Strategies and Measures to Prevent Substandard and Falsified Medicinal Products in Sub-Saharan Africa

Masterarbeit

zur Erlangung des Titels

„**Master of Drug Regulatory Affairs, M.D.R.A.**“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Dr. Anissa Boucherot

geboren in Algier (Algerien)

München 2025

Erstgutachterin: Dr. Birka Lehmann

Zweitgutachter: PD Dr. Hubert Rein

Danksagung

Mein Dank gilt Frau Dr. Birka Lehmann für ihre Bereitschaft, diese Arbeit zu betreuen und zu begutachten. Vielen Dank für die hilfreichen Ideen und die freundlichen Emails. Herrn PD Dr. Hubert Rein danke ich für die Übernahme der Zweitbegutachtung.
Bei Frau Dr. Fahnenstich möchte ich mich für die vielen Unterstützungen und aufmunternden Emails während der gesamten Studienzeit bedanken. Dem gesamten Team der DGRA danke ich für die Hilfe und die gute Organisation des Studiengangs.

Meinen Freunden Ony, Nike und den „Wanny‘s“ möchte ich für ihre Geduld und ihre Aufmunterungen in den letzten Jahren, die für uns alle nicht einfach waren, danken. Der Zusammenhalt war sehr wichtig.
Meiner Mutter möchte ich besonders für ihre Zeit danken, die sie in meiner Kindheit investiert hat. Ohne ihren Einsatz und ohne ihre Anstrengungen hätte meine Gesundheit erheblich unter der damaligen und ortsbedingten Situation sehr gelitten. Merci beaucoup M‘man!
Die Gedanken an diese Zeit haben mich zum Thema meiner Arbeit geführt.

Der allergrößte Dank gilt meiner Familie, die mich die ganze Zeit mit viel Geduld und Liebe unterstützt hat. Meiner Tochter danke ich für ihr Verständnis, dass ich wegen des Studiums nicht immer genügend Zeit für sie hatte. Meinem Mann danke ich dafür, dass er mir das Studium trotz seiner starken beruflichen Auslastung ermöglicht und mich während der Schreibphase immer wieder motiviert hat.
Merci Alessia, merci Thomas!

Table of Contents

List of Abbreviations

AAC	Antibody–antibiotic conjugate
AfCFTA	Africa Continental Free Trade Area
Africa-CDC	Africa Centres for Disease Control and Prevention
AIDS	Acquired Immunodeficiency Syndrome
AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonization Initiative
API	Active Pharmaceutical Ingredient
APROPHISP	Professional Association of Public Health Pharmacist Inspectors
APTF	African Pharmaceutical Technology Foundation
ATC	artemisinin combination therapies
AUC	African Union Commission
AUDA-NEPAD	African Union Development Agency-New Partnership for Africa's Development
BMFG	Bill and Melinda Gates Foundation
CHMP (Partners in MEDISAFE-project)	“Centre Humanitaire des Métiers de la Pharmacie” (Humanitarian Centre for Pharmacy Professionals)
CIOPF	International Conference of Francophone Pharmacists Associations
COVID-19	Coronavirus disease of 2019
EAC	East African Community
EC	European Commission
ECCAS	Economic Community of Central African States
ECOWAS	Economic Community of West African States
EDCTP	European and Developing Countries Clinical Trials Partnership
EEAS	European External Action Service
EIB	European Investment Bank
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FMD	Falsified Medicines Directive
GAVI	Global Alliance for Vaccines and Immunization
GIZ	Deutsche Gesellschaft für Internationale Zusammenarbeit GmbH

GMP	Good Manufacturing Practices
GPHF	Global Pharma Health Fund
GS1	Global Standards 1, an organisation
GSMS	Global surveillance and monitoring system
GTR	Global Trust Repository
HIV	Human Immunodeficiency Virus
ICRMA	International Coalition of Medicines Regulatory Authorities
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IGAD	Intergovernmental Authority on Development
INTERPOL	International Criminal Police Organization
LMIC	low- and middle-income countries
MAH	Marketing Authorised Holders
MAV+	Manufacturing and Access to Vaccines, Medicines and Health Technologies-Project
MEDICRIME	Council of Europe's Convention on the counterfeiting of medical products
MEDISAFE	European funded project to combat problems with SF Medical Products in Eastern and Central Africa
MRH	Medicine Registration Harmonization
mRNA	messenger ribonucleic acid
MSM	Member State Mechanism
MVV	Medicines for Malaria Venture
NAFDAC	National Agency for Food and Drug Administration and Control (Nigeria)
NGO	Non-governmental organization
NIRS	Near-Infrared Spectroscopy
NPHI	National Public Health Institutes
NRAs	National Regulatory Agencies
NRRAs	National or Regional Regulatory Authorities
PAHO	Pan American Health Organization
PAN	PAN African Parliament
PHAHM	Platform for Harmonized African Health Products Manufacturing
PMPA	Pharmaceutical Manufacturing Plan for Africa

PoD	point-of-dispense
R&D	Research and Development
RCC	Regional Coordination Centres
RECs	Regional Economic Communities
ReMed	Network for Medicines and Development
SADC	Southern African Development Community
SAHPRA	South African Health Products Regulatory Authority
SARPAM	Southern Africa Regional Programme on Access to Medicines
SDG	Sustainable Development Goal
SF	substandard and falsified
SME	Small and Medium-sized Enterprises
SOP	Standard Operating Procedures
SSFFC	substandard/spurious/falsely-labelled/falsified/counterfeit
T&T	Track and Trace
TEI MAV +	Team Europe Initiative on Manufacturing and Access to Vaccines, Medicines and Health Technologies
TLC	Thin Layer Chromatography
TRVST	Traceability & Verification System for Health Products
TVET	Technical and Vocational Education and Training
UN	United Nations
UNICEF	United Nations International Children's Emergency Fund
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
USAID	United States Agency for International Development
vfa	Verband forschender Arzneimittelhersteller
VTI	Verification and Traceability Initiative
WHO	World Health Organization
WTO	World Trade Organization
ZAZIBONA	First two letters of Zambia, Zimbabwe, Botswana and Namibia

List of Figures

Glossary

Term	Definition
Medicinal products	*A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action*. (9)
Medical Products	*Medical Products include medicines, vaccines, in vitro diagnostics, medical devices, immunization devices, cold-chain equipment, vector control products, blood and blood products, antivenoms, monoclonals and other biotherapeutic products.* (19)
Medicines	*Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.* (92)
Pharmaceutical products	*Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and /or the importing state.* (92)
Drugs	*Any substances or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug, medicine and pharmaceutical product are used interchangeably.* (92)

1. Introduction

1.1 Aims and Objectives

In 2024, the United Nations (UN) office on Drugs and Crime published a report (1) estimating that substandard and falsified (SF) medicinal products were responsible for around 500 000 deaths per year in the Sub-Saharan region. In addition, up to 267 000 deaths per year were linked to falsified and substandard antimalarial medicines. The World Health Organization (WHO) review on Malaria (2024) describes that young children, girls and pregnant women are at increased risk of malaria mortality due to a combination of biological and social determinants and should therefore be specifically targeted for antimalarial treatments (2). According to the WHO report, antibiotics and antimalarial products are the most falsified medicines in Africa (3). Effective treatment is critical to controlling the disease, but the proliferation of SF medicinal products is undermining global efforts to combat malaria. The availability of SF malaria medicines lead to treatment failures and can also accelerate the development of drug-resistant strains of malaria, thereby exacerbating the public health crisis.

Trafficking in these SF medicinal products not only endangers the health of the patients, but also has a direct impact on the economics of the countries concerned. The WHO estimates that the SF medicines for malaria treatments cost between $12 million to $44.7 million each year in Sub-Saharan countries (1).

In Sub-Saharan Africa, the high prevalence of infectious diseases such as malaria, combined with the problems of availability, affordability, and access to healthcare, creates an environment in which the demand for medicines is not adequately met through official channels. The discrepancy between the demand for and the supply of regulated medicinal products leaves room for illicit trade, providing an incentive for the involvement of organised criminal groups and thus endangering the health of people in these countries (1). The increase in SF medicines is largely due to weaknesses in regulatory control (insufficient laboratory infrastructure), porous borders and supply chain vulnerabilities (1).

This thesis highlights the prevalence of SF medicinal products in Sub-Saharan Africa and the threat they pose to the public health, such as treatment failure and increasing drugs-resistance, using malaria as an example for a representative disease to be combated. The aim of this study was to describe the measures taken by Sub-Saharan African countries to reduce the flooding of their markets with SF medicinal products. The idea was inspired by the "Fight-the-Fakes-Alliances" and the proposed principles of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) against SF-medicines (4) (5). The thesis provides an overview of existing regulatory frameworks and efforts to increase the effectiveness of the control of SF medicines, as well as the strategies of various international and local collaborations to combat the SF medicinal products. Technological solutions play an important role to strengthen this fight at different levels (from manufacturer to consumer). A functioning pharmacovigilance system, in combination with an international organisation such as INTERPOL, is important to reduce and eliminate SF medicinal products from the market and improve the safety of patient.

Finally, the risk of drug resistance due to SF medicines does not only have an impact in Sub-Saharan Africa countries. It is also a global public health challenge due to the influence of climate change, as weather patterns that lead to mosquito-borne diseases (malaria, chikungunya and dengue viruses) spray into new regions (locally transmitted malaria in Florida and Texas; dengue virus in Western-Europe, both 2023). (6)

"*With falsified medicines there is an intentionally attempt to pass these products as genuine approved medicines. Only a "collective fight" which require the involvement of multi-stakeholder and supported by the WHO can face this global health challenge*" (IFPMA (4) (5)).

1.2 Materials and Methods

This thesis is based on an extensive research of open-access articles in public and academic databases (Google scholar, PubMed) and reports from international organisations (WHO, EMA, IFPMA, INTERPOL) and further search on the websites of various organisations in Africa (national regulatory authorities, cooperation organisation and funding organisation; AUDA-NEPAD, Africa-CDC), of the funding organisation in Germany (GIZ, Deutsche

Gesellschaft für Internationale Zusammenarbeit GmbH), and further websites of pharmaceutical companies as well as from "vfa" ("Verband forschender Arzneimittelhersteller"). On the basis of the first results found, the search was expanded to include information (interviews, publications) referenced on the webpages or documents initially found. The search criteria used the terms "substandard falsified medicinal products, substandard falsified medicines, substandard falsified medical products, and counterfeit (all with the adding of "Africa"). Most of the publications concerning substandard and falsified (SF) medicines refer to the WHO terminology and refer to the results of WHO research. Therefore, the WHO definition may be used in the work that follows. In any case, this thesis focuses on medicinal products and not on medical devices. The detailed definitions are described in the next chapter. The impact of SF medicinal products will be discussed in the context of malaria disease and its treatment with anti-malarial medicines.

Publications were evaluated from 01. January 2017 until the date of 28. February 2025. In addition to the sources available online, some master thesis from former MDRA-student were quoted to avoid duplication of detailed information on organisations mentioned later.

2. Definitions and background information

2.1 Definitions

This thesis started with an intensive online search for information (publications, reviews, reports, etc.) on the topic of substandard and falsified medicinal products in the Sub-Saharan regions. From the beginning, different formulations emerged to denote similar or the same meaning. Below are the most commonly used definitions, depending on the organisations or countries involved.

It is important that countries working closely together use the same wording to facilitate the cooperative effort to improve the control and safety of medicines in the supply chain.

European Medicines Agency (EMA) definition: (7)

The EMA has introduced terminology for "falsified medicines" and for "counterfeit medicines". The agency clearly defines these two definitions to undermine the mixing and confusion of the products.

Falsified medicines (7) (8)

"*Falsified medicines are fake medicines that pass themselves off as real, authorised medicines.*

The European Union (EU) has a strong legal framework for the licensing, manufacturing and distribution of medicines, centred around the Directive o falsified medicines for human use, so that only licensed pharmacies and approved retailers are allowed to offer medicines for sale, including legitimate sale via the internet.

Falsified medicines may:

- *contain ingredients of low quality or in the wrong doses;*
- *be deliberately and fraudulently mislabelled with respect to their identity or source;*
- *have fake packaging, the wrong ingredients, or low levels of the active ingredients."*

These falsified medicines do not obtain their EU-authorisation-licence because they risk the health of patients.

The EMA underlines the difference between falsified medicines and counterfeits medicines:

Counterfeit medicines

"Counterfeit medicines are medicines that do not comply with intellectual-property rights or that infringe trademark law." (8)

WHO definition: (12)

Since 2017, the World Health Assembly decided to use the term "Substandard and Falsified (SF) medical products" as a uniform terminology among the member states mechanisms and in all future documentation on this type of medical products (11) (12). This consistent and standardised definition helps to analyse collected data around the different involved countries. The WHO has established three classifications of medical products (see definition below), which are used for reporting to the WHO global surveillance and monitoring system (GSMS): (11) (13)

Substandard*:" Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both."*

(Authorized medical products means medical products in compliance with national and regional regulations and legislation. National or Regional Regulatory Authorities (*NRRAs) can, according to national or regional regulations and legislation, permit the marketing or distribution of medical products with or without registration/license).*

When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition, or source, then the medical product should be considered "falsified".

Falsified: *"Medical products that deliberately/fraudulently misrepresent their identity, composition or source".*

Unregistered/unlicensed: *Medical products that have not undergone evaluation and/or approval by the National or Regional Regulatory Authority (NRRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation* (12)*."*

The new terms “Substandard” and “falsified” replace the former terms “substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC)”, which often caused misunderstandings and confusion between the meaning of substandard and falsified products and the protection of intellectual property rights. (14).

In any case, this thesis is focused on medicinal products, not on medical devices, and does not discuss medicines that do not comply with intellectual property rights (see “Counterfeits” - EMA definition above).

2.2 Background Information

The idea of the “Sustainable Development Goals” (SDGs) was born at the United Nations Conference on Sustainable Development in Rio de Janeiro in 2012. The aim was to create a list of goals to address important issues the world was facing concerning environment, political and economic challenges. The 2030 Agenda for Sustainable Development, led by the United Nations, was adopted by all members in 2015, with the creation of the 17 Sustainable Development Goals (SDGs) (15). It is a promise to secure the rights and well-being of everyone by all countries (poor, rich and middle-income) and so to promote prosperity while protecting the planet. These ambitious 17 goals are closely interlinked. The Sustainable Development Goal 3 (SDG 3) calls for health and well-being. Especially the goal 3.3 targets to end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases by 2030 (15).

