Chapter

# The Current Situation of Medicines Quality in Low- and Middle-Income Countries: New Challenges to be Addressed

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## Abstract

An estimated 10.5% of medicines worldwide are of poor quality, negatively impacting health, economies, and societies globally. This issue is particularly pronounced in low- and middle-income countries, where harsh climatic conditions and weaker regulatory frameworks exacerbate the problem. Research often focuses on economic losses or compliance with the quality standards. However, the quality of medicines is not always verified through pharmacopeial tests, and, in some cases, it is evaluated using unauthorized techniques by national or regional medicines agencies. While these technologies are currently proving useful for medicine quality screening, their implementation remains inconsistent. The medicines most studied include antituberculosis, antimalarial, and antiretroviral treatments, reflecting the high prevalence and mortality associated with these diseases in affected regions. Furthermore, many studies discuss the potential causes of poor-quality medicines in the market, but very few works comprehensively assess them. Such assessments are crucial to identifying strategies for ensuring the quality of post-commercialized medicines in each region.

**Keywords:** poor-quality medicine, pharmacopeial test, low- and middle-income countries, antituberculosis, antimalarial, antiretroviral, stability, climatic conditions

## 1. Introduction

Since the beginning of the twenty-first century, poor-quality medicines have posed a growing challenge, leading to severe economic and health consequences. In 2017, the World Health Organization adopted the following definitions [1]:

- *Substandard or "out of specification"*: Authorized medicines that fail to meet either their quality standards or their specifications, or both.

- *Unregistered/unlicensed*: Medicines that have not undergone evaluation or approval by the national or regional regulatory authority for the market.

- *Falsified:* Medicines that deliberately misrepresent their identity, composition, or source.

Pharmaceutical quality system (PQS) provides a structured approach to ensure product quality in the pharmaceutical sector, with quality assurance (QA) establishing the systems and processes necessary for compliance and quality, while quality control (QC) is focused on the actual testing and inspection of products. Together, they form an integrated system that is essential for delivering safe and effective pharmaceutical products [1].

However, the pharmaceutical supply chain remains highly susceptible to the infiltration of falsified, substandard, or unregistered medicines, a vulnerability exacerbated by globalization. This complex network involves multiple stakeholders (manufacturers, distributors, wholesalers, and retailers), who represent potential entry points for compromised products, while inappropriate distribution practices can also jeopardize the quality of medicines manufactured to high standards during transport and storage [2, 3]. **Figure 1** illustrates how the lifecycle of medicines is inextricably linked to the pharmaceutical supply chain, a global network of entities collaborating to ensure the availability of safe and effective medicines. In this sense, the quality and traceability of medicine should be ensured from manufacturing to dispensing.

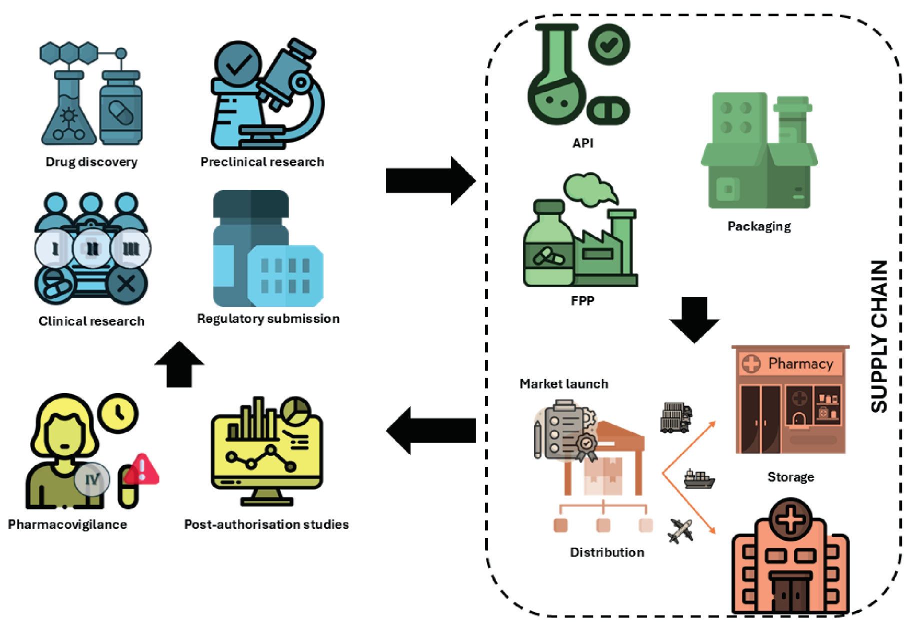


**Figure 1.**
*Lifecycle and supply chain of medicines. The lifecycle steps are defined in accordance with the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) [4]: Blue—Research and development stage; Green—Manufacturing and quality control stage; Orange—Commercialization stage; and Yellow—Post-commercialization stage.*

Postmarket surveillance systems, maintained by regulatory and health authorities, global health organizations, and the pharmaceutical industry, could provide crucial information to improve understanding of the prevalence of poor-quality medicines. This highlights the urgent need for national regulatory agencies and WHO-certified laboratories to perform thorough quality assessments and establish robust traceability systems [1].

