosis before proceeding with causality assessment.

The main topic covered included the overview of the pharmacovigilance system in Rwanda, the overview of the Immunization program in Rwanda, basics on adverse events following Immunization (AEFI), adverse drug events (ADE), reporting of adverse drug events, investigation of serious AEFI, substandard/falsified products, introduction to causality assessment, vaccine safety communication and in addition, different exercises were performed on reporting and investigation of serious AEFI.

2. Reporting and Investigating AEFI

In Rwanda, the pharmacovigilance system includes different pharmacovigilance methods for reporting of adverse events following Immunization (AEFI) which includes spontaneous (Passive) reporting. Healthcare providers or patients voluntarily submit AEFI reports to Rwanda FDA describing an adverse event or any other vaccine related problem that occurred after immunization. Adverse events following Immunization are reported using Rwanda FDA prescribed forms available in health facilities which include paper-based forms and online reporting system (PViMS) accessible online https://pvims.rwandafda.gov.rw/security/landing, which is mainly used by health professionals. During Covid-19 mass vaccination, recipients were sensitized to report an unusual adverse events on the Rwanda Biomedical Centre Hotline (114) or Rwanda FDA hotline (9707).

January 2022: Training of Healthcare Professionals from District Hospitals on AEFI surveillance and investigation in Musanze District. (Photo/Rwanda FDA)

Rwanda FDA has granted emergency use authorization to different novel covid-19 vaccines including Pfizer/BionTech, Astrazeneca, Moderna, Jansen, Sputinik V, Coronovac etc. Therefore, as the safety profile of the covid-19 vaccines is not yet established, this requires the special safety monitoring as a way for early detection of unknown events associated with the covid-19 vaccines.

The COVID-19 vaccines safety monitoring system is being implemented through the existing passive (spontaneous) surveillance that will be supplemented by the planned active surveillance through sentinel surveillance and cohort event monitoring to ensure that any safety signals can be rapidly detected and appropriately addressed.

Rwanda FDA has developed a special safety surveillance plan for COVID-19 vaccine. The COVID-19 vaccines safety monitoring system is being implemented through the existing passive (spontaneous) surveillance that will be supplemented by the planned active surveillance through sentinel surveillance and cohort event monitoring to ensure that any safety signals can be rapidly detected and appropriately addressed.

The COVID-19 vaccines safety surveillance is being strengthened to timely collect full information about all the vaccines, analyse, document AEFIs, and adverse event for special interest (AESI), to ensure an appropriate and rapid response to any serious event and community concerns in order to minimize the negative impact of these events on individuals' health and immunization programme, and maintain the public confidence in immunization.

2.1 Reporting of AEFI on covid-19 vaccines

In Rwanda, from the beginning of the covid-19 vaccination up to March 2022 , Rwanda FDA has received different adverse events following Immunization reports following covid-19 vaccination from different reporters mainly vaccine recipients and health professionals.

Through spontaneous reporting, Rwanda FDA has received AEFI reports on covid-19 vaccines where 351(63.13%) AEFI were reported by male vaccine recipients and 205(36.87%) were reported by Female vaccine recipients. Over the total reported events, 191 (34.35%) AEFI were reported by recipients aged 30 years old or below (≤30 years old). Furthermore 320(57.55%) AEFI were reported by recipients aged between 30-59 and greater than 45 years 45(8.09%) events by recipients aged 60 years old and above. Majority of AEFI reports, 411(73.92%) were reported on Pfizer/BionTech vaccine while 110 (19.78%) were reported on Astrazeneca vaccine, 9(1.62%) events on Moderna vaccine and 12 (2.16%) reported on Moderna booster vaccine.

Different adverse events following Immunizations were reported by a single reporter, after disaggregation of the reported events as per Medical Dictionary for regulatory authorities the analysis revealed that majority events, 529(71.10%) were reported on Pfizer/BionTech vaccine followed by 177 (23.79%) AEFI reports on Astrazeneca vaccine. 48(8.63%%) vaccine recipients that reported adverse events were taking other concomitant medication especially for their chronic diseases such as hypertension, HIV and diabetes. It was noted that 305(54.86%) AEFI reports required medicines for the management of the reported events, especially painkillers, anti-inflammatory drugs and others. Over the total reported AEFI, 56(10.1) fulfil the criteria for serious AEFI which include some cases that required hospitalization or prolonged hospitalization as per USFDA definition, as described in **Table 4**

Table 4: Socio-demographic and baseline characteristics for the vaccine recipients that reported AEFI AEFI (N=556)

Variable	Category	Number	%
Sex	Male	351	63.13
	Female	205	36.87
Age	≤30	191	34.35
	31 - 59	320	57.55
	≥ 60	45	8.09
Type of vaccine	Pfizer	411	73.92
	Moderna	9	1.62
	AstraZeneca	110	19.78
	Sinopharm	2	0.36
	Unknown	12	2.16
	Moderna boaster	12	2.16

AEFI Cases per vaccines	Pfizer	529	71.10
	Moderna	14	1.88
	AstraZeneca	177	23.79
	Sinopharm	8	1.08
	Moderna boaster	16	2.15
Concomitant medication	Yes	48	8.63
	No	508	91.37
AEFI Management	Required medication	305	54.86
	No medication required	251	45.14
AEFI Seriousness	Serious	56	10.1
	Not serious	472	89.9

2.2 Severity grading of adverse events

The severity of reported AEs (556) were graded as mild, moderate and severe following the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [33]. The incidences of mild, moderate, and severe Dizziness were 19(22.4%), 60(70,6%) and 6(7.1%) respectively. 163 cases of headache reported include 26 (16.0%) mild, 116(71.2%) moderate and 21(2.9%) severe cases of headache. Among the reported cases of fever, 8(10.8%) were mild, 61(82.4%) moderate and 5(6.8%) were severe. The details on the severity grading of the reported events is described in **Table 5**. Most of the events were documented in the vaccine facts sheets such as dizziness, headache, myalgia, partial paralysis, fever, chills, nausea, vomiting, lymphadenopathies and others. Some adverse events were not expected such as high blood pressure, hyperglycemia, hypotension, palpitations and respiratory distress which are subjected to deep investigation and causality assessment to establish causal relationship between the reported event.

Table 5: Adverse events following Immunization (AEFI) reported on covid-19 vaccines up to March 2022 (N=556)

		Mild	**Moderate**	**Severe**
AEFI	**Number**	**n(%)**	**n(%)**	**n(%)**
Dizziness	85	19(22.4)	60(70.6)	6(7.1)
Headache	163	26(16.0)	116(71.2)	21(12.9)
Fever	74	8(10.8)	61(82.4)	5(6.8)
Chills	50	9(18.0)	38(76.0)	3(6.0)
Nausea	41	10(24.4)	20(48.8)	11(26.8)
Vomiting	16	7(43.8)	6(37.5)	3(18.8)
Cough	15	2(13.3)	9(60.0)	4(26.7)
Myalgia	24	10(41.7)	11(45.8)	3(12.5)

Arthralgia	16	0(0.0)	11(68.8)	5(31.3)
Dysphagia	1	0(0.0)	0(0.0)	1(100.0)
Asthenia	102	10(9.8)	76(74.5)	16(15.7)
Respiratory distress	17	3(17.6)	7(41.2)	7(41.2)
High blood pressure	20	2(10.0)	12(60.0)	6(30.0)
Hypotension	4	2(50.0)	2(50.0)	0(0.0)
Hyperglycaemia	2	0(0.0)	1(50.0)	1(50.0)
Loss of appetite	14	2(14.3)	7(50.0)	5(35.7)
Lymphadenopathies	22	3(13.6)	19(86.4)	0(0.0)
Swelling at site of injection	26	2(7.7)	21(80.8)	3(11.5)
Pain at site of injection	51	16(31.4)	32(62.7)	3(5.9)
Partial Paralysis	8	2(25)	6(75)	0(0.0)
Palpitations	3	0(0.0)	0(0.0)	3(100.0)

2.3 Investigation and causality assessment of AEFI

As per Rwanda FDA guidelines on AEFI surveillance, the serious AEFI are investigated on site where detailed information is collected from the reporter, family, community and health facilities where the recipient was treated. Most of the 35 serious AEFI reports received were jointly investigated by Rwanda FDA, RBC/EPI and WHO country office. Among the information collected in AEFI investigation includes the details on the patient, information on vaccine quality and storage, information on Laboratory tests, clinical information and outcome. All collected information during investigation are submitted to Rwanda National AEFI committee for causality assessment. Upon receipt of the investigation reports, the national AEFI committee conducts causality assessment using WHO method. Causality assessment consists of assessing the causal relationship between the adverse events following Immunization and the vaccine. The conclusion of the causality assessment shall conclude on vaccine related product, vaccine quality related reaction, Immunization error related reaction, Immunization anxiety related reaction, and coincidental reaction.