In order to achieve this impressive commitment in Africa, it is essential to improve the access to safe medicines for patients as millions of peoples die every year due to SF medicines (16). This problem threatens to achieve the results set out in SDG 3 for Africa.

According to a 2017 WHO report (17), one to ten medicinal products that are circulating in low- and middle-income countries (LMICs) are substandard or falsified (5 094 out of 48 2180 total samples collected from 88 countries failed testing by analytical technique analysis (17) (18).

This high amount of SF medicinal products is due to gaps in the supply chain from the distribution of medicines to the patient. The circulation of SF medicinal products is made

possible by the weakness of regulatory systems and by regional difficulties (for example: not enough reliable personnel and institutions to control large regions with many cross-border and political conflicts). Illicit trade is also facilitated by less affordable or inferior technological tools to control the manufacturing and supply chain of medicinal products.
2019 the WHO decided on a five-year "regulatory action plan" to help building and improving the effectiveness of regulatory systems (19).
The 2017 WHO report (3) estimated that US$30 billion is wasted on SF medicinal products in LMICs every year. According to the WHO's Global Surveillance and Monitoring System (GSMS), most of these reported products are related to antimalarials (19.5% of total reports) and antibiotics (16.9%). It indicates that innovator and generic medicinal products, expensive and inexpensive, were affected. SF medicinal products were also detected in the public sector (pharmacies, public hospitals and health centres) and private sector (manufacturers and wholesalers) along the supply chain. Besides, internet purchasing of medicines facilitates the circulations of SF medicinal products in LMICs countries as well as in high-income countries (3).

The increasing globalisation of the medicinal products market is a major challenge for the African countries. The complexity of so many countries and regulatory agencies complicates the work of the regulators and makes it easier for criminals to break into supply chains.

This is why the WHO report proposed a response to the global challenge against SF medicines. It is based mostly on three main points: prevention, detection, and response. The World Health Assembly is the WHO decision making body that addresses specific health issues. The Assembly takes place annually in Switzerland and is attended by delegations from all WHO Member States (11) (14). The assembly established the Member State Mechanism (MSM, since 2012) to "*address this issue of SF medical products and to support the strengthening of national and regional capacities to address product access. It also facilitates the cooperation with relevant stakeholders and promotes the collaboration on surveillance of SF products*" (3). Since 2013, the WHO Global Surveillance and Monitoring System (GSMS) has improved the reporting of SF medicinal products and supported the immediate coordination and technical assistance in emergencies. It issues alert and address the scape and harm caused by SF medicines. The GSMS, through its

reporting and alert system helps to improve the post-market surveillance in countries and supports supply chain security and the reduction of SF medicinal products.

3. Factors that enable SF medicinal products

According to the EMA, the circulation of SF medicines is increasing. In wealthy countries, expensive lifestyle medicines (hormones, steroids and antihistamines) are falsified. Meanwhile LMICs (such as in Sub-Saharan Africa) face the threat of SF medicinal products, predominantly for life-saving medicines such as those for malaria, tuberculosis, and HIV/ AIDS (7) (8) (20).

The problem of SF medicinal products is compounded by the complexity of the global supply chain: products are manufactured in one country and may be packaged in another one and distributed across border to be finally marketed and sold to consumers in a third one (19).

The production or sale of SF medicinal products tends to increase when access to safe, affordable, and high-quality products is limited. This situation often coincides with weak governance systems and/or insufficient technical capacity for quality assurance during the manufacturing and distribution of medicinal products (17).

In the EU, the safety of patients from SF medicines has been addressed by the EMA Directive (Falsified Medicines Directive (Directive 2011/62/EU) (7) and the implementation of safety features (Commission Delegated Regulation (EU) 2016/161 (7). It helped strengthening the security of the medicine supply chain. This topic has already been presented in a previous MDRA-master thesis (21).

Nevertheless, the situation in the African countries is more complex:

The EU has 27 countries and a population of 443 million (2021). By comparison, the 55 member states of the African Union have a population of around 1.13 billion (2021) (22) (23). The continent also faces difficulties due to high levels of political instability in many regions. For example, there had been four coups/revolutions on the continent in 2023: in Sudan, Niger, Gabon and Burkina Faso; in Niger and Gabon, there have been changes in the country's leadership (24) (25). This has a direct impact on the population and an indirect impact on the security of the supply chain (24).

The WHO lists four major key drivers that facilitate the manufacturing and distributions of SF medicinal products (26)

1. *"weak regulatory systems: insufficient regulatory oversight, lack of enforcement, punitive actions to deter offenders and inadequate inspection mechanisms;*
2. *supply chain complexity: long and complex supply chains with multiple intermediaries increase the risk of product tampering and substitution,*
3. *lack of access to affordable medicines: elevated prices and limited access to authentic medicines compel consumers to seek more affordable alternatives, often from unregulated and potentially unsafe sources (informal markets, online),*
4. *consumer awareness and education: lack of awareness among consumers about the risks of substandard and falsified medical products and how to identify them; and*
5. *corruption: within regulatory bodies, law enforcement, and the supply chain, corruption can facilitate the production and distribution of SF products."*

The figure (1) below illustrates different ways how SF and unregistered/ unlicensed medicines can enter the supply chain of medicinal products (1).

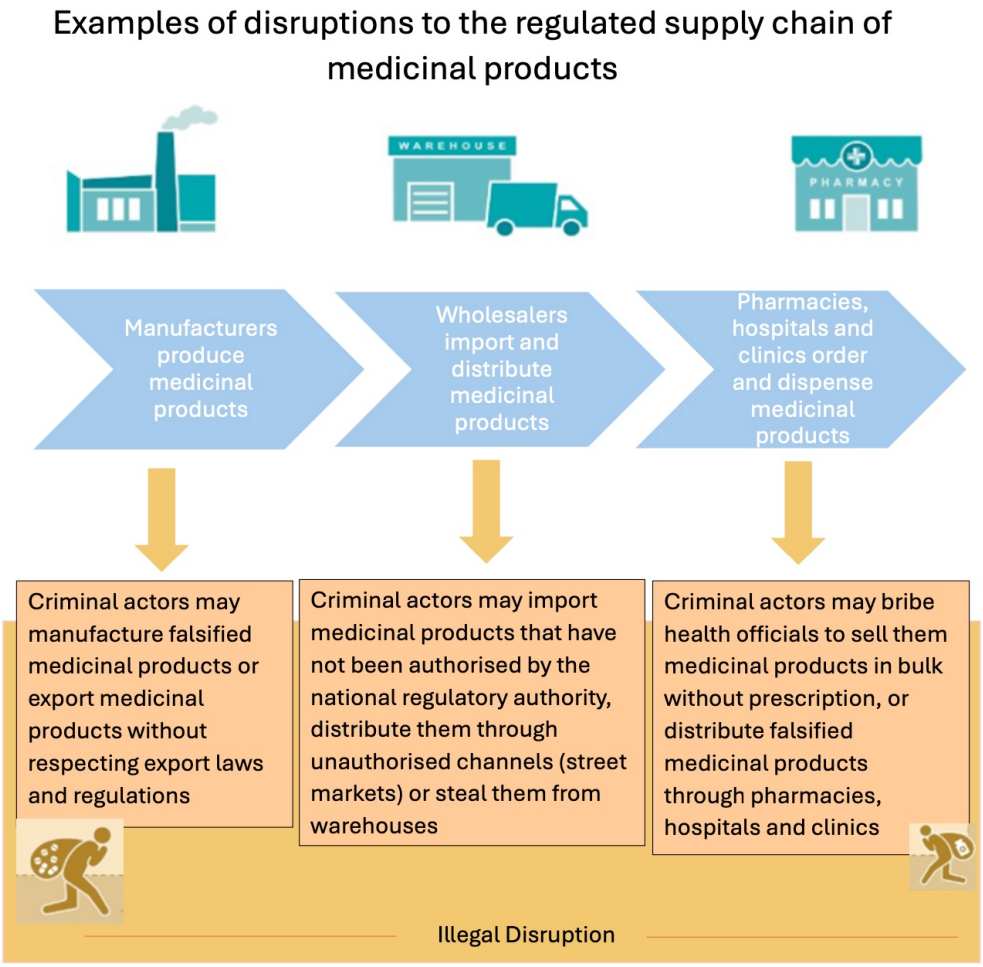

Figure 1: Examples of disruptions to regulated supply chain of medical products (Picture adapted from UNODC-publication (1))

3.1 Price and accessibility

The Sub-Saharan African region has a high incidence of infectious diseases, leading to a high demand for antimalarials, antibiotics and antiretrovirals (1).

Countries with low quality health systems have fewer skilled health workers, insufficient health facilities and limited access to essential medicines and medical equipment. In this case, as in many Sub-Saharan countries, especially in rural communities, people often have to travel long distances just to get access to basic health care. Even when they reach a clinic or hospital, treatment is not always guaranteed. Many are also required to pay out-of-pocket. As a result, countless individuals go without the care they need simply because they cannot afford it, while those who do manage to pay may end up with a huge financial burden. As a result, SF medicinal products for these medications are proliferating and many

consumers, unable to afford the genuine medicines, are turning to cheaper, often SF medicinal products alternatives.

In the end, people either suffer from untreated diseases or are being pushed into poverty due to overwhelming medical costs (even if they buy a cheaper SF medicinal product) (17).

Figure 2: (Illegal) market sell (17)

3.2 Internet sales

Like Europe, African countries are facing the problems associated with illegal online pharmacy. As presented by the IFPMA (5) and the WHO (17), the internet is a growing global marketplace for SF medicinal products.

In fact, unlicensed online pharmacies pose a significant challenge in the global fight against SF medicines. Research shows that half of the drugs sold through websites that conceal their physical address are fake, and nearly 90% of illegal online pharmacies operate without requiring a prescription. Thousands of these illicit websites claim to be legitimate but put countless lives at risk by distributing unsafe and low-quality medicinal products (17) (20).

3.3 Distribution and supply chain traceability

There are multiple challenges associated with the distribution of medicinal products in Africa. One of the main issues is smuggling and informal markets that allow SF medicines to be sold widely, often without regulatory oversight. Governmental regulatory control is

reduced by limited resources to properly inspect and enforce pharmaceutical quality standards throughout the supply chain. These regulatory gaps persist in many of the Sub-Saharan countries due to the lack of robust pharmaceutical regulatory frameworks. In addition, the global nature of pharmaceutical production makes enforcement difficult. These SF medicinal products are often manufactured in one country, transported across several regions, and finally sold in a completely different location (1).

Inadequate infrastructure in the Sub-Saharan Africa is also a challenge for supply chain visibility. Many regions lack reliable transport networks, making it difficult to track products in circulation.

In the case of antimalarial medications, for example, the artemisinin combination therapies (ATC) are widely used because of their efficacy. Unfortunately, they are also among the most SF-medicinal products flooding the African market. The following figure 3 shows the global picture of the product circulation for ATCs: China and India are the main producers of ATCs. The goods are then transported to the United Arab Emirates, Singapore and Hong Kong which serve as transit hubs in the global supply chain. The products are then distributed to the various target markets. (28) Due to regulatory weaknesses and gaps in control inspections along the supply chain, the quality of the medicinal products can be compromised at different stages. (1) (28)

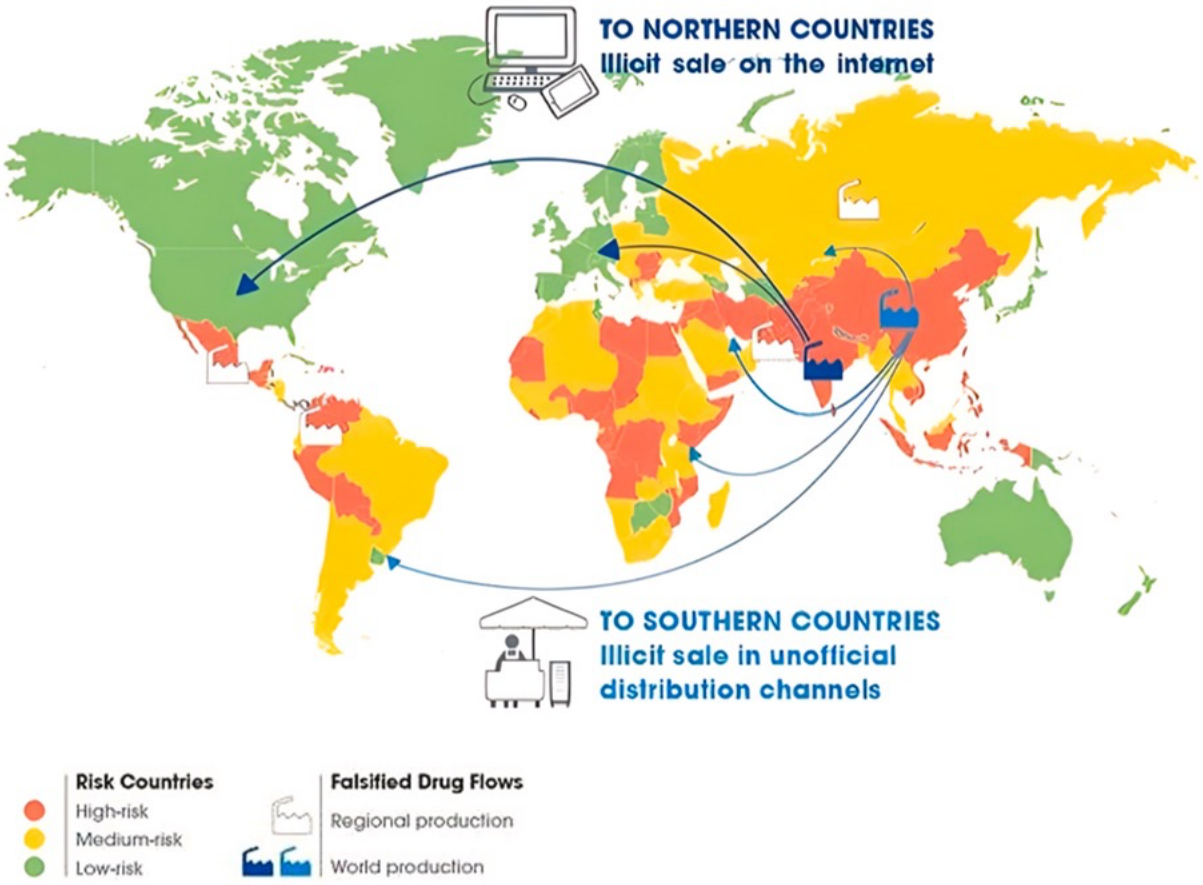

Figure 3: Global distribution of falsified medicines (28)

4. Impact for patients and public health

SF medicinal products pose a significant risk to consumers and public health, often with serious and even life-threatening consequences. Individuals may unknowingly take medications that contain harmful ingredients or incorrect dosages, which can lead to poisoning, ineffective treatment, or worsening their health conditions. Additionally, these SF medicines contribute to the rise of drug-resistant infections, turning a once manageable illness into a potentially fatal threat. The financial burden is also important, as families may spend their savings on ineffective therapies, while healthcare systems lose valuable resources. In addition, trust in medical professionals, their institutions and modern medicines is declining, leaving communities exposed and open to untrustworthy alternative medicine (26).