In 2019, WHO published a report indicating that the key challenges in detecting poor-quality medicines are as follows: lack of adequate infrastructure, insufficient or inconsistent regulations, resource scarcity, opaque supply chains, corruption and unethical practices, shortage of trained personnel, reliance on destructive testing methods, challenges in obtaining representative samples, proliferation of unregulated e-commerce, and limited access to advanced testing technologies [1].

It is estimated that 10.5% of medicines on the market are of poor quality, although the incidence of these products varies according to income level, with the majority found in low- and middle-income countries (LMICs), particularly in Africa and Asia. Moreover, the failure rate varies depending on whether the medicines are sourced from licensed or unlicensed outlets, with a higher prevalence in the latter [1, 2, 5]. With pharmaceutical sales in LMICs reaching nearly $300 billion, the estimated economic burden of these substandard products could exceed $30.5 billion [1]. In high-income countries (HICs), unlicensed marketplaces are rare, but they face a different challenge: e-commerce. The COVID-19 pandemic significantly accelerated the use of e-commerce, forcing patients to obtain medicines online, often from illegitimate sources [6, 7].

The objective of this chapter is to provide an overview of the situation of quality medicines, with a particular focus on LMICs. It aims to identify strategies to ensure the quality of medicines by considering country-specific factors such as climatic conditions and implementing recognized techniques like *in situ* quality controls.

## 2. Regulatory framework

National and regional medicines agencies (NRMAs) play a critical role in identifying poor-quality medicines, as they oversee the regulatory framework—a fundamental element in addressing this issue. This problem is legally prosecuted and penalized under the MEDICRIME Convention, which several countries are in the process of ratifying [8]. Established by the Council of Europe, the Convention targets the falsification of medicines and related offenses that pose a threat to public health.

From an international perspective, the pharmaceutical sector faces an imbalance between the supply and demand for medicines, as well as poor manufacturing and distribution practices, enabling poor-quality medicines to infiltrate the market [9]. Ensuring the safety, efficacy, and quality of medicines necessitates rigorous QCs throughout the entire supply chain. These controls not only safeguard public health but also enable the traceability of products, aiding in the detection and resolutions of errors that may occur during the various stages of the lifecycle.

However, the effectiveness of these controls depends on the ability of regulatory authorities to respond swiftly to incidents involving poor-quality medicines. In theory, corporate governance standards require companies to promptly report such issues to NRMAs. In practice, however, companies may hesitate to disclose this information due to concerns about reputational damage, loss of consumer trust in their legitimate products, or fears of unpredictable regulatory sanctions. This reluctance undermines the ability of regulatory agencies to act effectively, leaving gaps in the system that allow substandard medicines to persist in the market [2].

The globalization of pharmaceutical supply chains further complicates the regulatory landscape. A significant portion of affordable generic medicines is produced in a small number of countries, where NRMAs often have limited responsibility for the quality of products intended for export. Instead, the burden of oversight falls on importing countries, each operating within its own regulatory framework, frequently duplicating the efforts of neighboring nations. Although the principle of "buyer beware" suggests that governments are ultimately responsible for ensuring the health and safety of their populations, this approach becomes less practical in a globalized market where supply chains span multiple countries and regions [2]. To address this, the WHO has developed a platform that allows NRMAs to report the detection of poor-quality medicines, serving as a centralized database of published alerts [10].

Regulatory agencies have several tools at their disposal to identify poor-quality medicines. For instance, the quality of post-commercialized medicines can be assessed through pharmacopeial tests, which are applied based on the pharmaceutical dosage forms [11]. In addition, these agencies can also authorize portable field detection devices or develop simplified checklist to identify falsified or unregistered medicines [12, 13].

The disparity in regulatory frameworks is particularly evident when comparing HICs and LMICs. For example, Europe benefits from the European Medicines Agency (EMA), operational since 1995, which provides a unified and robust regulatory framework across the continent [14]. In contrast, many African nations are in the process of establishing the African Medicines Agency (AMA), which is expected to play a crucial role in harmonizing regulations and improving medicine quality across the continent [15]. The absence of such structures in LMICs contributes significantly to the high prevalence of substandard and falsified medicines, as these regions often lack the resources and regulatory capacity to enforce stringent controls.

Moreover, the legal consequences for distributing poor-quality medicines vary greatly between countries. In HICs, stricter regulations govern the manufacturing, distribution, and sale of medicines, making it more difficult for substandard and falsified products to enter the supply chain. However, even in these regions, the Internet has emerged as a new frontier for illicit trade. Criminals have increasingly exploited the market for substandard and falsified medicines by taking advantage of the ease with which such products can be sold online. The National Association of Boards of Pharmacy found in 2014 that only about 4% of online pharmacies operate legally, with most of the pharmaceutical trade on the Internet being illegal [6]. This highlights the significant risks posed by unregulated e-commerce, as demonstrated by the detection of substandard medicines like furosemide and atorvastatin calcium in the online market [16].