2.4 Reporting of AEFI to WHO-Uppsala Monitoring Centre (WHO-UMC)

Rwanda FDA is the 113th member of International program of Drug Monitoring, based on that Rwanda FDA provides adverse event reports including adverse event following Immunization reports to WHO collaborating centre for pharmacovigilance (Uppsala Monitoring Centre) to contribute to the global medicine safety monitoring. The AEFI reports are captured in the vigiflow system and are recorded in the international database (Vigibase) where also Rwanda FDA has access to check reports submitted by other countries. Rwanda FDA can also use the analytical system (Vigilyze) to analyse the submitted reports. So far, the Rwanda FDA has reported to the Uppsala Monitoring Centre around 160 adverse events following Immunizations on Covid-19 vaccine up to March 2021.

I.3. UMURINZI Ebola Vaccination

AEFI surveillance during UMURINZI Ebola vaccination program

WHO declared the Ebola outbreak as a public health emergency for International concern (PIHC), in 2019 some Ebola cases were reported in the western province of the Democratic Republic of Congo. At that time of the outbreak, there were no approved therapeutics nor a vaccine. In 2019, at the time of the Ebola outbreak in the western province of DRC, WHO has published a list of candidate Ebola vaccines on emergency use listing (EUL) including Janssen Ebola vaccine. Rwanda FDA granted the conditional approval under exceptional emergency of Ad26 and MVA vaccine regimen. Ad 26 and MVA Ebola vaccines consist of 2 doses 58 days apart.

The Ministry of Health launched the UMURINZI Ebola vaccination campaign on 9 January 2019 in Rubavu and Rusizi district identified as high risk districts based on the cross border movement. The vaccination was voluntary and the vaccines were contra-indicated in pregnant women and children aged below 2 years.

Ad26.ZEBOV is a monovalent, replication-incompetent Ad26-based vector that expresses the full-length GP of the Ebola virus (EBOV, formerly known as Zaire ebolavirus) Mayinga strain. it is produced in the human cell line PER.C6 ®. The Ad26.ZEBOV vaccine will be supplied at a concentration of 1x10 11 vp /Ml in 2Ml single-use glass vials as a frozen liquid to be thawed before use. Each vial contains an extractable volume of 0.5ml.

MVA-BN ®-Filo; is a recombinant multivalent modified vaccinia Ankara(MVA)-vectored vaccine.it expresses the EBOV GP, the Sudan virus(SUDV)GP, the Marburg virus (MARV) Musoke strain GP, and the Tai forest virus (TAFV, formerly known as cote d' Ivoire ebolavirus) nucleoprotein(NP). MVA-BN-Filo is strongly attenuated; the vaccine is propagated in primary chicken embryo fibroblast (CEF) cells and does not replicate in human cells. The MVA-BN-Filo vaccine is supplied at a concentration of 2x10 8Inf U/Ml in 2Ml single-use glass vials as a frozen liquid suspension to be thawed before use. Each vial contains an extractable volume of 0.5ml.

During the UMURINZI vaccination program, about 200,000 doses of Ebola Vaccine regimens were given to people who signed informed consent for the vaccine administration. The Ebola vaccine campaign started in Rubavu district and continued to Rusizi District. Johnson & Johnson pharmaceutical company has donated the 200,000 doses of Ebola vaccine regimens and other partners including Wellcome Trust and the UK Department for International Development (DFID) participated in the funding of the Umurinzi Ebola Vaccine Program. The injection was given to all those who accepted voluntarily to be the beneficiaries of the preventive vaccine aged two years and above in two injections.

The Ministry of Health has established 10 vaccination sites in the 2 districts (Rusizi and Rubavu). Rwanda FDA has put in place a mechanism for intensified reporting for adverse events following Immunization (AEFI). To implement the intensified AEFI reporting, recipients were informed on the vaccine information including adverse events following Immunization and were sensitized to report any unusual or suspected adverse events following Immunization and Pregnancies. The recipients were requested to report via Phone calls or come back to the vaccination site. The recipients that reported pregnancies after receiving the first dose (Ad26) were not administered the second dose and were monitored up to delivery to gather information on pregnancy outcome. The serious adverse events following Immunization were reported to Rwanda FDA within 24 hours as per Rwanda FDA safety and vigilance guidelines. Rwanda FDA conducted causality assessment to establish causal relationship between the reported adverse events and the vaccine taken.

Umurinzi ebola vaccination program (Photo from Ministry of Health website)

TABLE 6. ADVERSE EVENTS FOLLOWING IMMUNIZATION AND PREGNANCIES REPORTED FROM DECEMBER 2019 TO AUGUST 2021)

Reports	Number
Adverse events reported by phone	1404
Adverse events reported by visit	90
Serious adverse events reported	108
Pregnancies reported	747

Causality assessment for the reported AEFI

Causality assessment was conducted for the reported serious adverse events following Immunization using WHO causality assessment method, Over the total 108 serious reported AEFI, 17 (15.7%) reported serious adverse events following Immunization were concluded to be related to Ebola vaccine (Ad26 or MVA). Among 17 cases of adverse events concluded to be related to Ebola vaccine include mainly *weakness, vomiting, febrile convulsions, Gastroenteritis and Fever and children aged from 2-3 years old* were the most affected.

I.4. Medicine Safety Signals under investigation

Medicine safety signal is the information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (WHO).

Detection, identification and management of signals are key activities in Pharmacovigilance and this is supported by the Rwanda FDA regulations No. CBD/TRG/016 Rev_0 governing pharmacovigilance of pharmaceutical products and medical devices especially article 22, 23, and 24. On this note, after deep analysis of potential signals Rwanda FDA published the Director Healthcare professional communication with recommendations for signals management towards the improvement of the drug safety monitoring. Rwanda FDA has developed a standalone database on medicine safety

signals under investigation and has issued some medicine signal communication to health professionals for closer monitoring in gathering sufficient information that contribute to signal investigation and confirmation.

Table 7. New medicine safety signals and recommendations to healthcare professionals

Drug Product	Potential Signal	Recommendations to healthcare professionals
Amiodarone and Rivaroxaban	Drug-drug interaction resulting in gastrointestinal haemorrhage	• To be aware of this potential signals of drug-drug interaction and weigh the benefits of prescribing the combination of Amiodarone and Rivaroxaban as there is increased risk of gastrointestinal haemorrhage. • To take precautions for patients taking Amiodarone and Rivaroxaban in combination and monitor the occurrence of gastrointestinal haemorrhage. • To educate patients under treatment with Amiodarone and Rivaroxaban on signs and symptoms of gastrointestinal haemorrhage.
AstraZeneca COVID-19 Vaccine (VAXZEVRIA AND COVISHIELD)	Signal on rare adverse blood coagulation events following vaccination with AstraZeneca COVID-19 Vaccine **(VAXZEVRIA and COVISHIELD)**	• To closely monitor all AstraZeneca COVID-19 vaccinated persons; • To advise vaccine recipients to consult healthcare professionals if they develop any of the following symptoms after vaccination: ◆ New onset and persistent headache, focal neurologic deficits or change in mental status, focal neurologic deficits or change in mental status; ◆ Severe abdominal pain, breathlessness, unilateral leg swelling and chest pain • To include platelet count and radiological imaging studies to exclude possible thrombotic events • To be cautious on initiation of heparin- based therapy rather consider alternatives non-heparin based treatment modalities once the thrombosis is confirmed
Tramadol	Signal of hyponatremia following use of Tramadol	• To weight the benefits of prescribing Tramadol to patients as there is increased risk of hyponatremia associated with Tramadol use. • To consider monitoring serum sodium levels and any signs or symptoms of hyponatremia when administered Tramadol parentally. • To consider the non-prescription of Tramadol when a patient is receiving concomitant medications known to cause hyponatremia. • To educate patients how to recognize the signs and symptoms of hyponatremia.
Dolutegravir	Signal of hyperglycemia	• To perform a baseline and periodic monitoring of

	associated with the use of Dolutegravir	plasma glucose in ART regimens containing Dolutegravir as hyperglycemia is a potential and noticed side effect of the DTG-based ART regimen. • To educate patients under treatment with DTG-based ART regimen to report any signs or symptoms of hyperglycemia including but not limited to polyuria, polydipsia, visual changes and fatigue.