This chapter describes the impact of SF-medicinal products on patients and the public health system but will focus on SF of antimalarial medicines as an example. There are several publications on models analysing the effect of SF-antimalaria each for a specific country (29) (30). But there are still few reviews that try to estimate the health impact of SF medicines (31) (32) specifically for the entire Sub-Saharan Africa region. This thesis mainly refers to the review in which the malaria in Sub-Saharan Africa model was developed for WHO by the London School of Hygiene and Tropical Medicine model (17) (this study is one of the most used in all further publications on this topic (31).

4.1 Impact for patients

SF medicinal products without the appropriate concentration of Active Pharmaceutical Ingredient (API) and/or of inferior quality, resulting in poor dissolution and thus reduced absorption of the medicine, have a significant impact on the health of the consumer. If the concentration of API is lower than expected or not contained, the SF-medicines will result in treatment failure. If the amount of API is higher than expected, it may cause poisoning. Either way, it leads to an increase in disease at an individual level. This costs the patient's health and also has an economic cost. The family spends money on medicines ("out-of-

pocket" spending) that may harm and kill, instead of saving the life of the family member (17).

4.2 Impact on public health

The presence of SF medicinal products has severe consequences for both public health and state economy. The use of ineffective medicines leads to increased mortality and morbidity as malaria remains untreated. The medicinal products paid for by a health system represent an additional cost as they did not achieve their goal of curing the patient. In addition to these costs, the health system loses money on the cost of providing care by trained health staff and the use of infrastructure for testing and treatment. The effect of SF medicinal products also undermines the goal of cost-effective programmes such as vaccination. In this case, the problem of potentially increased resistance due to the use of SF-medicinal products is critical. These SF vaccines leave patients vulnerable to the disease rather than protected from it. Reduced or no recovery may lead to the inaccurate understanding of the unexpected lack of efficacy of the treatment.

Another potential consequence of SF medicinal products is a loss of public trust in medications and healthcare systems. If individuals are concerned about the quality of medicines and as a result avoid medical facilities, refuse vaccinations for their children or prescribed treatments, they are putting their health and the health of other members of the community at risk (eg. by refusing vaccination programmes). Furthermore, these people may choose to decline treatment altogether or turn to unregulated sources and alternative healthcare providers (17).

5. Global and regional Strategies to combat SF medicinal products

The threat posed by SF medicinal product is a global problem, starting with the way the medicines are manufactured and followed by their trade and distribution to consumers. In order to reduce the risk associated with SF medicines, it is important to address and to coordinate all efforts of parties involved in the supply chain of medicinal products (from manufacturers to regulatory authorities, to cross-border control authorities and to healthcare professionals) and to initiate a programme to raise public awareness on the issue and handling of SF medicinal products (26).

The challenges for Africa are gaps in the security of transported goods (in this case medicinal products) at the point of control along the distribution route across countries in the supply chain, resulting in the circulation of SF medicines over the continent. These multifaceted issues need to be addressed from the national to the regional level. Therefore, with the support from WHO, EU and other international organisations and authorities (e.g. AUDA-NEPAD, Africa-CDC) various collaborations (TEI-MAV+, MEDISAFE) have started to tackle the issues and implement the WHO proposed action plan.

This chapter provides an overview:

- of the main collaborations set up to improve the regulatory framework
- a study programme platform to enhance the expertise for regulatory authority staff
- public-private partnerships to boost manufacturing of essentials medicines directly in Africa.
- the role of effective technology for simpler identification and traceability of medical products to enforce the control of the safety of the products at pharmacist or consumer level

The aim is not to list all collaborations launched in Africa (it would go beyond the purpose of the thesis), but to list a few “pioneers” and to describe their goals and developments (or “lessons learned” for future collaborations). Also, the relevance of the technological tools can only be an approach with an example to present possibilities of today (issues will be considered in the “Discussion” chapter).

5.1 Overview Regulatory „Landscape" in Africa

Africa, with its 55 countries, presents various forms of regional cooperations: five Regional Economic Communities (RECs), five Regional Coordination Centre (RCCs) and others are alliances dedicated to achieving harmonised standards for safe and high-quality medicinal products (AMHR, MRH projects, ZAZIBONA, Africa-CDC).

This chapter presents some of the most important collaborations between organisations and authorities, but for further details, please refer to another master thesis specifically dedicated to these organisations (33) (34).

AMRH, African Medicines Regulatory Harmonisation Initiative (35)

Launched: 2009

Members:

From 55 countries: 29 countries have signed and ratified, 7 signed and 19 neither signed nor ratified the contract.

This partnership Initiative was established in collaboration with the Regional Economic Communities, (RECs), the National Regulatory Agencies (NRAs), the African Union Commission (AUC), the PAN African Parliament (PAN), the WHO, and funding partners as the Bill and Melinda Gates Foundation (BMGF), the World Bank and other development partners (as Global Alliance for Vaccines and Immunisation, GAVI).

Aims:

The AMRH has four priority programmes. The main programme is the harmonisation of member states' policies and regulatory frameworks. The concept follows a two-step approach: Firstly, harmonising the regulatory and technical requirements for medicinal product registration from 55 national regulatory agencies into five major regional communities for Medicines Registration Harmonisation "REC-MRHs", and secondly into a single harmonisation agency for the continent. The objective of AMRH is to improve the public health system for the people of Africa by establishing an African Medicines Agency (AMA) to oversee the registration of selected medicinal products and organise regional harmonisation systems (the EMA was used as a model for this new agency).

So far, the AMRH Initiative has been implemented in 5 RECs and resulted in the establishment of the EAC-MRH REC project (7 countries), ECCAS-MRH REC project (7 countries), ECOWAS-MRH REC project (15 countries), IGAD-MRH REC project (8 countries) and the SADC-MRH REC project (15 countries). (for more details, please refer to MDRA-master thesis-2024 (34)).

ZAZIBONA (36)

Launched: 2013

Members (9 actives): Drug Regulatory Authorities of Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia, Zimbabwe (plus 5 non-active members: Angola, Comoros Island, Madagascar, Seychelles, Swaziland; and "2 observer countries": Lesotho and Mauritius). Of the 16 members of ZAZIBONA, the "active members" are countries that have the capacity to carry out assessments and Good Manufacturing Practices (GMP) inspections.

Aims:

ZAZIBONA was established in 2013 by the four countries of Zambia, Zimbabwe, Botswana and Namibia with support from the Southern Africa Regional Programme on Access to Medicines (SARPAM) and WHO prequalification. This registration collaboration focuses on dossier assessments and Good Manufacturing Practices (cGMP) inspections. The initiative facilitates access to quality medicines by effort sharing among the members. The aim is to accelerate the regulatory process by faster evaluation of essential medicines and via sharing the workload for an improved implementation of inspections.

Today the ZAZIBONA serves as a platform for workload sharing, information exchange, capacity building and harmonisation of registration requirements (37) (38).

Africa-CDC (Africa Centres for Disease Control and Prevention)

Launched: 2017

Members: all 55 states represented in the African Union (AU) (39)

Aims:

The Africa-CDC is designed to operate a decentralised model that allows it to work with member countries' National Public Health Institutes (NPHIs) through five Regional

Coordination Centres (RCCs) for the Northern Africa, Central Africa, Eastern Africa, Western Africa, and Southern Africa regions.

The Africa-CDC is a specialised technical institution established by the African Union to serve as a platform for member states to share and exchange knowledge and lessons learned from public health interventions. It supports the public health institutions to detect, prevent, control and respond more rapidly to disease threats. The Africa-CDC provides coordinated and integrated solutions to weak public health infrastructure in human resource capacity, disease surveillance, and laboratory diagnostics. It responds to health emergencies and/or disease outbreaks.

Through the Africa -CDC, the African Union has established the regional coordination centres (RCCs). For example, the "East African RCC" was launched in 2021 to serve as a hub for Africa-CDC surveillance, alert and emergency response activities and to organise the regional public health initiatives in accordance with the Africa-CDC-Central. There are five regional collaborating centres (with the corresponding operational "host country" as Egypt, Kenya, Nigeria, Zambia, and Gabon). (40)

The Africa-CDC is also a partner in various collaborations, such as with the "Medicines for Malaria Venture" (MVV) to increase local production of medicinal products and improve the quality of public health in African countries (41).

AMA, African Medicines Agency-Treaty

Launched: 2019

Members: 28 countries have ratified it by December 2024) (42) 43)

Aims:

The purpose is to create a supportive regulatory environment for medicines in Africa. The AMA has five main objectives, ranging from supporting local pharmaceutical production (key objective of the Pharmaceutical Manufacturing Plan for Africa, PMPA) and trade support in the Africa Continental Free Trade Area (AfCFTA), to strengthening regulatory capacity for faster access to safe and quality medicinal products in Africa.

The AMA should help improve patient safety against the use of falsified and substandard medicinal products in African health systems.

Lomé-Initiative-Treaty (44)

Launched: 2020

Members: Leaders of seven countries (not of the Regulatory Authorities) - Republic of Congo, Gambia, Ghana, Niger, Senegal, Togo and Uganda have signed the treaty.

Aims:

In 2020 the leaders of seven African countries met at an international summit held in Lomé (Togo) and agreed on a joint response to combat the trafficking of SF medicines. The countries signed a political commitment, known as the "Lomé Initiatives", to act to strengthen their international cooperation and to endorse national legislation to criminalise the import, manufacturing, distribution and sale of "fake medicines". As a result, the members have signed and ratified international agreements such as the MEDICRIME Convention of the Council of Europe, the Palermo Convention against Transnational Organized Crime of the UNODC and the AMA-treaty. The Republic of Togo is responsible for political coordination.

As part of this initiative, several meetings were organised to network the respective ministers of health and directors of pharmacy, followed by the signing of treaties. These meetings were managed by the "Brazzaville Foundation". It developed a national action plan (aimed at strengthening the rule of law and the state security) and an "inter-ministerial" action plan. The second part is coordinated by the public authorities and involves the private sector and actors of the health system, supported by influential members of the civil society (for example: young people who have the capacity to influence purchasing behaviour and public opinion). (44)

PAHO-Africa-CDC

Launched: 2024

Members: The Pan American Health Organization (PAHO) and the Africa Centres for Disease Control and Prevention (Africa CDC). The PAHO (world's oldest international public health agency founded 1902) operates as the Regional Office of WHO and is responsible for the health cooperation between the American countries (45).

Aims:

This agreement was signed to cooperate to improve equitable access to vaccines, medicines and other strategic health technologies for their regions.

The two organisations will combine their expertise, involving resources such as PAHO's Regional Revolving Funds, to enhance regulatory frameworks, improve innovation, and boost local production capacities. Their efforts will contribute to the development of Africa's pooled purchasing mechanism while supporting the manufacturing of essential medicines, vaccines, and public health supplies across Africa and the Americas.

In addition, they will work together to drive research, innovation and the digital transformation of healthcare systems. The collaboration aims to strengthen responses to both current and emerging public health threats while improving readiness for future health crises.

A lesson learned from the COVID-19 pandemic is the need for greater resilience within the region. To achieve this, the partnership aims on expanding regional manufacturing capabilities and introducing innovative solutions to member states. These efforts will reduce dependencies on global supply chains during critical emergencies and future pandemics. Ultimately, by pooling their expertise, the organizations aim to enhance public health strategies and better serve the needs of their respective regions.

5.2 Collaboration of Health Authorities, NGOs and Pharmaceutical Industries

This chapter provides an overview of various initiatives of private-public partnerships supporting the fight against SF medicinal products:

- Involvement of organisations and authorities, NGOs, and the pharmaceutical industry to support local regulatory authorities (project support through international funding)
- Educational platforms to improve the qualification of health authority staff and other healthcare professionals involved in the distribution of medicinal products (eg. hospital pharmacists)

Access to Medicines Foundation

Launched: 2003

The list of members is not fixed but depends on the year of the commitment and the selected sector (for example, priorities such as access to medicines, or vaccines or generics). A global engagement for 2024 were: 55 companies, 152 academic institutions, 190 investors, 70 global health organisations (46).

The Foundation was established in 2003 by Dutch entrepreneur Win Leereveld with the aim to motivate the pharmaceutical industry to do more for the billions of people who lack access to medicines. The non-profit organisation has grown from a small initiative to a force for change. Companies are motivated to expand the access to their essential healthcare products in low- and middle-income countries (LMICs). This success led 2022 to expand the model across a wider range of healthcare sectors, including R&D -based pharmaceutical companies, vaccines, manufacturers, generic medicine manufacturers, diagnostic companies and medical gas companies. The Foundation started the “Access to medicine Index” in 2008. It focuses on pharmaceutical companies (including 20 of the world’s largest research-based companies) and provides an index list of what the companies can deliver and it stimulates them to compete to perform as best of this expectation list (46).