### 2.1 European Medicines Agency

The EMA is a worldwide reference agency with a high-working capacity. In 2023, EMA recommended 77 medicines for marketing authorization, and 39 of them were new active pharmaceutical ingredients (APIs) that have never been authorized in EU before [17].

The EMA plays a crucial role in the pharmacovigilance of medicines already on the market and oversees post-marketing QC studies of centrally authorized products

(CAPs). To optimize the use of existing expertise and resources, the EMA has implemented a coordinated approach to the sampling and testing of CAPs. This coordination aims to avoid duplication, thereby saving costs for the pharmaceutical industry and regulators. Moreover, it facilitates work-sharing and mutual recognition of test results across the European Economic Area, ensuring efficient regulatory oversight. One of the key features of this coordination is the establishment of independent testing capabilities for all CAPs, which can be activated during emergencies. To achieve these objectives, the EMA launched a sampling and testing program in collaboration with the European Directorate for the Quality of Medicines & HealthCare, and the Official Medicines Control Laboratories (OMCLs) of European countries. This program coordinates the selection of CAPs to be tested, the specific parameters for testing, the sampling of CAPs from the European market, and the reporting of results [18].

Between 1998 and 2017, over 700 products were collected and tested under this program. The most selected test parameters included: the assay of API (Category A), the potency of biological products and the purity of medicines (Category B) and the physical/pharmaceutical characteristics of the products (Category C), identity (Category D), and microbial/bacterial contamination tests (Category E) continue to be requested but less often. The value of market surveillance testing was demonstrated in 2017 when out-of-specification results were detected for an unknown impurity during a testing campaign for zoledronic acid CAP generics. This example underscores the importance of such coordinated efforts in maintaining the safety and quality of medicines available in the European market [18]. Therefore, since then, the market surveillance and quality defect studies have continued to be carried out. In 2023, the agency received 257 suspected quality anomalies notifications, the highest number recorded in recent years. Of these, 188 cases were confirmed as poor-quality and led to batch recalls of 9 CAPs. The reasons were manufacturing laboratory control issues, and product contamination and sterility, label, packaging, and physical issues [19].

In terms of pharmaceutical policies, the EMA ensures compliance with good manufacturing and distribution practices, both of which are essential for maintaining the quality of pharmaceutical products. To this end, the EMA relies on a working group of inspectors who conduct routine assessments and publish annual reports [20]. These guidelines are mandatory for medicines including those imported from outside the EU, ensuring that they meet European standards. Moreover, the EMA's guidelines are recommended for adoption by all WHO member countries [21, 22].

To address the growing threat of falsified medicines, the EU introduced Directive 2011/62/EU. The directive establishes a regulatory framework to prevent the entry of falsified medicines into the legal supply chain, ensuring product traceability. Technologies such as *blockchain* or QR codes offer promising solution in this regard. The decentralized nature of blockchain that all transactions are transparent and tamper-proof, making it easier to detect falsified medicines at any point in the supply chain [23–25]. An example of this application is the *Sistema Español de Verificación de Medicamentos* in Spain [26]. This approach can be adopted globally, providing LMICs with a simple and practical tool for detecting falsified medicines, thereby significantly improving public health outcomes.

Basically, the EMA is implementing measures at the European level to address this significant public health problem. However, further development of policies that impose severe penalties on illegal activities within the pharmaceutical sector remains necessary to deter such practices effectively.

## 2.2 African Medicines Agency

The African Union is working toward establishing the AMA, whose objectives include coordinating national and subregional medicines regulatory systems, overseeing the regulation of selected medicines, promoting cooperation, ensuring access to affordable medicines, and harmonizing and mutually recognizing regulatory decisions [15, 27].

The creation of the AMA marks a significant step toward improving the quality of life in Africa by addressing key issues such as pharmaceutical regulatory frameworks and, consequently, enhancing public health across the continent. However, this initiative is not without challenges. For instance, LMICs that are not members of the African Union cannot directly benefit from these advances made under the AMA framework. Additionally, the AMA may face obstacles related to funding, staffing, and infrastructure, particularly during its early stages.

To maximize the impact of the AMA, it is crucial to address these challenges by expanding membership, increasing financial support, and strengthening partnerships with international organizations. Such measures would ensure that the AMA's benefits reach a broader population and contribute to improving healthcare across Africa [28].

Although some LMICs have not signed or ratified the AMA agreement, they still maintain their own medicines regulatory systems. For instance, Gambia has a Medicines Control Agency [29], while the Islamic Republic of Mauritania relies on the Directorate of Pharmacy and Laboratories (DPL) to manage pharmaceutical affairs [30].

The implementation of traceability systems for finished pharmaceutical products (FPPs) is essential to ensure the integrity and safety of pharmaceutical supply chains. These systems mitigate the risk of falsified or substandard medicines, improve inventory management, and enable rapid responses to quality incidents. Traceability can be applied at various levels, from batch control to unit-level serialization.

The adoption of global standards for interoperability and coordination between countries is critical for establishing robust regulatory frameworks that facilitate effective market surveillance. However, implementing traceability systems in LMICs poses significant challenges due to high costs, technological and infrastructural barriers, and insufficient funding.