I.5. Medicine Safety Information

Early detection of new medicine safety information is one of the key activities in Pharmacovigilance and this is highlighted in the Regulations N° CBD/TRG/016 Rev_0 governing pharmacovigilance of pharmaceutical products and medical devices especially article 24 on safety information communication. Considering this, Rwanda FDA published new medicine safety information with recommendations and advice to healthcare professionals, patients and caregivers, and manufacturers/marketing authorization holders in order to improve patient safety monitoring.

Table 8. New Medicine Safety Information

Medicine	**New Safety Information**	**Recommendations to:**		
		Patients/Caregivers	**Healthcare Professionals**	**Manufacturers/MAH**
Sofosbuvir	Potential risk of severe cutaneous adverse reactions (SCAR) in patients using Sofosbuvir namely Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM), and bullous dermatitis (BD).	▪ Patients are advised to report any Sofosbuvir-induced cutaneous adverse reactions to health professionals or Rwanda FDA.	▪ Use Sofosbuvir with caution and consider withholding or discontinuing this drug in patients with such severe dermatologic manifestations. ▪ Recognize drug reactions early for further therapeutic actions. ▪ Mild and moderate cases improve with topical medications and supportive treatment, the severe and life-threatening cases also require permanent discontinuation of therapy.	▪ Update the safety information for Sofosbuvir to include the risk of SCAR including Stevens-Johnson syndrome (SJS).

Valproate	Risk of teratogenicity and/or lower IQ in babies born to mothers who took valproate products including valproate sodium and related products, and valproic acid (brands) like (Depacon, Depakenine) when pregnant.	▪ Stopping valproate suddenly can cause serious health problems to pregnant women and their developing babies. ▪ Use of effective birth control (contraception) methods while taking the drug for women of childbearing age.	▪ Weigh the benefits and risks of Valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. ▪ Valproate is contraindicated in pregnant women who have epilepsy unless other treatments are ineffective or not tolerated. ▪ Recommend use of effective contraception for women of childbearing age ▪ Inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal valproate exposure.	▪ Add boxed information on the risk of teratogenicity and /or lower Intelligence Quotient (IQ) in babies born to mothers who took Valproate products when pregnant.
Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs)	Increased risk of postpartum haemorrhage when selective SSRIs and SNRIs are used by mothers during the month before delivery.	▪ Report any suspected adverse reaction induced by the use of SSRIs and SNRIs to health professionals or Rwanda FDA.	▪ Continue considering the benefits of treating depression for the mother with the increased risk of postpartum haemorrhage. ▪ Continue to enquire about the use of antidepressant medicines, particularly in women in the later	▪ Update the medicine safety information for SSRIs and SNRIs by including the increased risk of postpartum haemorrhage during the month up to delivery.

			stages of pregnancy.	
Diclofenac	Risk of cardiovascular events (heart attack and stroke) associated with inappropriate use or overdose of Diclofenac such as high dose (150mg daily) and for long-term treatment.	▪ Use the recommended dose of Diclofenac as per the instructions on the label and not for a longer duration.	▪ Use the lowest effective dose of Diclofenac for shortest possible duration ▪ Not to use Diclofenac for patients with a recent medical history of myocardial infarction (within the last 6-12 months) ▪ Do the periodic review for effectiveness, adverse effects and development of cardiovascular risk factors in patients receiving long-term Diclofenac in addition to monitoring of blood pressure, haemoglobin levels and renal function.	▪ Update the patient information leaflet to more appropriately convey the risk even if the overall risk/benefit ratio remains favourable; and the following additions are recommended: ● Adding Patient with severe heart failure to the contraindications list ● Adding stronger warning about cardiovascular events to the precaution section together with the need to consider carefully the risk and benefits of treatment in individuals at higher risk of cardiovascular disease in line with these recommended for other traditional NSAIDs.

I.6. Rational Drug Use

The rational use of drugs requires that patients receive appropriate medications 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.

Ref: WHO, promoting rational drug use, 2002

A major global problem

Irrational use of medicines is a major problem worldwide. WHO estimates that more than half of all medicines (50%) are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly. The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards.

Irrational prescribing practices result in unsafe and ineffective treatment, aggravation or prolongation of disease state, harm and distress to the patients and increased costs. Irrational utilization of medicines can also cause an increase in morbidity and mortality associated with chronic conditions such as diabetes, hypertension, epilepsy and neurological disorders.

Examples of irrational use of medicines include:

i. use of various medicines per patient ("poly-pharmacy");
ii. inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections;
iii. over-use of injections when oral formulations would be more appropriate;
iv. failure to prescribe in accordance with clinical guidelines;
v. inappropriate self-medication, often of prescription-only medicines;
vi. and non-adherence to dosing regimens.

The core drug use indicators

WHO developed core and complementary drug use indicators for evaluation of drug use in healthcare settings. Among which, the core drug use indicators have been considered as the first line indicators validated by WHO for measurement of drug use. Therefore, the core indicators have been selected for better quantitative evaluation of Rational drug use.

There are three major categories of core drug use indicators namely:

- Prescribing indicators (average number of drugs per encounter; percentage of drugs prescribed with generic name; percentage of encounters with antibiotics prescribed, percentage of encounters with injections prescribed and percentage of drugs prescribed from Essential Medicine List)
- Patient care indicators (average consultation time, average dispensing time, percentage of drugs actually dispensed, percentage of drugs actually labelled and patient knowledge of how to take the drug)
- Health facility indicators (availability of essential drugs, availability of Standard Treatment Guidelines (STGs) formularies and Essential medicines)

Key interventions in Rwanda to promote rational drug use:

1) Standard treatment guidelines for different diseases and program available
2) Rwanda has developed the national essential medicines list to be used and which updated on regular intervals
3) Many hospitals in Rwanda have established drug and therapeutics committees.
4) University of Rwanda has a plan to include the problem-based pharmacotherapy training in undergraduate curricula for future health professionals.

Advise on rational drug use

1. Make a specific diagnosis
2. Consider the pathophysiology of diagnosis selected: if the disorder is well understood the prescriber is in a better position to select effective therapy.
3. Select a specific therapeutic objective or goal and medications should be selected based on it.
4. Select a drug of choice.
5. Determine appropriate dosing regimen to obtain desired therapeutic levels and the drug must be inexpensive, easily available and should be prescribed in generic name.
6. Drug interaction and adverse effects must be considered before initiating a combination of drugs.
7. Devise a plan for monitoring the drug's action and determine an end point for the therapy.
8. Plan a programme for patient education.

I.7. Active Surveillance Dolutegravir based antiretroviral regimens in Rwanda

Antiretroviral therapy (ART) has considerably contributed to longer life expectancy and improved quality of life for people living with HIV. Despite the high level of adverse drug reactions associated with ARV use, improved treatment has been highlighted where Dolutegravir (DTG) belonging to the class of Integrase Strand Transfer Inhibitors (INSTIs); acts by blocking the integration of the viral genome into the host genome. This second generation of INSTIs has been approved by USFDA in 2013 after resistance of Raltegravir and Elvitegravir thanks to its efficacy, safety and tolerance when combined with other medicines.

DTG-based regimens have been associated with hyperglycemia and elevated levels of glycated haemoglobin (HbA1c) even though more evidence is needed for confirmation. In addition, DTG-based regimens have been associated with weight-gain (excess body fat) and high blood cholesterol leading to the risk of cardiovascular diseases. DTG-based regimens that are currently used in Rwanda include Tenofovir/Lamivudine/Dolutegravir (varying strengths) and Abacavir/Lamivudine + Dolutegravir (varying strengths) and since its introduction in 2018 there is progressive shift from Efavirenz-based regimens to DTG-based regimens.

As a newly introduced drug, it's essential to know DTG safety profile by focusing on safety data from different drug development phases including clinical phases that reflect some peculiarities (genetic and environmental factors) of the Rwandan population. Based on the above mentioned background Rwanda FDA and RBC/HIV division in support of USAID/MTaPS Project are conducting an active surveillance on dolutegravir based regimen in Rwanda.