However, the 2024 Access to Medicine Index report shows that a stronger focus is needed on research and development specifically addressing the low representation of resource-poor populations in clinical trials. Only 43% of trials take place in the LMICs covered by the Index analysis, and even fewer, 3,5%, in low-income countries. This gap risks excluding genetically diverse populations and can result to inadequate access to medicinal products in LMICs, as companies typically choose market access in countries where clinical trials are conducted.

The progress report for the 2024 Index indicates that pharmaceutical companies should improve their voluntary licensing agreements and technology transfer to local manufacturers. It is a way to increase long-term and sustainable access to the essential healthcare products, especially in regions where the companies have limited or no presence (47).

MEDISAFE project (48)

Launched: 2018 (and closed 2023)

Partners: 5 operating partner organisations and 11 partner countries in Eastern and Central Africa:

Expertise France as project leader and the operating partners: CHMP (a Humanitarian Centre for Pharmacy Professionals: "Centre Humanitaire des Métiers de la Pharmacie"), APROPHISP (Professional Association of Public Health Pharmacist Inspectors), CIOPF (International Conference of Francophone Pharmacists Associations), ReMed (Network for Medicines and Development), SACCO (ASST Fatebenefratelli Sacco, Italian public governmental healthcare institution composed of four hospitals).

Partner Countries: Burundi, Democratic Republic of the Congo, Ethiopia, Ghana, Kenya, Malawi, Rwanda, Seychelles, Tanzania, Uganda, Zambia.

Aim:

From 2018 to 2023, Expertise France has implemented the MEDISAFE project, funded by the European Union, to tackle the important problem of the circulation and use of SF Medicinal products.

The MEDISAFE consortium addresses the fight against SF medical products in East and Central Africa - including the prevention, detection and response to SF medical products (in line with WHO recommendations), with measures to ensure the quality, safety and legality of the medicines distributed.

This project is part of a "Team Europe Initiative" on the production of and access to vaccines, medicines and health technologies in Africa (TEI MAV+) (see next project description (50)).

Results:

The MEDISAFE project has helped to improve the expertise of professionals in the legal, law enforcement and pharmaceutical sectors and to strengthen existing policies. It has also promoted national and regional cooperation. The consortium produced five key documents to strengthen the legal framework of the participating countries (49):

1. *"The Reference Manual on Legislation on SF Medical Products: An African Perspective*

2. *The Supply Chain Security Assessment and Implementation Guide* "(produced with the collaboration of 11 pharmaceutical experts and drug regulatory authorities in the target countries, as well as the World Health Organization)
3. *"The Standard Operating Procedures (SOP) on the identification and control of SF medical products for the law enforcement sector and national medicines regulatory authorities*
4. *The MEDISAFE communication strategy and the countries communication strategy on SF medical products*
5. *The 11 partners countries updated national action plan on SF medical products"* (recommendations on law enforcement, and awareness-raising for civil society in each country)

Another finding was that although different communication systems exist between the partners involved (throughout the supply chain), these systems were not being used sufficiently. It is therefore important to provide additional training at national level to improve an effective communication between the police, customers and pharmaceutical regulators.

As a follow-up and due to the success of the project, the European Union is planning to develop a second phase of this project. In 2025, it will be extended to West Africa using the same model.

Team Europe Initiative ("TEI" launch 2021) /MAV+ (an international partnership) (50)

Launched: 2021

Partners:

Team Europe: European Commission, European External Action Service (EEAS), EMA and network of European regulators, European and Developing Countries Clinical Trials Partnership (EDCTP), EU Member States – funders (Germany, France and Belgium) and EU Member States – supporters (Denmark, Hungary, Netherlands, Portugal, Czechia, Spain, Poland, Sweden, Malta, Austria, Italy, Lithuania, Greece), EIB and bilateral banks.

African organisations: AUC, African CDC, AUDA-NEPAD, African Medicines Agency (AMA), and African governments and national regulatory agencies.

International partners: WHO, Bill & Melinda Gates Foundation

MAV+ partners include also Regional Economic Communities, African universities and training programs and pharmaceutical manufacturing plants.

In addition, the efforts are being complemented by private initiatives: Production facilities of BioNtech (EU) are being established in Senegal, Rwanda and Ghana and Moderna (US has announced an investment in Kenya (50).

Aim:

Africa relies on imports for more than 99% of its vaccines and 94% of its medicines. The COVID-19 pandemic highlighted how this strong dependence on external supplies leads to insuitable access to essential health products and negative public health outcomes.

This has led to a call from the African leaders for 60% of vaccines to be produced in Africa by 2040, and the launch of the Team Europe Initiative on Manufacturing and Access to Vaccines, Medicines and Health Technologies in Africa (MAV+) in 2021 (51).

The aim of MAV+ is to enable access to quality, safe, effective and affordable health products as defined in the UN-SDG Target 3.8 and in the African Union's Agenda 2065. The initiative works with African partners to strengthen their local pharmaceutical systems and manufacturing capacity (see figure 4 below - as a pan-African project, the relevant countries of North Africa are also shown in the figure. Note: The map is also introduced in this thesis because of the relevant achievements of the project for the Sub-Sahara regions).

MAV+ focuses on three key topics: supply, demand and enabling environment. The project operates through six workstreams (51):

1- *"Industrial development, supply chains and private sector,*
2- *Market shaping, demand, and trade facilitation*
3- *Regulatory strengthening*
4- *Technology transfer and intellectual property management*
5- *Access to finance*
6- *R&D, higher education, and skills"*

Further the MAV+ aligns with four key activities on the African continent (51):

1- *"Support to Africa CDC's Platform for Harmonized African Health Products Manufacturing (PHAHM) with embedded experts,*
2- *Support to the operationalisation of AMA through twinning with EMA, embedded experts and funding to AUDA-NEPAD and WHO,*
3- *Establishment of an mRNA technology transfer programme with a hub in South Africa*
4- *Product development partnerships and clinical trials grants, through EDCTP and other funding sources"*

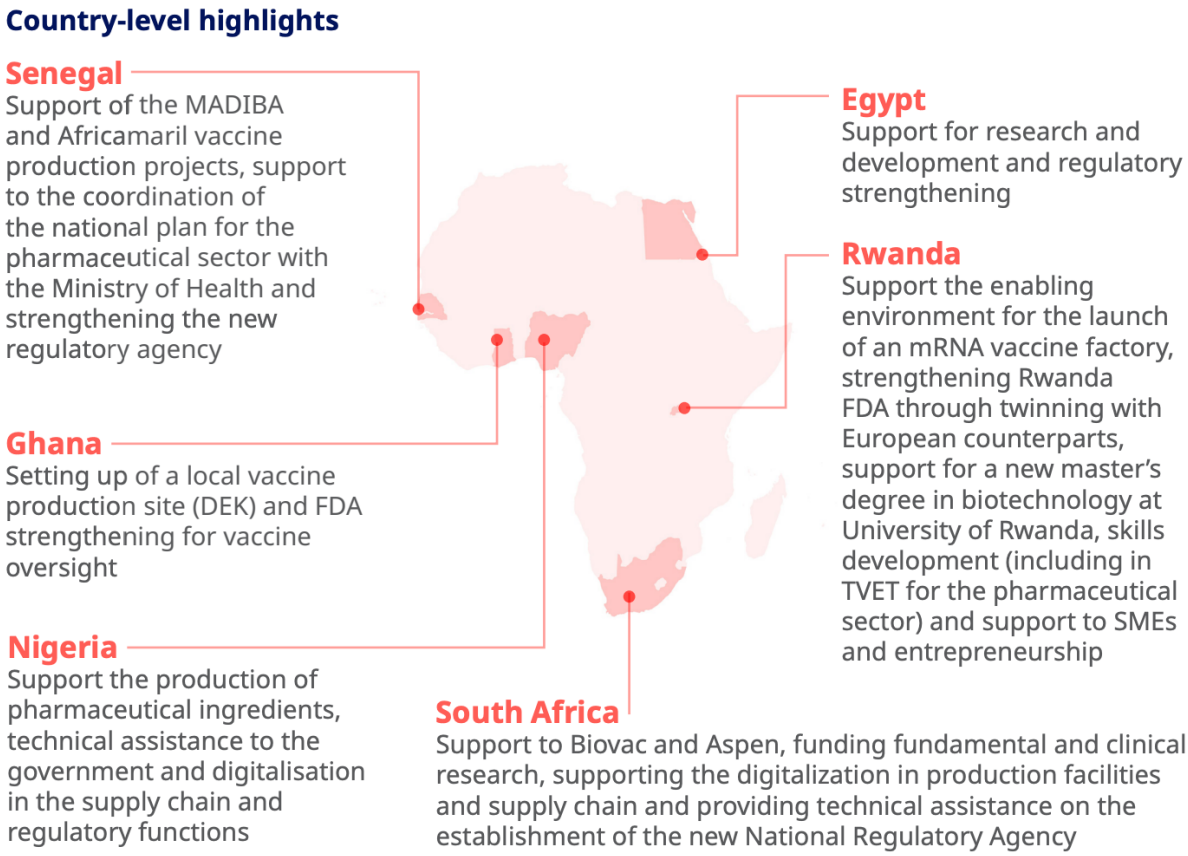

Figure 4: Summarising the highlights of MAV+ on country-level in Africa. (The project covered the whole of Africa. Therefore, Egypt was also included. But due to the relevant achievements of the project for the Sub-Sahara regions, it is relevant for this thesis). (51)

Pharmacometrics Africa (52)

Launched 2022

Members: The South African Health Products Regulatory Authority (SAHPRA),

nuvoteQ (a South Africa based software developer working on healthcare and clinical research solutions with global health implications),

H3D (Africa's first integrated drug discovery and development centre (founded 2010).

Infectious Diseases Institute (IDI, a centre of excellence, funded by public and private resources and part of Uganda's preeminent medical training institution. It is based at the Makerere University College of Health Sciences. Focus is on improving care and treatment of HIV and related diseases for people living across Africa),

Fundisa African Academy of Medicines Development (a non-profit organisation that provides and promotes education and training in medicines development in South Africa and other African countries. A key objective is to bring together all relevant stakeholders, including academia, industry, regulatory authorities and other institutions),

CP+Associates (a social venture that develops scientific capability in LMICs. The focus is on healthcare via the drug discovery and development sciences),

Strathmore University, University of Cape Town,

Makere-University,

H3D Foundation,

Bill & Melinda Gates Foundation.

Aims:

Pharmacometrics Africa is a non-profit company in South Africa. It has established a platform for open access clinical pharmacology education. It runs educational programmes in partnership with local research organisations and academic groups.

As an example of one specific course launched on this platform in 2023, "**A Primer for Clinical Assessors within African Regulatory Agencies"** (54):

Regulatory agencies across Africa face significant skills shortages, mostly due to limited resources and insufficient training opportunities. While some of these challenges are being

addressed through the agencies themselves, there remains a significant need for specialised training programmes tailored to clinical assessors across African regions (53).

To address this gap, Pharmacometrics Africa and its partners have launched the second edition of their course, "A Primer for Clinical Assessors within African Regulatory Agencies". This initiative leverages advanced technology platforms and a network of experts to provide essential training and strengthen regulatory capacity across the continent (54).

African Pharmaceutical Technology Foundation (APTF) (55)

Launched: 2022

In response to a request of the leaders at the African Union Summit in 2022, the African Development Bank has committed to the establish the "African Pharmaceutical Technology Foundation" (APTF).

Aims:

The Foundation shall improve access to and transfer of technology for domestic manufacturing in Africa, and it shall support the local pharmaceutical industry reaching WHO quality production standard and promoting talent development. The African Development Bank has pledged "*to spend at least $3 billion over the next 10 years to support the pharmaceutical and vaccine manufacturing sector under its Vision 2030 Pharmaceutical Action Plan*.". The foundation started its operation in January 2024 and announced its collaboration with different organisations as the Africa CDC, the AMA, the EU, the WHO, the WTO, the Medicines Patent Pool, and European Investment Bank. (56) (57).

5.3 Role of Technology in Strengthening Detection and Verification of SF medicinal products

The globalisation in the trade of medicinal products results in a complex distribution system. In order to reduce the risk of infiltration of SF medicinal products in the supply chain, an efficient traceability system is required. To address this issue, the "*EU published the Directive 2011/62/EU of the parliament and of the council the 8th of June amending the*

Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products on 1st of July 2011" (7). This directive is also referred to as Falsified Medicine Directive (FMD). The FMD requires a list of safety features to be affixed to the packaging of the medicinal products to prevent the entry of falsified medicinal products into the supply chain. Furthermore, the series of measures to counteracts falsified medicinal products continues with the "*Commission Delegated Regulation (EU) 2016/161 of the 2nd of October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use"*. (7) .

This verification system has been implemented since 9th of February 2019 and the Marketing Authorised Holders (MAH) are "*required to place safety features on the packaging of most prescription medicines and some over-the-counter medicines in the European Union*". (7) (8)

In any case, further experience has been gained and other systems have been developed in relation to the traceability of the supply chain for medicinal products. Accordingly, the WHO published "*a policy paper on traceability of medical products*" (2021) to summarise available traceability technologies (58). This thesis cannot explain in detail the different systems available (this would go beyond the scope of the topic), but can provide an overview of the two most commonly used systems (in EU and in the USA). Please refer for further details to former MDRA-master-thesis and the listed publications (59) (21) (58) (60).

As mentioned above, in order to simplify the description about traceability of supply chain of medicinal products, this section will focus on the following two most widely used "Track and Trace" (T&T) systems in the world (58):

- <u>One type of system is the reporting of traceability data to a single database or repository</u>. This is the so-called "Centralised Registration of Entities". This system can take on various characteristics. In the case of the EU-Model, it is a central hub without full track and trace capabilities but with a "point-of-dispense" (PoD) verification. In this approach, the medicinal products are being verified only at the PoD (e.g. at the pharmacy) or at the point of use (e.g. a hospital) and optionally at some point prior to that (wholesalers).

The goal of this type of verification is to protect patients while minimising costs along the supply chain. (Figure 5 on right side, simplified EU-Model).