To address these challenges in LMICs, the evaluation and implementation of traceability systems should focus on the following key aspects:

- *Accessibility and cost:* It is advisable to begin with batch-level traceability and progressively advance toward unit-level serialization, according to available resources.

- *Adoption of global standards:* The use of international standards, such as GS1, can reduce costs and ensure interoperability with other countries.

- *Capacity building and institutional strengthening:* It is crucial to train personnel and ensure that local regulatory authorities have the resources and expertise needed to manage and monitor these systems effectively.

- *Sustainability:* Sustainable financing mechanisms, through public-private partnerships or international support, should be integrated to ensure the ongoing maintenance and continuous improvement of traceability systems.

In Mauritania, the national pharmaceutical market is entirely supplied through the importation of medicines from various continents. The supply chain is predominantly controlled by private operators, who are not always pharmacists, which increases the likelihood of infringements by dealers or illegal brokers. According to DPL data, the licit pharmaceutical market (public and private sectors) had a turnover of 11–12 billion UM at wholesale prices in 2010 [31].

Two types of entities are responsible for importing medicines: Centrale d'Achat de Médicaments Essentiels et Consommables (CAMEC,) for the public sector, and around 20 private wholesale distributors. CAMEC is the primary supplier of Public Health Facilities nationwide through regional depots. It is obligated to supply up to 75% hospitals and to 100% of any other health establishment of their requirements. Consequently, CAMEC holds a near-monopoly on the distribution of the medicines to public health centers, which constitute its entire turnover. Retail distribution is managed by pharmacies and pharmacy depots [31].

Regarding antiretroviral (ARV) and antituberculosis (antiTB) medicines, free access supported by international partners has ensured satisfactory availability and accessibility. However, the supply system remains insecure. The strategic axes, selected based on the identified problems, for the implementation of the National Pharmaceutical Policy are as follows:

1. Improving the availability and accessibility of medicines

2. Ensuring the safety, efficacy, and quality of medicines

3. Promoting the rational use of medicines

4. Ensuring the monitoring and evaluation of pharmaceutical policies.

Despite the presence of one OMCL known as the Laboratoire National de Contrôle de la Qualité des Médicaments (LNCQM, from French), Mauritania is not included in the WHO Global Surveillance and Monitoring System (GSMS) [2].

## 3. Prevalence of poor-quality medicines

The prevalence of poor-quality medicines across therapeutic groups will be assessed globally and within LMICs. This evaluation will provide a comprehensive understanding of the therapeutic categories most affected by substandard and falsified medicines. By identifying these patterns, targeted regulatory actions and interventions can be developed to improve pharmaceutical quality, enhance supply chain integrity, and safeguard patient health.

### 3.1 Global perspective

Taking a global view, the WHO conducted a comprehensive literature review, which included several studies published before than 2019. The resulting report highlighted the distribution of collected samples by therapeutic category, emphasizing a significant focus on antimalarials and antibiotics, which together account for 64.5% of the total samples. Other critical therapeutic categories, such as antiTB and ARV medicines, are also included and show concerning failure rates [1].

For instance, antiTB medicines exhibit a 6.7% failure rate, which, while lower than the 11.8% failure rate of antimalarials, remains significant given the global burden of tuberculosis (TB), particularly in LMICs. These findings are especially alarming as effective TB treatment depends on consistent and high-quality medications to prevent the emergence of drug-resistant strains, which pose a severe threat to global TB control efforts.

ARVs, which are vital for the treatment of HIV, demonstrate a relatively lower failure rate of 4.2%. While this figure is encouraging, it still represents a notable risk, particularly in regions where access to quality-assured medications is limited. Failures in ARV quality could lead to suboptimal treatment outcomes, fostering the development of drug-resistant HIV strains and undermining decades of progress in combating the epidemic. Although the failure rates of TB and HIV medicines are lower compared to those of antimalarials and antibiotics, their impact cannot be underestimated. Both categories address critical diseases that rank among the top 10 leading causes of death in LMICs [32].

Additionally, platforms such as the Infectious Diseases Data Observatory (IDDO), coordinated by the Centre for Tropical Medicine and Global Health at the University of Oxford, provide valuable tools for monitoring medicine quality. The IDDO allows filtering data by product category (e.g., medicines, diagnostics), date, country, and therapeutic group [33]. The platform features a global quality map derived from studies published since 1985, indicating sample locations and quality outcomes. A color-coded system visually represents the quality failure rates of substandard medicines. Notably, the map highlights India and Kazakhstan in Asia, along with Chad, Kenya, Nigeria, and Sudan in sub-Saharan Africa, as countries with the highest failure rates (see **Figure 2**).

Since 2010, the IDDO platform has recorded 904 reports, with 34.85% concerning antibiotics, 18.14% focused on antimalarials, and 5.97% related to ARVs. For antiTB medicines, a mere 24 studies were reported during that period, all of them were from African, Asian, and American countries [34]. In the last 5 years, a total of 34 publications have been reported on the quality of antimalarial medicines and 14 publications were related to FPPs used for HIV, 12 of which directly addressed medicine quality. Alarmingly, approximately 70% of these reports detected falsified or substandard medicine [35, 36].