The overall objective of the ongoing active surveillance is to determine the safety profile of DTG-based regimens including Tenofovir/Lamivudine/Dolutegravir (TDF/3TC/DTG) and (Abacavir/Lamivudine + Dolutegravir) ABC/3TC+DTG among HIV patients in Rwanda. Specifically the active surveillance on dolutegravir based regimen aims at characterizing adverse event (AE) and adverse drug reaction, determining the incidence rate for Adverse events in patients using DTG-based regimens, assess causality between observed AEs and the use of DTG-based regimens, determine the effect of DTG-based regimens on weight gain as well as the blood glucose and lipid profiles and finally propose possible interventions to prevent AEs and ADRs associated with the use of DTG-based regimens where applicable.

The surveillance will involve 3000 HIV patients being managed with DTG-based regimens in selected sentinel sites and will be a prospective, observational study. Patients will be observed for the development of AEs over a one-year period.

The observation period will be extended in cases of pregnancies occurring three months after enrolment to ensure adequate follow up to document the outcome of the pregnancy. The medical history prior to commencement of DTG-based regimens will be collected for all patients enrolled in each cohort. A sub-cohort of patients (males and females belonging to different age groups and including both treatment-naïve and experienced patients) will be monitored for the development of signs suggestive of certain metabolic problems, including hyperglycaemia and hyperlipidaemia. Glucose and lipid profiles of 200 patients will be monitored during the study at different intervals (at baseline and after six months).

The twenty (20) study sites were selected based on the likelihood to get not less than 300 HIV-infected patients who are likely to be enrolled on DTG-based regimens during the enrolment period, the sites comprise: Muhima District Hospital, Kabutare District Hospital, Rwamagana Provincial Hospital, Byumba District Hospital, Bushenge Provincial Hospital, Gisenyi District Hospital, Kirehe District Hospital, Nyanza District Hospital, Masaka District Hospital, Gisenyi Health Center, Biryogo Health Center, Matyazo Health Center,, Munyinya Health Center, Rwamagana Health Center, Gikondo Health Center, Kacyiru Health Center,, Mulindi Health Center, Kamonyi Health Center, and Kibirizi Health Center.

Findings from this surveillance will provide information on the safety profile of DTG-based regimens specific to Rwandan patients, that will help the Ministry of Health and the National HIV program to establish strategies to control and manage AEs and ADRs associated with the use of these regimens. Study results may also inform review of HIV treatment guidelines in Rwanda that will be used by healthcare professionals to improve the quality of care provided to HIV patients.

Chapter II. CLINICAL TRIALS

II.1 Safety Monitoring in Clinical Trials

Clinical trials are studies that are conducted to determine whether medicine or any other medical product is safe and effective for humans. Trial participants are volunteers that could be patients or healthy people who want to help advance medical knowledge. The trial is conducted according to the comprehensive protocol. The latter outlines the types of trial participants who can enter the trial, the schedule for tests and procedures, drugs and dosages, necessary follow-up, and the length of the study. It also describes the results (endpoints) that will be measured and the type of information to collect, which is then shared with regulatory Authorities to obtain marketing Authorization.

II.2 Current Clinical Trial framework and Safety reporting structures.

The Rwanda FDA is mandated to regulate and inspect Clinical Trials through:

- Development of appropriate regulations, guidelines, standards operating procedures (SOPs), and other regulatory tools for the conduct of clinical trials
- Grant of Clinical Trial Approval Certificates (CTAC) or rejection for clinical trial conduct in Rwanda
- Conducting Good Clinical Practice (GCP) inspections at trials sites to ensure compliance of trials to international best practices and regulatory requirements.
- Monitoring of safety reports from authorized clinical trials
- Suspension or stopping clinical trials when deemed necessary
- Coordinating stakeholders in clinical trials

The Authority is responsible for the review and approval of the scientific aspects of clinical trials or clinical research involving regulated products. According to the provisions of regulations governing the conduct of clinical trials in Rwanda, the Authority receives and analyses the safety information that encompasses serious adverse events (SAEs) and serious unexpected suspected adverse reactions (SUSARS) from ongoing authorized trials involving products under investigation.

These regulatory requirements help the Authority to minutely monitor the safety of medical products under investigation (Investigational Products) and better protect human participants enrolled in the trials and future users of the products.

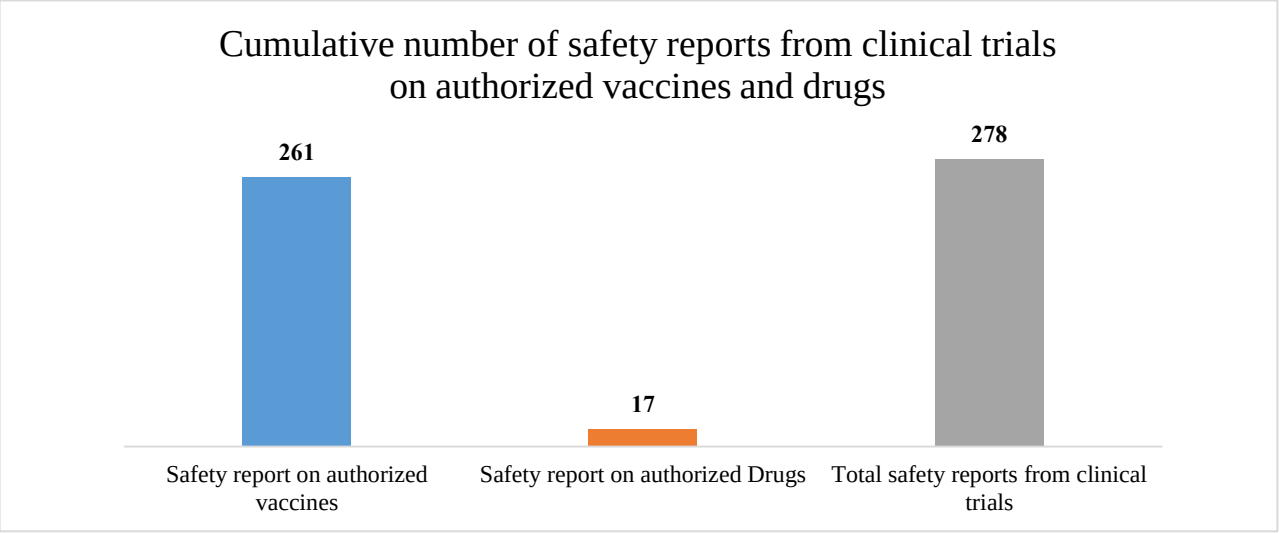
Sponsors and principal investigators are compelled to submit initial and follow up safety reports within prescribed reporting timelines for any event with the following or similar outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A congenital anomaly/birth defect

Table 9. Reporting timelines as Serious reports from clinical trials

Type of Safety Report	Timelines in calendar days	
	Notification	Full report
In country Serious adverse event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) that are fatal or life-threatening	Immediated but not later than 7 days	8 days
Other in country Serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)ng	15 days	
Out side the country Serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)	30 days	

Graph 1. A summary of the cumulative number of Safety reports (SAEs and SUSARs) from clinical trials on authorized medicines and drugs until March,2022.



Reduce your risk!

In clinical trials, there may be added risk to participating subjects compared to patients treated with marketed products. If you participate in a clinical trial, you should understand what is involved and give your consent before starting the trial. Read the informed consent form before you decide to participate. By understanding the benefits and the risks, you can make an informed choice about participating. It is also a good idea to talk to your family and friends. If you have questions, talk to your health care provider.

If you choose to participate in a clinical trial, take medicines exactly as you are told and respect your scheduled visits. Remember to contact your clinical trial doctors and/or medical research team members if you have any side effects, even if you are not sure whether the trial is the cause. Remember that you have the right to quit a clinical trial at any time.