- The other type of T&T system for the supply chain of medicinal products, is a "full-T&T" approach and involves a complete traceability documentation and verification applied at each change of ownership in the supply chain. The goal is to detect the infiltration of SF-medicinal products as early as possible and to withdraw the SF products faster. This system is more complex and has an impact on the process costs. (58).
(Figure 5 On left side, simplified USA-Model)

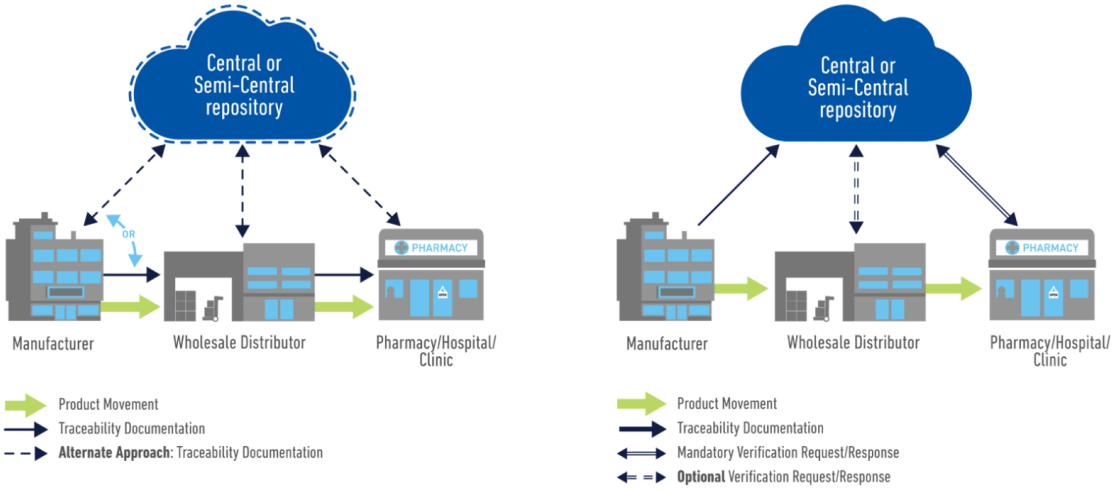

Figure 5: Two approaches in medicinal products traceability: Full-track-trace model on left side (USA model, with semi-centralised repository) and "Point-of-Dispense"- Verification model on right side (EU model, with central repository). (58).

Both systems have their advantages and disadvantages. However, the question of cost and the technical infrastructure required for maintenance are very important factors when deciding which system to opt for and about the way of implementation. The central database must also be very well protected considering cybercrime.
Accordingly, the WHO and ICMRA also recommend that the regulation of the respective NRAs be examined before and how it can be implemented for global companies to optimise costs for patients and the healthcare system (58).

In this context, the **"Traceability & Verification System for Health Products" (TRVST)** (61), was launched in 2022 to increase global coordination and to address the trade in SF medicinal products, especially in LMICs. The TRVST – system aims to allow the participating countries to trace and track the medicinal products through the supply chain and verify the authenticity of medicines on a single common platform (repository-database). "*The system was developed under the Verification and Traceability Initiative (VTI), a multi-stakeholder partnership composed of the Bill & Melinda Gates Foundation, the European Commission, Gavi, the Global Fund, UNICEF, USAID, the World Bank, and the national regulatory authorities in Nigeria and Rwanda*." (61) (62).

For this purpose, the VTI has established a database called the Global Trust Repository (GTR). All data is stored and validated on this single database. The system started with the verification of vaccines, but it is intended to be used for other medicinal products and medical products.

The TRVST allows the validation of the medicinal products in five steps:

1. standard interface for connection to manufacturers
2. Global Trust Repository (GTR)
3. smartphone app for on-site verification (verification user)
4. TRVST Dashboard
5. TRVST interface for verification and tracking with the national systems.

The product data is either sent to the interface of the GTR or it can be scanned using a free verification mobile application. National systems (such as NRAs) can scan and track movements along the supply chain. "*The GTR database supports the end-to-end traceability of all vaccines, HIV, tuberculosis, malaria medicines, and other healthcare products*." (63).

The objective of this verification system is clear: to protect patients and assist the authorities. It can also help with product recalls, monitoring supply shortages and improving pharmacovigilance. The mobile verification application makes it easier to validate the authenticity of the medicinal products.

There are four stages describing the progress of discussion and implementation in each country. The most advanced countries are in Groupe 1 and have already implemented the system. Currently, Nigeria and Rwanda are in Groupe 1 and have fully implemented the system for vaccines and medicinal products since 2022 (64).

The TRVST system uses the common GS1 standards and is applied for the supply chain of donated products (61).

Sub-Saharan solutions (for regular supply chain of medicinal products):

Other management systems are currently being used in Sub-Saharan countries (Ivory Coast and Nigeria) to secure the supply chain of medicinal products (but not donor products such as describe above). The following two systems are based on the technology called blockchain system, where products data is deposited in a decentralised system.

Background on the technology:

Blockchain is a type of digital ledger that consists of a series of interconnected data blocks, secured by encryption. Unlike traditional databases, which are stored in a single central location, blockchain distributes its data across a network of computers. This system ensures that data is transparent, tamper-resistant, independently verified, and managed in a decentralised manner.

Project in Ivory Coast with "authentic.network " for anti-malarial medicinal products (65)

Project launched in 2021 and was funded by GIZ ("Deutsche Gesellschaft für Internationale Zusammenarbeit"; a German provider of international cooperation services).

Partners: the German company "authentic.network" and the Ministry of Health and industry associations of Ivory Coast.

The "authentic.network" is a start-up company based in Chemnitz, Germany, that has developed a digital code ("crypto-tag") based on a blockchain technology system. The code takes the form of a green tick and is affixed to the medicinal products. The pharmaceutical companies (or the importers) can add the special label with the corresponding code to their product packaging. Consumers are able to verify the products by scanning the code with a mobile phone application. This application will reveal if it is the authentic product or it will give a warning in the case of a SF medicinal product.

This technology system is currently being tested as a pilot-project in the Ivory coast specifically for anti-malarial medicines. "authentic.network" is currently expanding the

range of medicinal products supported by its system and is cooperating with a a consortium, that will manufacture rapid COVID-19 tests in the Ivory Coast.

According to the Labelling-technology company, the “crypto-tag” cannot be copied due to its unique printing process. The code cannot be scanned or copied by unauthorised personnel and an alert will be raised when a copy is circulated. That enables the company to track back in time and act fast accordingly.

The company Sproxil Technology from Nigeria uses a similar idea of blockchain technology to secure the supply chain of medicinal products (66). They have already 11 companies (not only from pharmaceutical industry sector) amongst their customers (status of February 2025).

The technology assigns unique and tamper-proof codes to each product. It meets the regulatory requirements for traceability and serialisation. A major benefit is that consumers can verify the authenticity of products themselves using a mobile phone application (Figure 6), increasing the consumer confidence in the medicine they use.

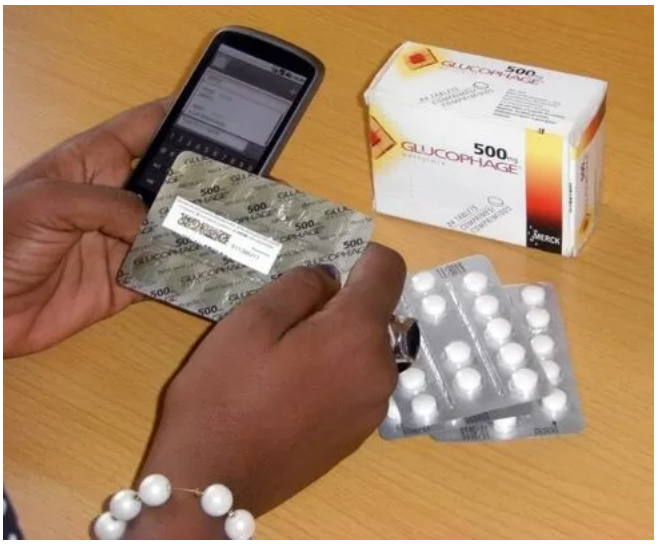

Figure 6: Example of the Sproxil application based on blockchain technology to defend brands from counterfeit (66)

Field-detection and verification devices:

The traceability systems described above are important to secure the supply chain of medicinal products, but they are not yet applied in most countries of the Sub-Saharan regions. Therefore, until similar methods are implemented across the African Countries, other technological tools are relevant to prevent the distribution of SF medicines.

Quality control in the distribution system is a financial burden because of the large number of samples to be tested and analysed. This cannot be adequately addressed in LMICs because they do not have enough centres of excellence to conduct these expensive analyses in the quantities required. (31).

The following two products (an analysis kit and a scanning device) are specifically designed for the detection and verification of SF-medicinal products and can be used by pharmacists.

GPHF-Minilab and TLC Chromatographic analysis Test: (67)

The Global Pharma Health Fund (GPHF) is an organisation initiated and funded exclusively by donations from Merck KGaA (Germany). The objective of the GPHF is to improve healthcare and currently supports the fight against the spread of SF medicines with the GPHF-Minilab™.

The aim of this minilab- Kit (Figure 7) is to support medicinal product quality monitoring in LMICs with a low cost and simple test method for rapid drug quality verification and detection of SF medicines. The Global Pharma Health Fund (GPHF) developed and supplied these inexpensive field test kits for LMICs. It is a mobile mini laboratory for rapid drug quality verification to help detect SF medicinal products anywhere in developing world (67). It is used, for example, by pharmacists or in clinics to test stored medicinal products before they are supplied to patients. The GPHF-Minilab™ is currently being delivered to 616 sites in Africa (January 2025). (68)

Figure 7: GPHF-Minilab™ - Protection Against SF Medicines (68)

Scan of Tablet and Liquid: RxAll-scanner: (69)

The RxAll-scanner is a portable spectrometer connected to a mobile application that allows its users to test a tablet without destroying it. The scanner reads the spectrum generated by the tablet when it is placed in the spectrometer. By comparing the result with the RxAll online database of drug spectral signatures, the mobile phone application identifies the drug and evaluates its quality level, recording the test result against a blockchain ledger and sending a quality report to the mobile application in a short time. The IR spectrum of the scanned medicine will be different from the reference if there is a change in the excipient or in the Active Pharmaceutical Ingredients (API), or if the medicine has any kind of contamination. In this case, the scanned tablet will be identified as a SF-medicinal product.

The scanner uses near-infrared spectroscopy (NIRS) at wavelengths from 750 to 1500nm. NIRS technology is less expensive than laboratory analysis and can be used to identify a wide range of substances in a tablet, although there are some limitations with high fluorescence and deflection. This scanner method is an affordable drug quality testing

device that can be placed at various stations to monitor the quality of the medicinal products through the supply chain in a country (it is currently used in Nigeria by the agency (NAFDAC) to screen imported drugs at ports and during post-marketing surveillance).

6. Discussion

Strengthening Legal and Regulatory Frameworks

The Sub-Saharan African countries are facing many challenges with SF medicinal products as they are confronted with a widespread of infectious diseases, which leads to a considerable need for antimalarials, antibiotics and antiviral medicinal products. As long as the need for affordable and essential medicines for patients remains unmet and regulatory gaps remain, organised criminals will continue to flood the market with SF medicines.

The initial aim of the cooperation among the different regulatory authorities was to increase their efficiency and thus contribute to faster access to safe medicines and answer the need of the patients. Currently, there are still difficulties in controlling the cross-border trafficking of SF medicinal products, e.g. due to insufficient security and control measures by border personnel and insufficient technology applied. The inadequate infrastructure for the monitoring all medicinal products imported into the countries should be improved and compensated for by cooperation between the regulatory authorities. Another aim of harmonising the regulatory agencies was to create clarity and avoid duplication of work when processing dossiers for product approval. Today, the international efforts between the countries in Africa (and with support from EU and WHO organisations, for example) have led to the establishment of the AMRHs for the harmonisation of regulatory framework for human medicines across Africa. The AMA Treaty, signed by 28 out of 55 countries, is still in its infancy, but will be further developed and adapted to the needs of Africa, using the EMA as a model structure.

In any case, the cooperation with the REC-MRHs, which were developed in relation with the AMRHs, is not always as efficient and optimal as initially hoped. There are replications and redundancies between the RECs, as certain countries are members in more than one REC (Kenia and Uganda are in EAC and COMESA, Tanzania is in EAC and SADC) (70). It complicates the regulatory environment and therefore, instead of simplifying, it delays the process of products approval.

As for the ZAZIBONA initiative, one of the main objectives was to reduce the timeframe for the authorisation of medicinal products, aiming for a median of 9 months. However, most of the participating countries did not believe that shorter timelines could be achieved,

resulting in periods of up to 18 months (37) (34). This could create a problem in the future and result in a low motivation for participants to follow this procedure. However, the ability to conduct assessments and inspections has improved significantly as a result for the cooperating countries of this initiative (37) (34).

Nevertheless, the work of the Africa-CDC and its division into RCC regions appears to be better coordinated and to have less overlapping (34). Even if their purposes are different from the REC-MRHs the organisation-model of the RCCs has benefits and could be advantageous if applied on the REC-MRHs. (for further details to this topic, please see master-thesis from 2024 (34). Still, these collaborations are very important, as are the efforts towards harmonisation.

Additionally, there has been an improvement at some NRAs in reaching the "WHO maturity Level 3", which is the minimum required for a good regulatory oversight. (71). Until December 2024 seven countries in Sub-Saharan Africa achieved this level of maturity. The Agencies have established a system in line with international regulatory standards: Tanzania (2018), Ghana (2020), Nigeria and South Africa in 2022, and since 2024 also Rwanda, Senegal, and Zimbabwe (72).

A low level of maturity means that a country does not have the ability to provide adequate regulatory oversight to ensure high quality, safe and effective products. It also means that the country has limited ability to reduce the circulation of SF medicines. (71)

These results are steps in the right direction in the fight against SF medicinal products. Cooperation between Regulatory Authorities should be further promoted and readjusted over time. It would be beneficial to review this type of cooperation after a certain period of time and, if necessary, adapt the structures accordingly.

In this context, further training measures and specific workshop programmes for regulatory staff and others involved in the supply chain are proving to be important instruments for increasing efficiency in the approval of medicinal products and in the fight against SF medicines. The Pharmacometrics Africa learning platform is exactly addressing these needs by providing clinical pharmacology training and specific education as the primer course for assessors of African regulatory agencies. Overall, additional support for the recruitment of qualified specialists is desirable as it will help to address the shortage of staff at the authorities and thus ensure the timely authorisation of medicinal products.