This underscores the need for targeted interventions to safeguard the quality of TB and HIV medicines as well as antimalarial, as these treatments are foundational to global health initiatives aimed at controlling infectious diseases in vulnerable populations.

### 3.2 African perspective

Not surprisingly, a similar situation exists in Africa. One of the latest systematic reviews of the prevalence of substandard, falsified, unlicensed, and unregistered medicines in Africa, focusing on data collected from 2014 to 2024, shows the significant risks posed by such medicines. The medicines that were most affected were antibiotics, antimalarials, antihypertensives, and antiparasitics. The estimated prevalence of substandard/falsified medicines in Africa is 22.6%, with unregistered medicines at 34.6% [37].

If data are observed per therapeutic group, it confirms that antibiotics were the most extensively studied therapeutic group, with a wide range of studies reporting a prevalence of substandard or falsified products, averaging 44.3%. Antimalarial

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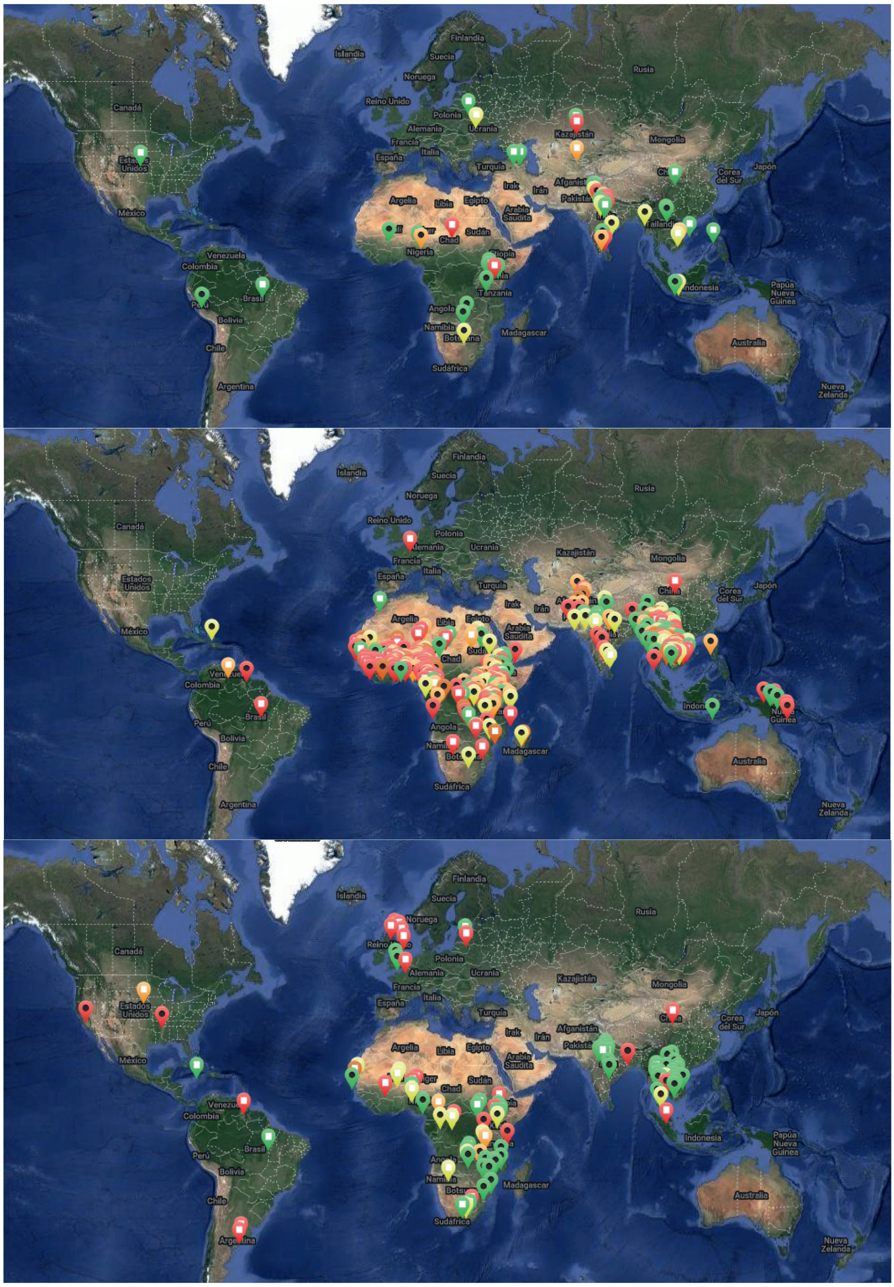


**Figure 2.**
*Medicine quality map from IDDO. Filtering by therapeutic group: antituberculosis (A), antimalarials (B), and antiretrovirals (C). Green color indicated zero-substandard medicines, yellow-orange color indicated a failure rate from 1 to 75%, and red >75% substandard medicines detected.*

medicines were also heavily studied, with an average prevalence of 15.6%, reflecting the high burden of malaria in Africa. On the other hand, antihypertensive medicines and anthelmintic medicines received comparatively less attention, though still significant, with antihypertensives showing a prevalence of 16.3% and anthelmintics at 60.7% [37].