Chapter III. MARKET SURVEILLANCE AND CONTROL

III.1. Market Complaints

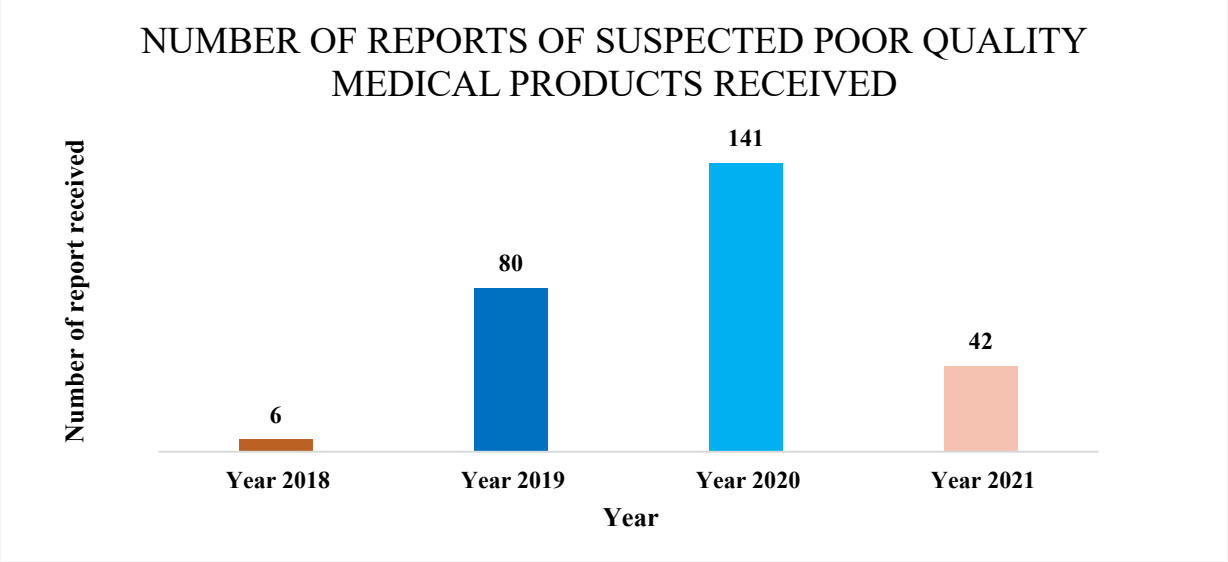
The burden of substandard and falsified medicinal products is a global public health problem causing loss of confidence in health systems leading to treatment failure, increase of treatment cost and may lead to drug resistance, disability, injury and/or death. The estimated burden of substandard and falsified (SF) pharmaceutical products within the East African region is not known but around 10% of globally traded medicines are estimated to be falsified with an even higher number in low income countries.

The Authority establishes and maintains a national post-marketing surveillance system to monitor the overall quality and safety of regulated products and respond to public health risks. All stakeholders have joint responsibility for carrying out post-marketing surveillance activities and cooperate with the Authority to ensure the quality of medical products on the Rwandan market.

The post-marketing surveillance system ensures support of the product life cycle, particularly through post-approval activities that include registration and approval of variations to the marketing authorisation; regular inspections of approved premises in the supply chain; quality control testing; pharmacovigilance, promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products.

Rwanda FDA has put in place a mechanism for reporting suspected poor quality products from different stakeholders in post marketing surveillance. There are reporting forms available on Rwanda FDA website that are used by health professionals and hotline (**9707**) that is used by the general public. Complaints related to medicines quality are reported to Rwanda FDA by central medical stores, importers, wholesalers, manufacturers, retail pharmacies and clients. Upon receipt of the quality complaints, Rwanda FDA conducts investigation including sampling and laboratory quality control analysis and actions are accordingly taken to protect the public health.

Graph 2. Number of quality complaints report on medical products from 2018-April 2021

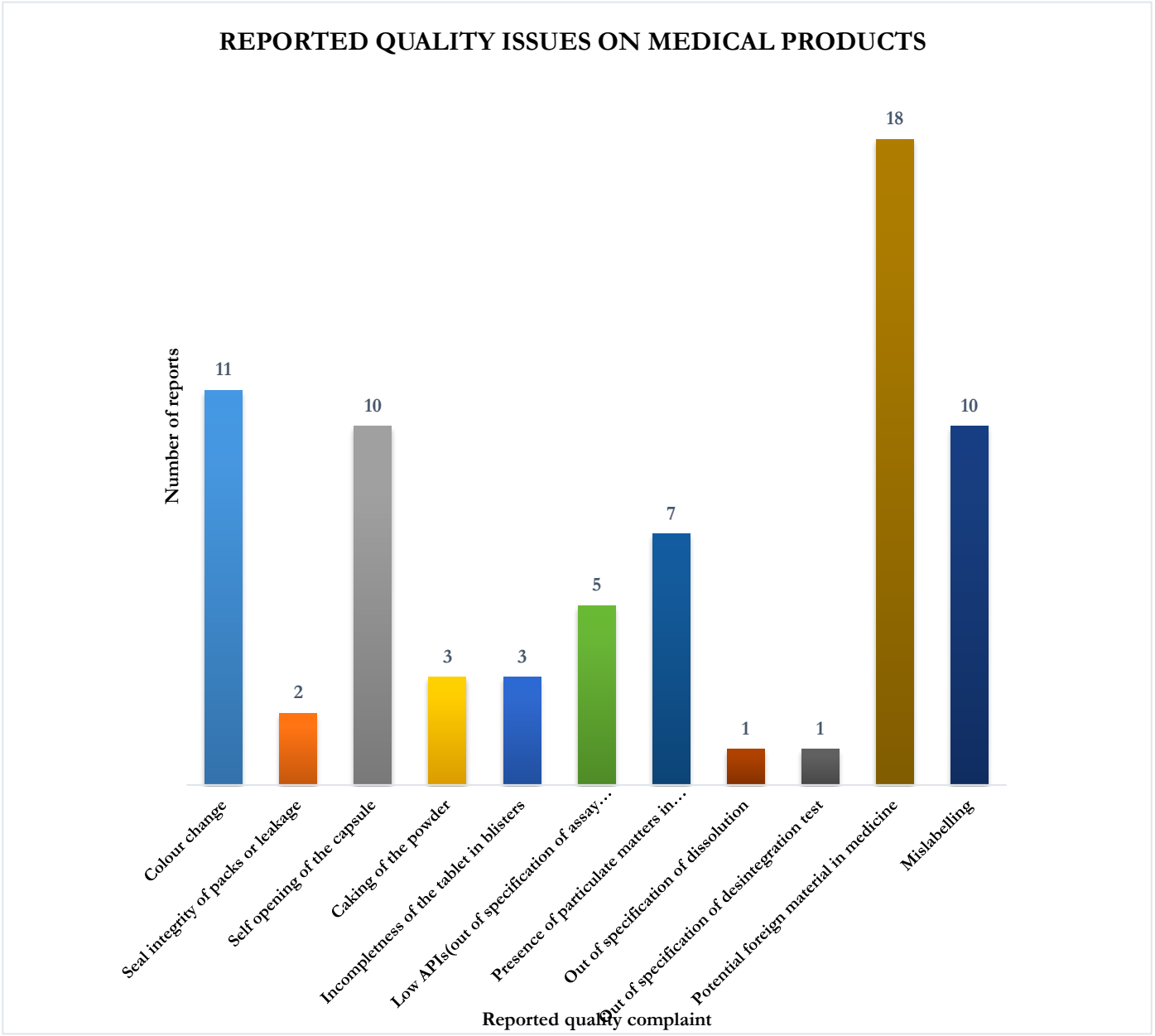


As described in **Graph 2**; from 2018 up 2021, the Authority has received 269 quality complaints on medical products which include 6 in 2018, 80 in 2019, 141 in 2020 and 41 in 2021. When an issue

related to medicine quality is identified, it should be reported promptly to the Authority, this ensures the issue can be investigated and any corrective action, if necessary, can be taken quickly.

During investigation, the authority may also conduct sampling and testing of medicines following complaints from health professionals or consumers due to lack or concern about efficacy or apparent adulteration. The authority may also decide to sample and test products that were reported to be non-compliant with quality specifications by other countries. It may also sample and test products for which severe adverse events have been reported. Rwanda FDA inspectors may collect samples at inspection sites if the inspected facility raises concern.

Graph 3. Quality complaint reports on medical products up to March 2022



Medicine quality complaints encompass a wide range of issues identified after medicines have been released for distribution. These issues can affect the identity, quality, durability, reliability, safety or effectiveness of a medicine, which may make it unsafe or unfit for purpose.

III.2. Recalled medical products

A “recall” is the removal of product or batches of products because of defects that may compromise safety, efficacy and purity of the product. A recall is necessary when a product is found to be defective in some way and removing it from the market is the only way to ensure consumer safety.

Recalls are said voluntary when undertaken by the manufacturer or distributor at any time or statutory when initiated at the request of the regulator such as Rwanda FDA

A recall usually results from one or a combination of the following situations:

1. Company discovery: A company discovers, through its own routine testing program, that a product lot does not meet one or more of the specifications that are established for that product.
2. Customer complaint: A problem is often discovered from customer complaints.
3. Rwanda FDA findings: Recalls can also be necessitated because of a finding/ made by the regulator or significant compliance deficiencies noted during an inspection.