A targeted approach to training is a commendable initiative, and it is encouraging to note that some regional collaborations, such as the EAC, are pursuing similar actions. For example, the EAC Regional Centre of Excellence for Vaccines, Immunisation and Health Supply Chain Management (EAC RCE-VIHSCM) has successfully promoted and managed its second short course (November 2024 in Nairobi, Kenia) on the "Global Standards for Traceability of Health Products and Technologies (GSTHPTs)" (73).The course focuses on the effectiveness of supply chain management and how global traceability standards should be implemented to ensure the timely supply of medicines and how they play a key role in preventing SF medicinal products.

This training is part of the implemented measures elaborated by a dedicated taskforce: "EAC Regional Health Supply Chain Management (HSCM) Taskforce on Professionalisation". (73). This task force created a comprehensive roadmap outlining key approaches for the "Health Supply Chain Management Professionalization Strategy". This initiative aims to establish standards and educational programs for the training of health supply chain professionals in the region, ensuring alignment with both global and regional commitments to strengthen the healthcare systems. (The topic of supply chain management will be further discussed later below).

Another important issue in combatting the SF medicinal products is the insufficient prosecution of criminals. In 2020, the AUDA-NEPAD provided a guide "*for domestication of the African union model law on medical products regulation*". However, the implementation of laws regulating the trade and sale of these medicines is still inconsistent across different regions. (1) (74) (75).

In this context, the project MEDISAFE has helped to enhance the expertise of legal, law enforcement and pharmaceutical professionals. It has strengthened existing strategies and promoted collaboration between the eleven participating countries at both national and regional level. The consortiums members have produced an "SOP on Law reinforcement, sector and council for Interpol" and the "11 Action Plan" has raised the awareness of the legal aspect. It is hoped that the outcomes of this project will be prolonged, as announced, through follow-up projects in neighbouring countries. It would be desirable to continue the implementation of these results and to strengthen the law enforcement in the area of trade in SF-medicinal products.

In line with the idea of awareness and an action plan against SF medicines, the “Lomé Initiative” has helped to raise the attention of the heads of seven countries concerning the Impact of trafficking SF medicines in their countries and to contribute to an action plan through “inter-ministerial” cooperation. Following this first “Lomé-agreement”, the Brazzaville foundation continued to support the initiative with a coordinated “programme 2022-2024” (44). This programme includes the development and implementation of national plans to combat SF medicinal products. At this stage, the initiative has resulted in commitments by the participating countries as well as their signature and ratification of the MEDICRIME Convention of the Council of Europe, the Palermo Convention against transnational Organised Crime of the UNODC, and the AMA-treaty (44). In addition, the respective ministers of health have agreed to support the “2022-2024” action plan starting with a pilot project in Togo focused on public health, safety and the rule of law. Currently, the initiative’s Togolese political coordinator is continuing his commitment to convince other African countries to join the initiative and to commit themselves to the AMA-treaty for joint action against SF medicinal products.

The planning of the project was expected to result in a national plan for combatting the SF medicines in Togo by the end of 2024 and to be implemented within 2024-2027. Unfortunately, no further detailed results were available until February 2025. Nevertheless, the Brazzaville foundation is drawing attention to the risk of trafficking in SF-medicines and is encouraging more and more African countries to sign the AMA treaty. It will be interesting to see how the “national action plan” of Togo develops and to what extent it can be transferred to other countries (44) (76).

<u>Promoting the establishment and development of the local pharmaceutical industry</u>

According to a WHO report from 2024, the “*WHO African Region import between 70% and 100% of finished pharmaceutical products (FPPs), 99% of vaccines, and between 90% and 100% of medical devices and active pharmaceutical ingredients (APIs), with little or no capacity for manufacturing of pharmaceutical quality excipients, vaccines, medical devices, and other health technologies* “(77).

This is an important issue in the context of combating the illegal trade in SF medicinal products. One reason for the use of SF medicines is the insufficient and slow access, despite

high demand, e.g. for antimalarials or vaccines (in the event of a pandemic or local outbreak). (3)

It was therefore an important first step to promote the production of vaccines directly in Africa following the COVID-19 pandemic. The „Team Europe Initiative on Manufacturing and Access to Vaccines, Medicines and Health Technologies" (TEI-MAV+) programme involves many different stakeholders, from funding organisations to the pharmaceutical industry and regulatory authorities. It is focussed on five countries (Senegal, Ghana, Rwanda, and South Africa) and should be seen as a "boost-promotion" to motivate more countries to support their local production and invest in their health system (from regulatory strengthening, regional vaccine manufacturing, supply chain management system and R&D hubs to talent development). By 2022, only four countries had reached the "WHO maturity level 3" (72), which is the minimum required for good regulatory oversight. Currently (by December 2024), seven countries in Sub-Saharan Africa have reached the WHO maturity level 3, indicating a stable regulatory system (Egypt is the eighth country of Africa to have reached the maturity level 3 in 2024, but it is not located in the Sub-Saharan region). (72)

Nevertheless, the 2024 WHO report makes recommendations for the 2025-2035 timeframe to strengthen local production of medicines and vaccines in the WHO African regions.

The results achieved within the MAV+ Project were consistent with the those described in the summary of the "African Vaccine Manufacturing Mapping" of October 2024 (see Figure 8 below; the Map shows the overall supplier maturities and capabilities for all Africa (78)). The project is part of the "Partnership for African Vaccine Manufacturing" (PAVM) and was developed with the support of the AU, Africa-CDC and funded by USAID and the Bill & Melinda Gates Foundation.

At this stage, 11 out of 15 "African Vaccine Manufacturing" suppliers are in the development phase: South Africa, Ghana, Nigeria, Ethiopia, Kenya, Uganda, Mozambique, Zambia (another ten are in Egypt and Algeria, but they are not part of the Sub-Saharan region, so are not part of this discussion). The stage of development varied from just started (building ground prepared) to the stage of where GMP inspection is expected in 2025. The project shows promising results, and it will be interesting to follow the progress of these

constructions and implementations, as the aim of the PAVM-Action plan was to produce 60% of the vaccines needed on the continent by 2040.

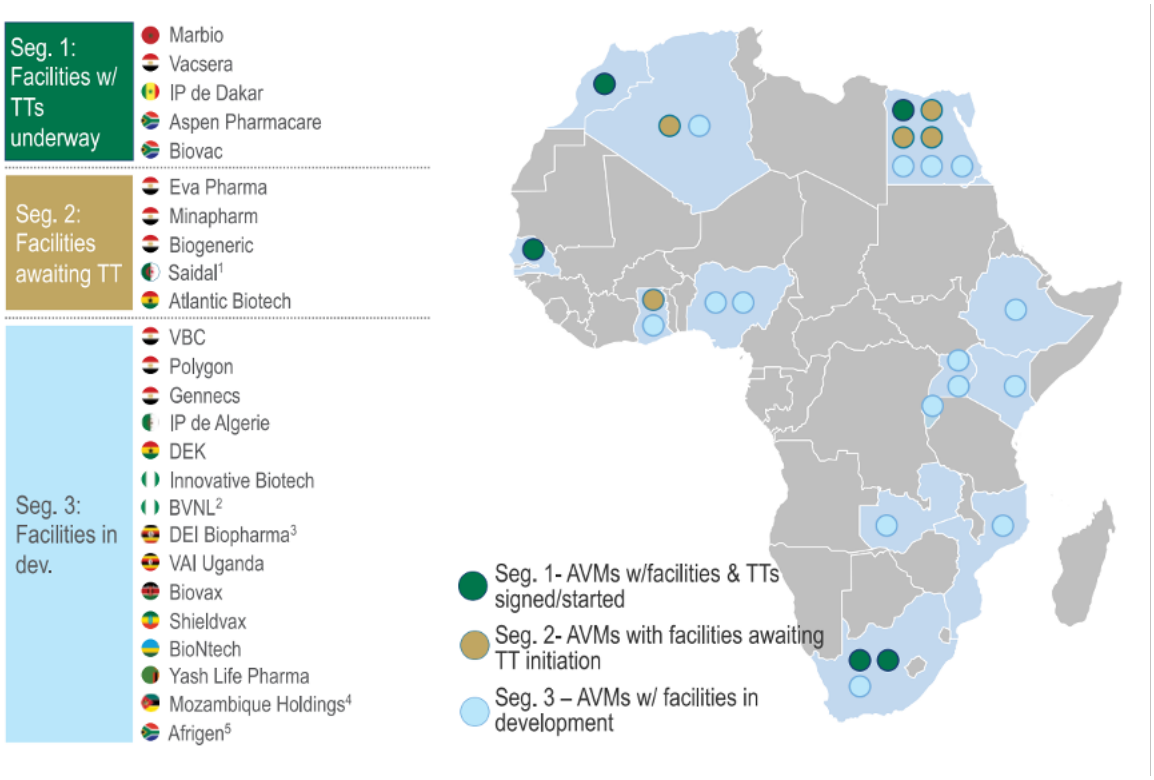

Figure 8: African Vaccine Manufacturing Mapping - Supply and Demand Landscape October 2024 (The PAVM action plan is applied across Africa. Therefore, results in Morocco, Algeria and Egypt are shown on the map. However, due to the important progress of the project for the Sub-Saharan countries, the map is also included in this thesis.) The AVM projects are divided into three segments based on the suppliers' maturity (WHO-Level) and capabilities. (78)

("[1)] "Saidal" may have a commercial scale facility ready to receive an influenza vaccine Tech-Transfer; [2)] "BVNL" did not have a facility at this period of time; [3)] Construction of a modular vaccine facility started in the US and should be shipped to Uganda in 2025; [4)] Unofficial reports indicate they have broken ground on a F/F facility; [5)] R&D facility complete, larger commercial facility built, expecting GMP inspection in 2025; Source: CHAI/PATH/PAVM Current State Vaccine Supply Mapping" (78)).

The "Access to Medicines" initiative could support the goal of increasing the access to vaccines and other essential medicinal products through voluntary licensing of patented medicines between the international pharmaceutical companies (20 listed in the Index

2024) and local African manufacturers. Unfortunately, only 6 companies agreed towards technology transfer to Sub-Saharan regions. These transfers were mainly focussed on South Africa (5 out of a total of 47 LMICs transfer Initiatives worldwide) (47). The technology transfer initiative in Africa included products for HIV, Hepatitis, COVID-19, diabetes mellitus and neglected tropical diseases. The low number of voluntary licenses may be related to the current lack of production sites in the regions. In this case, it will be interesting to see in a few years' time to what extent this transfer has improved as the PAVM action plan is further developed and implemented.

Additionally, the "Medicine for Malaria Venture" (MMV, an NGO founded in Switzerland in 1999) is working in partnership with African manufacturers to support them meet the WHO - Good Manufacturing Practice (GMP) and Prequalification (PQ) standards and strengthen the production of qualified antimalarial medicines in Africa (79). The MVV supported three African pharmaceutical manufacturers to obtain WHO-PQ for antimalarial medicinal products used to prevent the disease in children and pregnant women in 2024. The organisation partnered with Africa CDC (November 2024) to increase this number to seven manufacturers by 2030 (80). This decision is a positive step in the fight against SF-medicinal products as it will increase the access to much needed antimalarial medicinal products.

Furthermore, in 2024, the Africa-WHO reported on the need for skilled industry professionals and stressed the importance of investing in specialised training and higher education. At present, not enough universities in Africa provide the required industrial and regulatory training to produce adequately trained pharmacists, biomedical engineers, biological laboratory scientists and chemists. (77). To address these issues, the African Pharmaceutical Technology Foundation (APTF) has launched a virtual post-doctoral workshop on "Vaccine Production for Epidemic and Pandemic Preparedness in Africa", which has started in March 2024 (81).

In any case, since the COVID-19 pandemic, various measures have been taken to improve access to medicinal products for the African population, by placing more emphasis on self-sufficiency and less on importing essential products. These actions, such as promoting local

production and supporting training workshops, have a direct impact on the fight against SF medicines. By providing timely access to needed medicines. Increasing the number of local manufactures for vaccines and essential medicinal products is a first step and will continue with support for already existing local production sites to achieve a Good Manufacturing Practice certification (a GMP programme of the APTF) (82).

In addition, it is also interesting to note that at the 37th Assembly of the African Union in 2024, Africa-CDC together with the leaders of AU-member states decided to upgrade the current "Partnership for African Vaccine Manufacturing" (PAVM) to the "**Platform for Harmonized African Health Products Manufacturing**" (PHAHM) (83). This is because the platform aims to consider not only vaccines, but also the production of other health products in the future. At the same meeting, it was also approved that the previous AMSP (African Medical Supplies Platform) would be developed into the continental **African Pooled Procurement Mechanism** (APPM) under the leadership of the Africa-CDC. (84). This change is supported by the Afreximbank (Africa Export-Import Bank) and should ensure that all African countries have an access for to essential medical supplies (medical not only medicinal products).

The APPM is important in supporting the new African manufacturers and ensuring that they are self-sustaining once they are up and running. To achieve this objective, the manufacturers must not only respond to the needs of their own country, but also extend their targeted market to the regions of Africa. Collective purchasing would be a powerful tool to balance costs and to be able to produce the needed medicinal products at an affordable price (it was a lesson learned from PAHO organisation. (85)

Technological Innovations for Drug Verification

Tools for identification and traceability ("Track and Trace, T&T) play a crucial role in protecting the legitimate supply chain of medicinal products. They make it possible to monitor these products as they move through the various stages of the complex supply chain (58).

Currently the EU- T&T system is fully implemented and functioning (7) (59), while the US system ("Drug Supply- Chain Security Act, DSCSA) (89) required a longer implementation

period (deadline has been postponed as it should have been already implemented in 2023) (89). The differences in time may be due to the requested deliveries for each system (59).

It was therefore promising that the "Verification and Traceability Initiative" (VTI) opted for the TRVST-system for donated medicinal products, which was faster to implement (in two countries in two years) (62). It certainly has the advantage of being easier to use with the mobile application. It remains to be seen how long it will take for all African countries to integrate this system into their "Donated-Products-System" (if they decide to use the TRVST system).