As for countries, only one study included Mauritania, alongside other sub-Saharan African countries such as Benin, Burkina Faso, Congo-Brazzaville, the Democratic Republic of Congo, Senegal, Togo, Niger, Côte d'Ivoire, and Guinea. This study focused on cardiovascular medicines, specifically furosemide, hydrochlorothiazide, captopril, simvastatin, and amlodipine. The findings revealed a 16.3% prevalence of substandard or falsified medicines across these regions [38].

## 4. Climatic conditions influence on product quality

Special attention must be given to climatic conditions, particularly in LMICs, as globalization has highlighted them as a potential contributor to the presence of substandard medicines. Even when strict adherence to Good Distribution Practices and manufacturers' storage recommendations are followed, the extreme climatic conditions prevalent in some regions can still compromise medicine stability and quality.

According to the ICH Q1F guideline, stability data must demonstrate the product's robustness under the climatic conditions of the target country throughout its intended shelf life. National and regional medicines agencies (NRMAs) are responsible for verifying this data during the market authorization approval process [39]. The 2021 WHO guideline on stability conditions identified many African countries as falling under the 30°C/65% RH (Relative Humidity) climatic zone for long-term stability studies [40].

However, real-world conditions can be harsher than those defined by stability guidelines. For instance, in Mauritania, while the assigned stability conditions align with 30°C/65% RH, these figures are based on national averages across the country's vast geography (1,030,700 $km^2$). A more localized analysis reveals significant deviations, such as in the coastal capital, Nouakchott, where the average temperature during the May–October period exceeds 30°C. This timeframe also corresponds to the rainy season, leading to a spike in RH levels, often reaching around 90% [41]. Such extremes are likely to accelerate the degradation of certain pharmaceutical products, especially those sensitive to heat and moisture.

Several studies have confirmed the sensitivity of medicines to such harsh climatic conditions. Degradation of APIs, changes in physical properties, and reduced potency have all been observed when products are stored outside the recommended conditions [42–49]. These findings stress the necessity of replicating the climatic conditions of sampling sites during post-market QC tests to verify that the FPPs comply with their specifications and are stored according to the labeled instructions.

## 5. Impact: Health, economic, and social consequences

The quality of medicines is a critical determinant of the health of individuals and, consequently, their quality of life. This relationship is multifaceted, with far-reaching effects on the healthcare, economic, and socioeconomic spheres [1]. While the adverse consequences of poor-quality medicines are well-documented, accurately measuring their impact remains a formidable challenge. The inherent difficulty lies in the lack of precise data regarding the absolute number of substandard and falsified medicines, the ethical barriers to conducting human research involving these products, and the absence of uniform price regulation across global market [2]. Although all medicines are susceptible to being substandard or falsified, certain therapeutic groups are disproportionately affected, necessitating greater regulatory and research focus due to their critical role in managing major public health challenges.

In 2022, Ozawa et al. published a review identifying seven models designed to estimate the health and economic impacts of substandard and falsified medicines, focusing primarily on antimalarial and antibiotic treatments. These models assess the effects of poor-quality medicines at national, regional, and global levels. Despite their utility, there are voids such as the limited focus on other therapeutic areas, like uterotonics and antihypertensives, and the lack of country-specific data beyond sub-Saharan Africa. The review also suggests that future models need to better address population heterogeneity, incorporate detailed simulations of supply chains, and evaluate the costs and effectiveness of interventions to ensure medicine quality [50]. This underscores the critical importance of thoroughly assessing the impact of antimicrobial medicines, as they play a vital role in addressing many of these issues and why the infectious diseases are one of the top leading causes of deaths in many LMICs.

The public health impact of substandard and falsified medicines manifests in increased mortality, disability, and morbidity, with broader repercussions on health systems. Metrics like years of life lost, quality-adjusted life years, and disability-adjusted life years (DALYs) measure mortality and morbidity, while metrics such as disease prevalence and antimicrobial resistance are more complex and often reliant on mathematical models.

In 2019, Woskie et al. provided a landmark estimate of the global burden of substandard and falsified medicines. Their findings attributed 327,298 deaths and 9.69 million DALYs annually to these products. This accounted for 14% of global TB deaths and 7% of HIV-related deaths [51].

Beyond the direct health impacts, substandard and falsified medicines erode public confidence in medicines and healthcare systems. This loss of trust not only affects health-seeking behaviors but also has broader economic and socioeconomic ramifications, as individuals' declining confidence in healthcare systems directly influences their quality of life. This, in turn, negatively impacts both national economies and social structures. The estimation of economic and socioeconomic impacts of substandard and falsified products are limited by the lack of studies available. A key issue is the difficulty in attributing health outcomes to these products, which complicates economic analysis. Two significant direct costs are identified: the expenditure by individuals and health systems on ineffective or harmful products, and the losses incurred by involving agents in the supply chain due to the sale of products lacking QA. These costs vary widely between countries, influenced by factors such as levels of health insurance coverage [1, 52].