Rwanda FDA Regulations No. CBD/TRG/019 Rev_1 Governing Recall, Treatment and Disposal of Unfit Regulated Products provides a legal framework for the effective and efficient regulation of recall, treatment and disposal of unfit regulated products and providing an open transparent and non-discriminatory process for the treatment and disposal of unfit regulated products.

As per the Rwanda FDA Regulations No.: CBD/TRG/019 Rev_1, articles 21 and 22, Marketing Authorization holder (MAH) or local technical representative (LTR) are required to identify the root cause of the problem and implement the remedial action taken and corrective and preventive action (CAPA) and submit analytical report to the Authority who evaluate the report and informs the MAH if satisfactory.

Since its establishment up to April 2022, Rwanda FDA has recalled about 98 batches of pharmaceutical products including human and veterinary medicines. The table below shows the recalled human medical products from ***July 2021 up to April 2022***.

Table 10. List of recalled pharmaceutical products from June 2021-April 2022

No.	DESCRIPTIONS	BATCH N0. & EXPIRY DATE	Types & Classification of recall	DATE OF RECALL	MANUFACTURERS AND ADDRESSES	REASON FOR RECALL
1	AGOMYCIN Suspension (Erythromycin Estolate Oral Suspension 125mg/5ml)	BN: L96013 Mfd:11/2019, Exp:10/2022	Statutory recall	14/04/2021	Agog Pharma Limited, India	Low level of Content of Erythromycin Estolate eq. to Erythromycin,36.476mgl 5m1. while normal range should be 112.50 - 143.75mg15ml
2	Unibrol (Aminosidine) 250mg	All batches Available on market	Voluntary recall	28/04/2021	Universal corporation/Kenya	Change of color for some tablet with yellow color instead of white color
3	Phytomenadione Inj. BP 10mg/ml	SA20C008E, Mfd:03/2020, Exp:02/2022	Statutory recall	25/05/2021	SANJAR PHARMA LLP, Himatnagar-VijapurHighway, Dedhrota,Hitmatnagar-383 220, GUJARAT,INDIA	Presence of particulate matters in vials
4	Hyoscine Butyl bromide Injection BP 20mg/ml,	BN:3H20001,Mfd:07/2020, Exp:06/2022	Statutory recall	25/05/2021	Centurion Healthcare Private Limited/601, Atlantis Heights, Sarabhai Compound, Vadi Wadi, Vadodara-390 007, Gujarat, INDIA	Presence of Particulate matters in Vials and Piece of broken glass in the vials
5	Hyoscine Butyl bromide Injection BP 20mg/ml	BN: 3H20002, Mfd:08/2020, Exp:07/2022	Statutory recall	25/05/2021	Centurion Healthcare Private Limited	Particulate matter in vials
6	Furosemide injection 20mg/2ml	BN:JFDIE-001, Mfd:11/2019, Exp:10/2022	Statutory recall	25/05/2021	Laborate Pharmaceuticals India	Presence of Particulate matters in vials
7	Atropine injection	BN:16222001, Mfd:05/2020,Exp date:04/2023	Statutory recall	25/05/2021	Pharmax India Pvt.Ltd/India	Presence of Particulate matters in vials

8	Amoxicillin 250mg capsule	BN:MP18485A, Exp:09/2021	Statutory recall	25/05/2021	MILAN LABORATORIES (INDIA) PVT. LTD	Presence of unidentified solid dark blue / black particles.
9	Azithromycin dry powder for suspension (ZEROCIN)	BN:75363, Mfd:09/2019, Exp:08/2021	Statutory recall	25/05/2021	Laboratory&Allied Ltd./Kenya	Caking of the powder in the bottom of the bottles causing poor flowability
10	Nystatin oral suspension BP 100 000 IU/ml	BN:2006004, Mfd:06/2020, Exp:05/2022	Statutory recall	25/05/2021	DAWA Limited/ Kenya	Bottles were found with a solid lower sediment which is very difficult to shake to the homogeneous status, and several bottles seem to have developed microbial growths that led to the cloudy/misty appearance in the bottles
11	Losar-Denk 25 mg film Coated ALL BATCHES	All	Voluntary recall	07/10/2021	DENK PHARMA	Genotoxic impurity was detected in the Active Pharmaceutical Ingredient (API)
12	Losar-Denk 50 mg film Coated ALL BATCHES	All	Voluntary recall	07/10/2021	DENK PHARMA	Genotoxic impurity was detected in the Active Pharmaceutical Ingredient (API)
13	Losar-Denk 100 mg film Coated ALL BATCHES	All	Voluntary recall	07/10/2021	DENK PHARMA	Genotoxic impurity was detected in the Active Pharmaceutical Ingredient (API)
14	Colosar-Denk 50mg /12,5mg film coated tablet ALL BATCHES	All	Voluntary recall	07/10/2021	DENK PHARMA	Genotoxic impurity was detected in the Active Pharmaceutical Ingredient (API)
15	Colosar-Denk 100 mg /12,5mg film coated tablet ALL BATCHES	All	Voluntary recall	07/10/2021	DENK PHARMA	Genotoxic impurity was detected in the Active Pharmaceutical Ingredient (API)
16	ALBAMAS-400 (Albendazole	BN: MTE20007, Mfd: 05/2020,	Statutory recall	10/12/2021	Mascot Health Series Pvt. Ltd, Plot No. 78,80,	change colour and most of tablets crumble upon

	tablets 400mg)	Exp.: 04/2023			Sec-6A, IIE, Sidcul, Haridwar-249403, Uttarakhand, India	unpacking from blisters

III3. Post Marketing Surveillance (PMS) Plan

Reference made to the regulation No CBD/TRG/018 governing post marketing surveillance of regulated products especially in its article 8 and 11, the Authority prepares and implements annual post marketing plan, conducts customer complaint survey and carry out sampling activities guided by a developed and approved sampling plan.

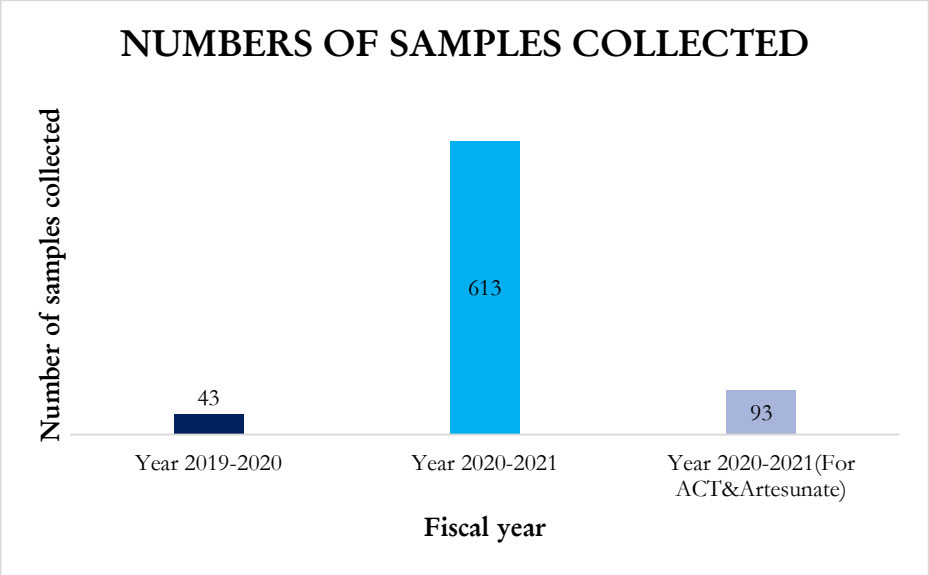
Post-marketing surveillance involves systematic sampling of pharmaceutical products from distribution systems such as central medical stores, wholesale pharmacies, retail pharmacies, hospitals and health centers using pre-arranged sampling plan, screening and laboratory testing.

Rwanda FDA conducted annual sampling 2019-2020, 2020-2021; and sampling targeting anti-malaria medicines conducted in November 2020 where samples of pharmaceutical products were taken countrywide within different levels of supply chain. The sampled medicines covered a wide group of pharmaceutical products such as analgesic, antibiotics, antiretroviral medicines, anti-tuberculosis medicines, antihypertensive medicines, and anti-diabetic medicines.

Annual sampling 2019-2020 and 2020-2021

In 2019-2020 annual sampling, a total 43 batches of pharmaceuticals products were collected and analyzed in Rwanda FDA Quality control laboratory where it found that all tested pharmaceutical products were complied with the specification of performed parameters.