It will also be interesting to see which traceability system will dominate the usual (i.e. non-donated medicines) supply chain system of medicinal products in Sub-Saharan Africa. Currently, T&T systems are not yet the same in all African countries. The example of Nigeria shows that two technology systems are in parallel use (one for the "medicine-donated" supply chain and one implemented by the pharmaceutical companies themselves for the public sector as pharmacies and clinics).

It would probably be advantageous to conduct a survey on experiences with the implementation of a traceability system for medicinal products, similar to the WHO survey of 2023 (that was conducted in countries around the world) (87). This survey should focus only on the Sub-Saharan region. This type of study should best be addressed to national regulatory authorities, the manufacturers and the health distribution sector (pharmacists and clinics).

An impressive survey could therefore be undertaken initially by one region under the leadership of the corresponding RCC of the Africa-CDC. The grouping of countries into RCCs would avoid an overlapping of responsibilities and duplication of responses.

Nevertheless, in the long term, a T&T system applied to all the Sub-Saharan countries on the same basis could be beneficial to all stakeholders and effectively reduce the infiltration with SF medicinal products into supply chains. However, which technology to use (if even a blockchain technology is applied), this decision should address many challenges (implementation costs, availability of infrastructure and ease of use), but an important factor will also be the security of the database (to protect against "cybercriminal" infiltration of the systems) (88).

Until secure supply chain management is in place in all Sub-Saharan countries to ensure that only legitimate medicines reach the market, pharmacists, for example, can only rely

on the support of simplified and affordable detection and verification tools (e.g. GPHF-Minilab) to analyse medicinal products before those are distributed it to their patients. These test methods have their limitations (mostly qualitative and semiquantitative results), they can uncover medicines that do not contain the specified API at all. However, they do not detect the majority of SF medicinal products that contain insufficient amounts of API or have insufficient dissolution of the API (89). In any case, they help to reduce the circulation of SF-medicinal products until better controls are in place along the supply chain. (90) (91).

Field detection methods (such as the GPHF-Minilab or any mobile IR-based device) are also important for reporting when SF-medicines are in circulation. In this context, the role of community awareness is crucial. All healthcare workers have a key role to play in educating consumers on how to identify SF medicines and in assisting in the use of the "field-detection" devices. Individual reports through a reporting system based on a mobile application (for example) would support the alert process and contribute to remove the SF medicinal products from the market faster.

Finally, any effort to strengthen the pharmacovigilance system by providing the necessary tools to monitor and evaluate the safety of medicines is an important step in the fight against SF medicinal products. (Tools such as secured supply-chain-management, but also well implemented reporting alert systems). (3)

7. Conclusion and Outlook

Substandard and falsified (SF) medicinal products pose a significant threat to global health, particularly in low- and middle-income countries (LMICs) such as Sub-Saharan region. In 2017, a WHO report estimated that up to 116 000 deaths were caused by SF-Antimalaria medicinal products in Sub-Saharan Africa, where malaria remains a major public health concern.

The fight against SF medicinal products is crucial and requires a multifaceted approach, involving stronger regulatory frameworks, addressing the security gaps along the supply chain of medicinal products, and responding faster to increased demand for essential medicines (especially during disease outbreaks). This thesis provides an overview of strategies and the related measures to prevent the distribution of SF medicines in the Sub-Saharan region. These African countries are already in the process of harmonising regulatory frameworks through regional collaborations to compensate for the inadequate infrastructure of national regulatory agencies (in alignment with the African Medicine Regulatory Harmonisation initiative. AMRH). Consideration is also being given to adjust the law enforcement for SF medicinal products in the harmonisation process. A long-term objective is to establish a continental African Medicines Agency (AMA) to enhance the regulatory oversight, similar to the European EMA, but adapted to the African region (today only 28 from 55 countries have ratified the treaty).

In the aftermath of the COVID-19-Pandemic, several projects have been launched to increase local production of vaccines and other medicinal products to meet the demand for essential medicines. International collaborations (such as Medicines for Malaria Venture, MMV) support local manufacturers in upgrading their facilities and in obtaining “Good Manufacturing Practices” (GMP) certification to produce the necessary antimalarial medicinal products to quality standards. These results are in line with the newly established “Platform for Harmonised African Health Products Manufacturing” (PHAHM), led by the Africa Central Disease Control and prevention (CDC) and supported by international cooperations (e.g. AUDA-NEPAD, EU, WHO, Gates Foundation, AfDB). The PHAHM aims to respond to the demand for essential medicinal products in long term and to counter the proliferation of SF medicines. In addition, various specialised training programmes have been initiated to improve the skills of the regulatory authorities and to increase the number

of staff required by the industry. These education programmes are designed to support faster registration of and access to medicinal products.

While progress has been made in supporting local manufacturers, significant challenges remain, for example in preventing the infiltration of SF medicinal products into the regular supply chain. Currently, there is no harmonised or centralised traceability and verification system for the whole Sub-Saharan region (such as the system used in the EU). However, a newly established track and verification system "TRVST" for supply chain of donated medicinal products has been implemented in two countries and is being rolled out in other Sub-Saharan countries. This could be the start of a more unified secure cross-border traceability system for the Sub-Saharan region. Until secure supply chain management is in place in all Sub-Saharan countries, pharmacists rely mostly on a combination of "field detection" systems (e.g. GPHF-Minilab, IR-scanner) to detect SF-medicinal products before distribution to patients.

Nevertheless, future surveys should explore the experiences with traceability systems for medicinal products specifically in the Sub-Saharan countries and consider if novel technological solutions (e.g. blockchain technology) are applicable and affordable for the target regions. Furthermore, the implementation of SF-medicines alert systems should be evaluated to improve effective communication between the partners involved. The effects of regulatory reforms and the impact of workforce training should be evaluated after a period of time. Additionally, research is needed to understand consumer behaviour (such as the use of alternatives to conventional medicines) and the drivers behind the demand for SF medicinal products. This could provide valuable information for designing effective public awareness campaigns.

Finally, addressing the challenge of SF medicinal products will require sustained commitment from the African governments, international organisations, the private sector (e.g. pharmaceutical industry), and local communities. Only continued efforts and targeted investment in the health system can reduce the prevalence of SF medicinal products and improve health outcomes. These SF medicines contribute to increased morbidity and mortality and delay efforts to eradicate diseases. The resulting risk of drug resistance due to SF medicinal products is not only limited to the Sub-Saharan countries. It is also a global

health challenge due to the influence of changing weather patterns that lead to mosquito-borne diseases spraying into new regions (dengue virus in Western-Europe in 2023).

8. Summary

Substandard and falsified (SF) medicinal products pose a significant threat to regions where regulatory oversight is weak. WHO reported up to 116 000 deaths due to SF Antimalarial medicines in Sub-Sahara-countries in 2017. The fight against SF medicinal products is crucial and requires a multifaceted approach, involving stronger regulatory frameworks, addressing the security gaps along the supply chain of medicinal products, and responding faster to increased demand for essential medicines. This thesis provides an overview of strategies and associated measures to achieve the prevention of SF medicinal products in the Sub-Saharan region as listed:

• Reducing weaknesses in regulation of medicinal products:

- Strengthening regulatory frameworks through harmonisation and collaboration: e.g. AMRH, ZAZIBONA, MEDISAFE-project, AMA treaty (28 ratification out from 55 countries)
- Enabling upgrade to WHO maturity level 3 for stable regulatory environment

• Responding to demand for essential medicinal products through local productions:

- Increasing local production through cooperation and supporting start-up platforms: PAHO-Africa-CDC; Platform for Harmonized African Health Products Manufacturing (PHAHM), African Pharmaceutical Technology Foundation (APTF), African Pooled Procurement Mechanism (APPM), technology transfer through “Access to medicines” initiative
- Supporting local manufacturers to obtain GMP-certification and produce medicinal products in quality standard, supported by e.g. Medicines for Malaria Venture (MMV)

• Addressing gaps in security along the supply chain of medicinal products:

- Implementation of Verification system “TRVST” for donated medicinal products supply chain; Verification system based on Blockchain technology (in Nigeria for example)
- Application of field detection systems (e.g. GPHF-Minilab, IR-scanner)

• Talent development to address shortages of required workforce:

- Pharmacometrics Africa-platform: training for “Clinical Assessors within African Regulatory Agencies”; EAC Regional Centre of Excellence for Vaccines, Immunisation and Health Supply Chain Management (EAC RCE-VIHSCM): “Global Standards for Traceability of Health Products and Technologies” training.

Nevertheless, future surveys should explore the experiences of the Sub-Saharan countries with traceability systems for medicinal products. Further, the impact of regulatory reforms and workforce training should be assessed after a period of time. Research is also needed to understand consumer behaviour and drivers behind the demand for SF medicinal products.

Finally, addressing the challenge of SF medicinal products will require sustained commitment from the African governments and support from international organisations, the pharmaceutical industry and local communities. Only continued efforts and targeted investment in the health system can reduce the prevalence of SF medicinal products. These SF medicines contribute to increased morbidity and mortality and delay efforts to eradicate diseases. The resulting risk of drug resistance due to SF medicinal products is not limited to Sub-Saharan countries. It is also a global health challenge due to changing weather patterns that lead to mosquito-borne diseases spraying into new regions (dengue virus in Western-Europe in 2023).

9. References

(All websites were accessed until 28. February 2025)

1) United Nations Office on Drugs and Crime (2022). *Trafficking in Medical Products in the Sahel*. Available at: https://www.unodc.org/documents/data-and-analysis/tocta_sahel/TOCTA_Sahel_medical_2023.pdf

2) World Health Organization (2024). *World malaria report 2024: addressing inequity in the global malaria response.* Available at: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024

3) World Health Organization (2017). *Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Available at: https://iris.who.int/bitstream/handle/10665/326708/9789241513425-eng.pdf

4) Fight the Fakes Alliance. Website available at: https://fightthefakes.org/

5) IFPMA. Alliance. Website available at: https://www.ifpma.org/initiatives/the-fight-the-fakes-alliance/

6) Gavi (2023). *The Vaccine Alliance. Malaria in the US – is climate change affecting disease spread?* Available at https://www.gavi.org/vaccineswork/malaria-us-climate-change-affecting-disease-spread .

7) European Medicines Agency. *Falsified medicines.* Website available at: https://health.ec.europa.eu/medicinal-products/falsified-medicines_en

8) European Medicines Agency. *Falsified medicines: overview.* Website available at: https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/falsified-medicines-overview#:~:text=Falsified%20medicines%20do%20not%20pass,can%20be%20a%20health%20threat

9) European Medicines Agency. *Glossaries.* Website available at: https://www.ema.europa.eu/en/about-us/glossaries/glossary-regulatory-terms

10) World Health Organization (2019). *The WHO Member State Mechanism on Substandard and Falsified Medical Products*. 2019. Available at: https://www.who.int/publications/i/item/WHO-MVP-EMP-SAV-2019.04

11) World Health Organization. *The WHO Member State Mechanism*. Available at: https://www.who.int/teams/regulation-prequalification/incidents-and-SF/mechanism

12) World Health Organization (2017). *Definitions of Substandard and Falsified (SF) Medical Products.* Available at: https://www.who.int/teams/regulation-prequalification/incidents-and-SF/background/definitions

13) World Health Organization – Global Surveillance and Monitoring System. Available at: https://www.who.int/who-global-surveillance-and-monitoring-system

14) World Health Organization (2012). *Member State mechanism on substandard/spurious/falsely-labelled/falsified/ counterfeit medical products.* WHA65.19. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA65-REC1/A65_REC1-en.pdf#page=25

15) United Nations- Sustainable Development Goals (UN-SDG). Website available at: https://www.un.org/sustainabledevelopment/health

16) World Health Organization (2018). *The state of health in the WHO African Region: an analysis of the status of health, health services and health systems in the context of the Sustainable Development Goals*. Available at: https://www.afro.who.int/sites/default/files/2018-08/State%20of%20health%20in%20the%20African%20Region.pdf

17) World Health Organization (2017). *A study on the public health and socioeconomic impact of substandard and falsified medical products.* Available at: https://www.who.int/publications/i/item/9789241513432

18) World Health Organization. WHO-press release (2017): *1 in 10 medical products in developing countries is substandard or falsified.* Available at: https://www.who.int/news/item/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified

19) World Health Organization (2019). *Delivering Quality-Assured medical Products for All 2019-2023: WHO's five-year plan to help build effective and efficient regulatory systems*. Available at: https://iris.who.int/bitstream/handle/10665/332461/WHO-MVP-RHT-2019.01-eng.pdf?sequence=1

20) European Commission (2023). *Study supporting the report to the European Parliament and to the Council on trends in the falsification of medicinal products and measures provided according to Directive 2011/62/EU*. Available at:

https://health.ec.europa.eu/document/download/59efb019-57a1-4161-99a2-9b5cc63d3d26_en?filename=trends_medicinal-products-falsification_study_en.pdf

21) Keyer M. (2018). *Avoiding of falsified medicines: An overview of the legal situation and the impact on the pharmaceutical industry - with a focus on regulatory implementation*. MDRA master thesis. Available at: https://www.dgra.de/en/degree-programme/in-your-studies/masters-thesis

22) Website available at: https://de.statista.com/statistik/daten/studie/14035/umfrage/europaeische-union-bevoelkerung-einwohner/

23) Wikipedia website available at: https://en.wikipedia.org/wiki/Africa,

24) Website available at: https://supplychainnuggets.com/5-common-supply-chain-security-threats-in-africa/

25) Wikipedia website: available at: https://en.wikipedia.org/wiki/Coup_Belt

26) World Health Organization (2024). WHO-press release: *Substandard and falsified medical products.* Available at: https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products#:~:text=Overview,their%20identity%2C%20composition%20or%20source

27) Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH. Website available at: https://www.giz.de/en/aboutgiz/97733.html

28) Health Policy Watch. Website available at: https://healthpolicy-watch.news/fight-the-fakes-campaign-raises-awareness-of-falsified-substandard-medicines/