At an individual and household level, the most immediate costs are the financial losses from purchasing harmful or ineffective products, often leading to additional spending on further treatments. In LMICs, households bear a substantial share of these costs, particularly for medicines [53].

For health systems, poor-quality medicines result in increased expenditure on testing, treatments, and resources, placing additional strain on often overstretched services (**Table 1**). These products can also contribute to the spread of disease and antimicrobial resistance, further escalating costs. The socioeconomic impact, while challenging to quantify, includes lost income, reduced productivity, and costs arising from prolonged illness or death, as well as broader effects on an economic and social development of a country. These include impacts on gross national income, employment levels, and public trust in healthcare systems [1].

| Region/ country | Age | Medicines | Prevalence of poor-quality medicines | Impact | | Ref. |
|---|---|---|---|---|---|---|
| | | | | Deaths, median | Costs (USD mill, 2017) | |
| Sub-Saharan Africa | < 5 | Antimalarial | 0–40 | 122,350 | ND | [54] |
| Global | < 5 | Antimicrobials | 10 | 72,430-169,271 | ND | [1] |
| Sub-Saharan Africa | < 5 | Antimalarial | 7.6 | 116,000 | 38.5 | [1] |
| LMIC | ND | All | 13.6 | ND | 31,250 | [55] |
| LMIC | All | AntiTB | 6.7 | 255,115 | ND | [56] |
| LMIC | All | ARV | 4.2 | 72,183 | ND | [56] |
| Nigeria | All | Antimalarial | 12–50 | 12,300 | 892 | [57] |
| Congo | < 5 | Antimalarial | 19 | 10,370 | 151 | [50] |
| Uganda | < 5 | Antimalarial | 21–31 | 1100 | 31 | [58] |
| Benin | ND | Antimalarial | 32.5 | 700 | 20.8 | [59] |
| Mauritania | All | AntiTB | 69.3 | ND | ND | [60] |
| Mauritania | All | ARV | 33 | ND | ND | [61] |
| Mauritania | All | Antimalarial | 33 | ND | ND | [61] |

*LMIC: low- and middle-income countries. Age is expressed as years old. ND: Not determined. It is adapted from Orubu et al. [52].*

**Table 1.**
*Impact of poor-quality medicines from modeling studies.*

## 6. Quality assurance strategies for pharmaceutical products

QA refers to the systematic processes and activities designed to ensure that products meet specified requirements and quality standards throughout the medicine lifecycle. It encompasses all planned and systematic activities implemented within the PQS, including documentation, training, and audits. QA focuses on preventing defects and ensuring that processes are in place to maintain quality. QA and QC are interdependent, without robust QA practices, QC may not be able to effectively identify or address quality issues [62].

### 6.1 Methodologies for assessing poor-quality medicines

This section outlines the methodologies used to identify and assess the poor-quality medicines, including certain analytical techniques used. Some of these methodologies are as follows:

- *Visual inspection*: Checking for obvious discrepancies in packaging, labelling, or product appearance (e.g., incorrect logos, spelling errors, or inconsistent batch numbers). It is done by comparison of the packaging of the FPPs or even employing an ultraviolet (UV) light to detect hidden authenticity marks. It allows identification of falsified or even unregistered medicines when the packaging is not recognized.

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- *Analytical testing*: Using advanced techniques such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), or near-infrared spectroscopy (NIR) to confirm the identity, purity, impurities, degradation products, and dosage of the APIs. The selection of each one will be dependent on the resources of the countries, the prequalification of the staff, and the objectives of the research. However, these methodologies could by apply for all poor-quality medicines, according to the discrepancy between the labelling and the detection done.

- *Supply chain auditing*: Reviewing the distribution history of the FPP and verifying the authenticity of suppliers and manufacturers through documentation and traceability systems. It is part of the inspection process that can help to identify the involved agents (as illegal dealers).

- *Track and trace technologies*: Implementing systems like barcode scanning or radio frequency identification tagging to trace the origin and movement of medicines through the supply chain. It allows the entrance of the unregistered or falsified FPPs in the market.

- *Quality control testing*: Assessing product samples for compliance with the established pharmacopeial standards (e.g., disintegration, dissolution, and uniformity of mass tests) approved in each country. It is also related to the analytical testing to quantify suitably the amount of API. It is specially focused on detecting substandard products.

- *Sampling protocols*: Conducting systematic sampling of FPPs across various stages of the supply chain (e.g., manufacturer, distributor, retailer) to ensure consistency and adherence to quality specifications. The proper sampling protocols permit to identify the critical factor that can affect to the quality and the weakest stage of the supply chain to take actions on the matter.

- *Stability testing*: Examining how products perform under different environmental conditions (e.g., temperature (T), relative humidity (RH)) to detect issues with degradation or loss of specifications over time.

- *Regulatory review*: Verifying whether a FPP has the required approvals or licenses from NRMAs for importation, sale, and distribution. This focuses on detecting the unregistered medicines, normally is associated with other methodologies as the market surveillance or the visual inspection of the packaging.