Graph 4. Annual sampling of pharmaceutical products for post-marketing surveillance



In the annual post-marketing surveillance sampling 2020-2021, the total samples of 613 batches of pharmaceutical products were collected at the central medical store, all branches of Rwanda Medical Supply, wholesale Pharmacies, retail Pharmacies and health facilities countrywide.

Over 613 batches of medicines sampled and tested in the Laboratory only 3 batches of medicines failed to meet specification for the tested parameters.

III.4. Post Marketing surveillance (PMS) on Antimalarials

Background: To attain greater success of the Rwanda's Extended Malaria Strategic Plan 2013-2020 in its strategy 3 "Strengthen quality assurance and control of all malaria consumables and commodities", the President's Malaria Initiative (PMI), through the USAID/Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) funding, supports the National Malaria control program and Rwanda Food Drug Authority (Rwanda FDA) to conduct the quality control of antimalarial medicines across the country as part of post-marketing surveillance activities.

Objective: The overall objective of this activity was to assess whether antimalarial medicines keep or not the quality after being stored and distributed throughout the supply chain levels.

Methods: A total of 93 samples including 84 for tablets of Artemisinin-based combination Treatment (ACTs) and 9 for Artesunate injectable were collected from all 5 provinces (based on low and high malaria cases) at different supply chain levels (central, district, health center, and community) and analysed between November 2020-February 2021. In respect of the storage conditions, coded samples were sent for laboratory analysis in Germany "InphA Gmbh Medicine Control Laboratory".

Samples were collected from different districts based on geographical and endemic zones. The selected sites in each province are Nyagatare, Kirehe, Burera, Ruhango, Gisagara, Rusizi, Gasabo and Rwanda Medical Supply Ltd. headquarters.

Photo 1 picture taken during sample collection at RMS Gasabo Branch

Table 11. Quantities of samples per product category

Products	#of tablet per sample sites	# of tablet per blister	#of blisters per ACTs age group/Site	Unit of measure	#of blisters for 2 sites DP and HC	#of samples
AL 6X1	100 Tablets	6	17	Blisters	34	2
AL 6X2	100 Tablets	12	9	Blisters	18	2
AL 6X3	100 Tablets	18	6	Blisters	12	2
AL 6X4	100 Tablets	24	5	Blisters	10	2
Total ACTs samples per district						8
Total ACTs in 8 districts						64
ACTs from MPPD						4
AL (4age groups) from the community in 4 endemic districts						16
Artesunate injection						9
Total samples						93

AL: Artemether Lumefantrine

Laboratory quality control analysis

Tests performed for ACTs tablets are uniformity of mass, disintegration / dissolution), identity test and related substances impurities and assay while compliance with the monograph for parenteral preparations of artesunate were performed and includes the parameters such as clarity and color of solution, Particulate matter, pH, water content, sterility, filling quantity variation), identity tests, bacterial endotoxins, related substances assay and sterility.

Results: Of all the 93 tested samples, 100% of ACTs tablets and Artesunate injectable met the quality standards (chemical and physical).

Conclusion: The samples collection and transportation as well as the quality control testing of ACTs and Artesunate vials were successfully conducted and brought to an end. 100% of all the samples of ACTs and Artesunate injectable met the quality standards and this gives confidence that not only quality ACTs and Artesunate are being procured for Rwanda but also the same quality is maintained during storage and distribution across different supply chain levels including the community.

III. 5. Risk Based Post-Marketing Surveillance (RB-PMS)

Rwanda FDA adopted the Risk-Based Post-Marketing Surveillance (RB-PMS) to combat Sub-standard and Falsified (SF) medical products. “SF products cause significant threats to health system, increased disease prevalence, loss of public confidence in healthcare professionals and health systems, and antimicrobial resistance.”

Rwanda FDA is committed to prevent substandard and falsified (SF) medical products and their consequences. The Authority implements different functions to combat SF products on Rwandan market that include: registration of all medicines, GMP inspection; import and export control, laboratory quality control analysis, pharmacovigilance and Post marketing surveillance activities.

A risk-based post-marketing surveillance (RB-PMS) approach was adopted by the Authority to detect and remove any SF products on market.

Rwanda FDA supported by USP PQM+ is strengthening post-marketing surveillance system through capacity building of the workforce with a focus on quality control and assurance, improvement of its Laboratory Quality Management System (LQMS) and quality control capability, and performance of regular risk-based PMS and compendia tests for selected medicines including the Family planning (FP) and Maternal, Newborn and Child Health (MNCH) products.

Training on Risk-Based Post-Marketing Surveillance (RB-PMS)

In the framework of the partnership of USAID/PQM+ and Rwanda FDA, a two-weeks workshop was conducted for Rwanda FDA staff and different stakeholders in post marketing surveillance program mainly Ministry of Health, National Pharmacy Council, Hospitals, central medical stores, wholesale pharmacies, industries, Rwanda Community Pharmacy Union, Rwanda Investigation Bureau, Rwanda National Police, University of Rwanda and Rwanda Revenue Authority. The workshop was held at La Palisse Nyamata Hotel and was facilitated by experts from USAID/PQM+. The workshop has been an opportunity for participants to be trained on principles of RB-PMS and to establish the first Risk-based PMS technical working Group referred to as Risk based PMS technical Committee in Rwanda FDA.

February 2022: Training of Rwanda FDA staff and other stakeholders on risk-based post-marketing surveillance (RB-PMS) in Bugesera District. (Photo/Rwanda FDA)

Post-Marketing Surveillance Technical Committee (PMS-TC)

The committee was established in compliance with article 15 of Regulations No.: CBD/TRG/018Rev_0 Governing Post-Marketing Surveillance of Regulated Products and is composed by different members mainly stakeholders' representatives and Rwanda FDA staff from different divisions mainly Quality Control Laboratory, Inspection and compliance, Import and Export control, Assessment and registration and Pharmacovigilance and safety monitoring.

The main goal of this RB-PMS TC is to ensure coordination of the relevant stakeholders in the building of PMS systems, periodic planning of RB-PMS activities and advise Rwanda FDA to assure the quality of Health products and technologies in the country. The committee shall lead the building of a robust risk-based post-marketing surveillance system for all health products and technologies that are available on the Rwandan market.

Participants were trained on the use of the online Medicines Risk-based Surveillance (MedRS) tool developed by PQM+ to support the implementation of risk-based approaches during PMS activities. This tool facilitates developing sampling protocols for post-marketing quality surveillance utilizing a risk-based approach. The tool applies risk management principles to evaluate multiple factors in several dimensions of risk to facilitate selection of medicine, geographic location as well as the facility/outlet within the supply chain for sample collection. The tool assists countries identify the most susceptible medicines to be collected, prioritize sampling to the most vulnerable locations and determine the number of samples required for a statistically significant assessment.

February 2022: Director General of Rwanda FDA with the nominated risk-based post-marketing surveillance (RB-PMS) Technical Committee. (Photo/Rwanda FDA)

III.6. Field investigation on factors related to the inefficacy of acaricides on the Rwandan market

i) Background

Ticks' resistance to acaricides is a challenge threatening livestock production in many African countries. Ticks are vectors of serious, even dead full animal diseases such as theileriosis/East Coast fever, babesiosis, and anaplasmosis. Tolerance to acaricides by ticks makes the control of these diseases very challenging. Following complaints from many stakeholders that acaricides on the Rwandan market are no longer efficacious against ticks, Rwanda Food and Drugs Authority organized a field investigation to identify some of the factors associated with the reported acaricide resistance.

ii) Objectives

The main objective of the investigation was to establish some of the factors associated with the inefficacy of acaricides against ticks that are on the Rwandan Market. Specifically, the investigation assessed the range of acaricide active ingredients on the market and practices related to the use of acaricides among different stakeholders.

iii) Methodology

In September 2021, an investigation was carried out in Kigali City, Eastern Province (Bugesera, Kirehe, Kayonza, and Nyagatare), and the South Province (Muhanga, Nyanza, Huye, and Nyaruguru). Inspectors visited veterinary wholesale pharmacies, veterinary retail pharmacies, veterinary

professionals, and a few cattle farmers. Inspectors used a predesigned questionnaire to collect information about acaricides on the Rwanda market and the practices related to the use of acaricides.