29) Bui V, Higgins CR, Laing S, Ozawa S (2021). *Assessing the Impact of Substandard and Falsified Antimalarials in Benin*. Am J Trop Med Hyg. 2021 Nov 8;106(6):1770–1777. doi: 10.4269/ajtmh.21-0450, PMCID: PMC9209916 PMID: 34749311. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9209916/

30) Jackson KD, Higgins CR, Laing SK, Mwila C, Kobayashi T, Ippolito MM, Sylvia S, Ozawa S (2020). *Impact of substandard and falsified antimalarials in Zambia: application of the SAFARI model*. BMC Public Health 20, 1083 (2020). Available at: https://doi.org/10.1186/s12889-020-08852-w

31) Bakker-'t Hart IME, Ohana D, Venhuis BJ (2021). *Current challenges in the detection and analysis of falsified medicines*. Journal of Pharmaceutical and Biomedical Analysis 197 (2021) 113948. Available at: https://doi.org/10.1016/j.jpba.2021.113948

32) Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE. *Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis*. JAMA Netw Open. 2018 Aug 03;1(4):e181662. PMID: 30646106; PMCID: PMC6324280. Available at: https://doi.org/10.1001/jamanetworkopen.2018.1662

33) Weselmann B. (2017). *International cooperation among Drug Regulatory Authorities*. MDRA master thesis. Available at: https://www.dgra.de/en/degree-programme/in-your-studies/masters-thesis

34) Hatem K. (2024). *Towards Harmonised Medicine Regulation in Africa: Analysing the Feasibility of Adopting the Centralised Procedure of the European Medicines Agency for the African Medicines Agency*. MDRA master thesis. Available at: https://www.dgra.de/en/degree-programme/in-your-studies/masters-thesis

35) AMRH (2025). AUDA-NEPAD- AMRH. Website available at: https://amrh.nepad.org/

36) ZAZIBONA. Website available at: https://zazibona.com/about-zazibona/

37) Sithole T, Mahlangu G, Walker S, Salek S (2022). *Regulatory Authority Evaluation of the Effectiveness and Efficiency of the ZaZiBoNa Collaborative Medicines Registration Initiative: The Way Forward*. Front Med (Lausanne). 2022 Apr 25;9:898743. PMID: 35547217; PMCID: PMC9082034. Available at: https://doi.org/10.3389/fmed.2022.898743

38) Sithole T, Salek S, Walker S. (2022). *Regulatory work-sharing initiative in Africa: ZaZiBoNa, past, present and Future*. Available at: https://cirsci.org/publications/regulatory-work-sharing-initiative-in-africa-zazibona-past-present-and-future/

39) Africa- Centres for Disease Control and Prevention (Africa-CDC). Website available at: https://africacdc.org/about-us/our-history/

40) African Union. Website available at: https://au.int/fr/node/40878

41) Medicines for Malaria Venture. Website available at: https://www.mmv.org/newsroom/news-resources-search/powerful-role-local-manufacturing-fight-against-malaria

42) African Medicine Agency (AMA). Website available at: https://www.nepad.org/microsite/african-medicines-agency-ama

43) International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). (2024). *The African Medicines Agency: Building a New Gold Standard in Regulatory Excellence Insights from DIA Europe 2024*. Available at https://globalforum.diaglobal.org/issue/july-2024/the-african-medicines-agency-building-a-new-gold-standard-in-regulatory-excellence/. (Accessed 29 Oct 2024).

44) Brazzaville Foundation-Lomé-Initiative. Website available at: https://www.brazzavillefoundation.org/en/our-actions/fight-against-medicines-that-kill/#initiative-lome

45) Africa- Centres for Disease Control and Prevention (Africa-CDC). Press release (2024). Website available: https://africacdc.org/news-item/paho-and-africa-cdc-strengthen-collaboration-to-address-access-to-essential-medicines-and-vaccines/

46) Access to medicine - Foundation. Website available at: https://accesstomedicinefoundation.org/healthcare-inequity/our-story

47) Access to medicine - Foundation. Report (2024). *Access to medicines Index*. Available at: https://accesstomedicinefoundation.org/sectors-and-research/index-ranking#index--download-2024-access-to-medicine-index

48) Expertise France- project press release (2024). *Combating falsified medicines in East and Central Africa with the MEDISAFE project*. Website available at: https://www.expertisefrance.fr/en/actualite?id=903477

49) MEDISAFE - project press release (2023). *MEDISAFE Project Closing Meeting*. Website available at: https://www.medisafe-p66.eu/medisafe-project-closing-meeting/

50) European Commission- International Partnerships. *Team Europe Initiative on manufacturing and access to vaccines, medicines and health technologies in Africa*. (TEI-MAV+) Website available at: https://international-partnerships.ec.europa.eu/policies/team-europe-initiatives/team-europe-initiative-manufacturing-and-access-vaccines-medicines-and-health-technologies-africa_en

51) European Commission- International Partnerships. TEI-MAV+ (2024). Factsheet: *MAV+ Supporting manufacturing and access to vaccines, medicines and health technologies in Africa*. October 2024. Website available at: https://international-partnerships.ec.europa.eu/document/download/11b4599f-5a5d-405e-b55c-8218b704233a_en

52) Pharmacometrics Africa. Website available at: https://pmxafrica.org/

53) Semete-Makokotlela B, Gugu N Mahlangu GN, Mukanga D, Darko DM, Stonier P, Gwaza L, Nkambule P, Matsoso P, Lehnert R, Rosenkranz B, Pillai GC. (2021). *Needs-driven talent and competency development for the next generation of regulatory scientists in Africa*. Review Br J Clin Pharmacol. 2022 Feb;88(2):579-586. doi: 10.1111/bcp.15020. Epub 2021 Aug 24. Avaibale at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9291465/

54) South African Health Products Regulatory Authority (SAHPRA) Report (2023). *A Primer for Clinical Assessors within African Regulatory Agencies -project summary and report-2023*. Website available at: https://www.sahpra.org.za/document/a-primer-for-clinical-assessors-within-african-regulatory-agencies/

55) African Pharmaceutical Technology Foundation. Website available at: https://www.afdb.org/en/news-keywords/african-pharmaceutical-technology-foundation

56) African Pharmaceutical Technology Foundation. Press release (2023). *African Pharmaceutical Technology Foundation, Government of Rwanda to Sign Host Country Agreement*. Website available at: https://www.afdb.org/en/news-and-events/african-pharmaceutical-technology-foundation-government-rwanda-sign-host-country-agreement-67249

57) African Pharmaceutical Technology Foundation. Press release (2024). *Rwanda: the African Development Fund commits $12 million to the rapid operationalization of the African Pharmaceutical Technology Foundation (APTF)*. Website available at: https://www.afdb.org/en/news-and-events/press-releases/rwanda-african-development-fund-commits-12-million-rapid-operationalization-african-pharmaceutical-technology-foundation-aptf-69095

58) World Health Organization (2021). *Policy paper on traceability of medical products*. Available at: https://www.who.int/publications/i/item/policy-paper-on-traceability-of-medical-products

59) Bick AF. (2021). *Gesetzgebung und Maßnahmen zum Fälschungsschutz bei Arzneimitteln in der Europäischen Union, den USA und Brasilien - ein Vergleich aus behördlicher Sicht unter besonderer Berücksichtigung der Serialisierungsvorhaben*. MDRA-Master thesis. Available at: https://www.dgra.de/en/degree-programme/in-your-studies/masters-thesis

60) International Coalition of Medicines Regulatory Authorities (ICMRA) (2021). Recommendations on common technical denominators for traceability systems for

medicines to allow for interoperability. Available at: https://icmra.info/drupal/en/strategicinitatives/supplychainintegrity

61) Unicef-supply division. Press release (2023). *Traceability and Verification System (TRVST) - Combatting counterfeit and falsified medicines to ensure continuous availability of safe and high-quality health products for all*. Website available at: https://www.unicef.org/supply/traceability-and-verification-system-trvst

62) World Health Organization. Joint UNICEF-UNFPA-WHO-Meeting-press release (2023): *The Verification and Traceability System (TRVST).* Available at: https://extranet.who.int/prequal/sites/default/files/document_files/day1-session4_traceability.pdf

63) Tracekey. Website available at: https://www.tracekey.com/en/trvst-system-tracking-verification/

64) Unicef-supply division. Press release (2022). *First serialized vaccine scan in Africa marks milestone in tackling falsified medical products*. Website available at: https://www.unicef.org/supply/stories/first-serialized-vaccine-scan-africa-marks-milestone-tackling-falsified-medical-products

65) Authentic.network. Press release. Website available at: https://media.authentic.network/presse/

66) Sproxil. Website available at: https://sproxil.com/

67) The Global Pharma Health Fund. Website available at: https://www.gphf.org/en/

68) The Global Pharma Health Fund. News. *GPHF-Minilab™ - Protection Against Counterfeit Medicines*. Website available at: https://www.gphf.org/en/minilab/index.htm

69) RxAll. Website available at: https://rxall.net/rxscanner/

70) Apiko P, Bisong A, Byiers B, Medinilla A, Ronceray M, Tadesse, Staeger U (2022). *Regional organisations in Africa: What are the political economy dynamics?* Ecdpm publication Available at: https://ecdpm.org/work/regional-organisations-in-africa-what-are-the-political-economy-dynamics

71) World Health Organization. (2024). *Senegal and Rwanda achieve WHO Maturity Level 3 in medicines regulation*. Available at: https://www.who.int/news/item/05-12-2024-senegal-and-rwanda-achieve-who-maturity-level-3-in-medicines-regulation

72) World Health Organization. (2024). *List of National Regulatory Authorities (NRAs) operating at maturity level 3 (ML3) and maturity level 4 (ML4)*. 20 December 2024;

Available at: https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4

73) EAC Regional Centre of Excellence for Vaccines, Immunization and Health Supply Management (EAC RCE-VIHSCM). Press release (2024). *EAC RCE Taskforce Develops Roadmap for Health Supply Chain Professionalization.* Website available at: https://hscm.ur.ac.rw/eac-rce-taskforce-develops-roadmap-for-health-supply-chain-professionalization/

74) Wada YH, Abdulrahman A, Muhammad MI, Owanta VC, Chimelumeze PU, Khalid GM. (2022). *Falsified and substandard medicines trafficking: A wakeup call for the African continent*. Public Health in Practice 3 (2022) 100240. Available at: https://doi.org/10.1016/j.puhip.2022.100240

75) African Union Development Agency - NEPAD (2020). *A Guidance Document for the Domestication of the African Union Model Law on Medical Products Regulation*. Available at: https://www.nepad.org/publication/guidance-document-domestication-of-african-union-model-law-medical-products

76) Brazzaville foundation. Website available at: https://www.brazzavillefoundation.org/

77) World Health Organization - Regional Committee for Africa, 74. (2024). *Framework for strengthening local production of medicines, vaccines, and other health technologies in the WHO African Region 2025–2035: report of the Secretariat*. World Health Organization. Regional Office for Africa. Available at: https://iris.who.int/handle/10665/378851

78) Africa- Centres for Disease Control and Prevention (2024). *African Vaccine Manufacturing Mapping - Supply and Demand Landscape*. Website available at: https://africacdc.org/download/african-vaccine-manufacturing-mapping-supply-and-demand-landscape/

79) Medicines for Malaria Venture (2024). *The powerful role of local manufacturing in the fight against malaria*. Available at: https://www.mmv.org/newsroom/news-resources-search/powerful-role-local-manufacturing-fight-against-malaria

80) Medicines for Malaria Venture (2024). *Enabling malaria drug supply by strengthening local manufacturing in Africa*. Available at: https://www.mmv.org/our-work/access-to-medicines/african-drug-manufacturing

81) African Pharmaceutical Technology Foundation. Website available at: https://www.aptfound.org/news

82) African Pharmaceutical Technology Foundation- Programs. Website available at: https://www.aptfound.org/our-programs

83) Africa- Centres for Disease Control and Prevention. Press release (2025): *The 2nd Vaccines and other Health Products Manufacturing Forum for African Union Member States*. Website available at: https://africacdc.org/news-item/communique-the-2nd-vaccines-and-other-health-products-manufacturing-forum-for-african-union-member-states/

84) United Nations Economic Commission for Africa (2024). *An African Pooled Procurement Mechanism will enhance quality and safe medical supplies for a resilient continent*. Website available at: https://www.uneca.org/stories/an-african-pooled-procurement-mechanism-will-enhance-quality-and-safe-medical-supplies-for-a

85) Devex (social enterprise and media platform for the global development community). Interview 2024. Available at: https://www.devex.com/news/regional-vaccine-and-drug-production-is-coming-can-it-survive-108536

86) US Food and Drug Administration. Drug Supply Chain Security Act (DSCSA). Website available at: https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa

87) World Health Organization. Report (2025). *Country experiences on implementation of traceability for medical products*. Geneva: World Health Organization; 2025. Available at: https://www.who.int/publications/i/item/9789240103535

88) Islam I, Islam MN (2024). *A blockchain based medicine production and distribution framework to prevent medicine counterfeit*. Journal of King Saud University - Computer and Information Sciences, Volume 36, Issue 1, January 2024, 101851. Available at: https://doi.org/10.1016/j.jksuci.2023.101851

89) Gabel J, Martus P, Heide L. 2024. *Relationship between Prices and Quality of Essential Medicines from Different Manufacturers Collected in Cameroon, the Democratic Republic of the Congo, and Nigeria*. Am J Trop Med Hyg. 2024 Oct 8;111(6):1378-1395. doi: 10.4269/ajtmh.24-0309. Print 2024 Dec 4. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11619510/

90) Pisani E, Hasnida A, Rahmi M, Harsono S, Kok MO, Anggriani Y. (2021). *Substandard and falsified medicines: proposed methods for case finding and sentinel surveillance*. JMIR

Public Health Surveill. 2021 Aug 16;7(8):e29309. doi: 10.2196/29309. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC8406122/

91) Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C (2018). *Field detection devices for screening the quality of medicines: a systematic review*. BMJ Glob Health. 2018;3(4):e000725. doi: 10.1136/bmjgh-2018-000725. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6135480/

92) World Health Organization (2020). *Quality Assurance of Medicines Terminology Database - List of Terms and related guideline*. Available at: https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461cfc_5

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München, 07.04.2025

_____ _____

Ort, Datum Anissa Boucherot