iv) Results

Amitraz was reported as the main active ingredient of the most frequently used acaricides in the study areas. The other active ingredients found on the market include the combination of pyrethrin and permethrin, the combination of pyrethrin, deltamethrin, and permethrin, flumethrin, and cyhalothrin. The assessment of practices related to the use of acaricides revealed that most of the stakeholders misuse acaricides. They do not follow the indications related to the dilution and frequency of use specified by the manufacturers on the product labels. In Kigali city and Eastern province, responses of 62% and 92% of interviewed veterinary professionals and farmers respectively, were not in agreement with the recommendations of the manufacturers. It was also noted that many farmers (64% of interviewed) in the Eastern province use plant insecticides or veterinary acaricides acquired through unofficial circuits (36%) to fight against resistant ticks. In the southern province, responses of 64% and 83% of interviewed veterinary professionals and farmers respectively, were not in agreement with the recommendations of the manufacturers. In the south, none of the farmers reported using plant insecticides or veterinary acaricides acquired through illegal circuits.

v) **Conclusion**

The investigation revealed a lack of variety of acaricide active ingredients on the Rwandan market. This may underpin the development of tick resistance as few active ingredients are being utilized. More active ingredients should be introduced on the market in a controlled manner to allow a rotation scheme of acaricide classes; hence avoiding the development of acaricide resistance. The investigation also revealed malpractices regarding the usage of acaricides among stakeholders. Awareness campaigns to promote the proper use of acaricides should be conducted.

III.7. Quality Control Laboratory

Photo: Quality control Laboratory (photo/Rwanda FDA)

1. Introduction

Rwanda FDA is mandated to establish the quality assurance and quality control of regulated products, in addition to conducting research and studies on food and pharmaceutical products. The Authority is mandated to publish findings in order to promote investment as stipulated in article 8 of the law establishing Rwanda FDA, paragraph (6) and paragraph (14) respectively.

Quality Control Laboratory Division is the stand-alone division in Rwanda FDA 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' compliance with the set standards and enables the Authority to make evidence-based regulatory decisions.

The Quality Control Division has the following major goals:

- Conducting quality testing of food and drugs samples and provide accurate and precise results to assist in regulatory decisions
- 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 Rwanda FDA
- Ensure customer satisfaction

Testing is performed to ensure that finished products continue to meet national and or international quality and safety standards throughout their lifecycle. The laboratory findings and data provide strong support for pharmacovigilance, post-marketing surveillance and regulatory actions

The generated quality control results are also important in ensuring that the Authority makes evidence-based regulatory decisions during marketing authorization and enforcement of the Rwanda FDA Law.

1. About Quality Control Laboratory

The QCL Division operates under four (4) Units:

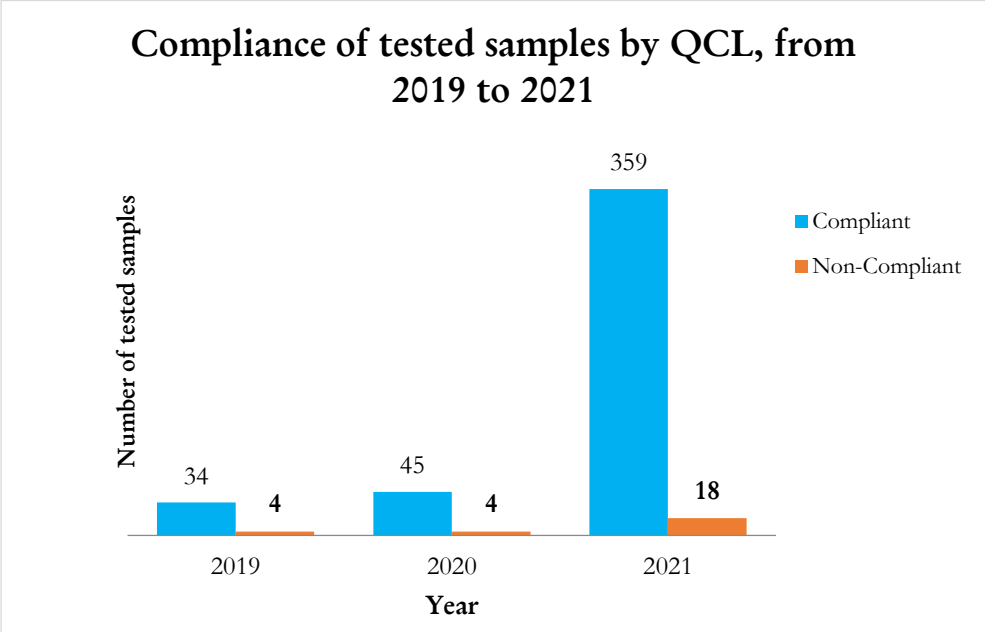
1. **Medicines and Cosmetics Testing Unit:**
   The Medicines and Cosmetics Unit is responsible for testing of Medicines and medicated Cosmetics, ensuring timely analysis and preparation of scientific analytical reports.
2. **Food Testing Unit:**
   Food testing unit is responsible for testing and timely analysis of food products and preparation of scientific analytical reports.
3. **Pesticides & Poisons Substances and Chemical Unit**
   Pesticides & Poisons Substances and Chemical Unit is responsible for testing of pesticides, poisons substances, and other chemicals; and ensuring the timely analysis and preparation of scientific analytical reports.
4. **Medical Devices & Instrumentation Unit**
   The Medical Devices & Instrumentation unit is responsible for effective and efficient performance of medical devices analysis and timely preparation of test results' reporting.

2. Quality Control Laboratory achievements in 2021

In 2021, the Quality Control Laboratory has achieved the following:

i. Testing and reporting of 377 samples of medicines from pre-market, post-shipment and Post-Market Surveillance where 18 of them failed to comply with the quality standards requirements as detailed in graph below.

Graph 5: Medicines and medicated cosmetics tested between 2019 and 2021.



As mentioned in the graph 5, in the last 3 years, 464 samples were analyzed, the majority of which (377) were performed in 2021 (81%). During this period the rate of non-compliance varied from 4, 4 and 18, respectively in 2019, 2020 and 2021.

ii. Development of the regulations governing the analysis of regulated products by Rwanda FDA and 30 Standards Testing Procedures (STPs) as per the 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, 30 Protocols for methods validation and method verification, and 11 validation reports and 19 verification reports were elaborated. Those activities of verification and validation will continue as planned.

iii. Registration and successfully participation in the inter laboratory comparisons (ILC) for the following parameters:
   - Qualitative analysis of Atazanavir related substances: From USP Ghana
   - Disintegration of paracetamol: From USP Ghana
   - Assay and Dissolution of Ciprofloxacin: From Muhimbili University of Health and Allied Sciences (MUHAS)

The African Medicines Quality Forum (AMQF) Interlaboratory comparison (ILC) results showed that Quality Control Laboratory passed the disintegration test of paracetamol tablet and related substances

tests for Atazanavir tablet while waiting for the proficiency test results from Muhimbili University to be published.

Photo:

iv. Rwanda FDA has also signed a contract for testing services with Mission of Essential Drugs and Supplies (MEDS)-Contract Number 000002//NC/2020/2021/Rwanda FDA

v. The Laboratory has acquired new equipment such as ICP/OES (Inductively coupled plasma-optical emission spectroscopy) GC-FID (Gas Chromatography-Flame ionisation detector)

vi. Installation and training of laboratory staff on LIMS (Laboratory Information Management System)

3. Laboratory testing Scope

The laboratory has capacity to conduct assay on the active ingredients and purity (e.g. chromatographic methods, titration methods, and spectrophotometric methods), identity of product (e.g. using spectrophotometric methods, and chromatographic methods), uniformity of mass, uniformity of content, friability, disintegration, dissolution test, heavy metals analysis, water content (Karl Fisher titration method)**,** appearance**,** acidity and alkalinity of solution, weight per ml, pH, hardness test, impurities and related substances.

The commonly used and available equipment at Rwanda FDA are Gas Chromatography (GC) with Mass Spectrometer Detector (MS), Gas Chromatography with FID detector (GC FID), Fourier transform infrared Spectrophotometer (FTIR), High Performance Liquid Chromatography (HPLC - DAD; UV-Vis, RI, FLD), pH Meter, density meter , refractometer, Karl Fisher automatic titration equipment, hardness tester, friability tester, disintegration test apparatus, dissolution test apparatus, AAS, ICP/OES,HPTLC, UV-Vis Spectrophotometer.

The scope of testing was increased to the establishment of a lab for testing of Medical Devices (disposable gloves and condoms testing equipment) which is currently functional.

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

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

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