- *Market surveillance*: Conducting proactive inspections of pharmacies, hospitals, and informal markets to identify the presence of any poor-quality medicines.

- *Cross-border monitoring*: Collaborating with customs and border control agencies to track the importation of unregistered or illegally imported medicines.

- *Database comparisons*: Using databases such as the WHO GSMS or regional regulatory systems to cross-check if a medicine is classified as poor quality in other country and the reason.

Some of these methodologies require the work of health authorities because regulatory information can be needed. However, there are others that just require prequalified staff, but it highlights the need to have adequate training programs.

### 6.2 Designing a suitable work plan

The design of the work plan will depend on the specific objectives that need to be achieved. However, a well-designed work plan for a QC study should indeed include these three key elements:

#### *6.2.1 Sampling methodology*

The objectives of the post-marketing sampling and testing program are to supervise the quality of medicines placed on the market, checking the compliance of specifications [63]. Therefore, sampling design is a critical factor in the overall challenge of poor-quality medicines as a representative sample must be taken. The representativeness of a sample depends on two factors: the sampling frame from which products are selected and the method used to choose samples from within that sampling frame. Despite the urgent need for data of sufficient sample size with random sampling design to reliably estimate the prevalence of poor-quality medicines, resource limitations may make meeting this goal difficult for researchers [1].

The selection method refers to the process or technique used to choose which units or elements from a sampling frame will be included in a sample for a research study [64]. Various sampling techniques are globally recognized: random (simple, systematic, stratified, or cluster), non-random (convenience, judgmental, or snowball), or mixed (stratified systematic or cluster stratified) [65].

#### *6.2.2 Validation of analytical methods*

The selection of appropriate analytical techniques is crucial for achieving research objectives, as each method presents distinct advantages and limitations. Additionally, different types of poor-quality medicines require adapted strategies for effective identification.

Due to the importance of the selection of the technique for the study, several techniques will be discussed. Some of these are considered gold standard technique by international regulatory authorities, and others are widely used as an alternative to detect falsified or substandard medicines despite of not being authorized by the NRMAs [66].

HPLC remains the most widely used technique for QC, in line with pharmacopeial recommendations. However, in 2004, ultra-high performance liquid chromatography (UHPLC) has emerged, offering reduced analysis time while maintaining high precision and accuracy [67]. Moreover, HPLC can also be coupled with MS, which allows for the analysis of APIs when they lack a chromophore group or when the detection of impurities is required [68]. These techniques require specialized infrastructure and trained staff, limiting their global availability although it is gradually becoming more frequent in some LMICs to achieve the qualification as reference laboratory because HPLC is the gold standard technique [69].

However, the rise of portable devices has revolutionized the capability to conduct on-site testing, even in remote areas [70]. Among the most significant devices are portable Raman and NIR spectrometers, which enable rapid identification of genuine and falsified medicines without the need for sample preparation. These devices have proven effective in detecting incorrect or missing APIs in medicines [71], but they need to be validated using chemometric methods recognized by the pharmacopeia [72], and its suitability is still limited by the variations in the spectra recorded between devices [73].

Additionally, the Counterfeit Detection Device (CD3), developed by the FDA, is another promising tool that has been evaluated for use in LMICs. This non-destructive device utilizes visible and infrared light to analyze packaging and detect signs of falsification, offering more affordable and easily implementable option in the field [74].

When the proper analytical technique is selected, analytical methods must be validated following International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines to ensure the linearity, accuracy, precision, and robustness [75]. A suitable validation, which includes robustness testing, ensures that the method can be reliably transferred while maintaining consistency, even with minor variations in experimental conditions. One of the purposes of the NRMAs should be to establish strict guidelines for analytical method validation, ensuring that medicines on the market meet the highest standards of safety and efficacy.

#### *6.2.3 Performing quality controls*

Once the sampling and the validation of analytical methods is finished, the tests to analyze the samples are performed. The QC of a medicine is predetermined by its pharmaceutical dosage form, which must meet specific criteria evaluated through internationally established tests. However, the criteria for compliance with these tests may vary depending on the country. For instance, in the United States of America (USA), the United States Pharmacopeia (USP) compiles monographs for individual medicines, outlining the specific requirements for each. In contrast, the European Pharmacopeia (Eu. Ph.) provides only a general criterion for each test and pharmaceutical dosage form, offering broader guidelines.

NMRAs, as authorities in the pharmaceutical field, must control the quality of commercialized medicines in accordance with pharmacopeial tests established in their national legislation. **Table 2** lists the pharmaceutical technique procedures that are performed according to the pharmaceutical dosage forms, and they are recognized in the Eu. Ph [76–80]. Regardless of the pharmaceutical form, it is essential to conduct an analysis that includes both the identification of the API and the detection of impurities. This process is critical to ensure the quality, safety, and efficacy of the medicine, thereby safeguarding public health and ensuring compliance with the established regulatory standards. Furthermore, all these tests should be reassessed over time, as the climatic conditions in LMICs can impact on the established standards, as previously mentioned.

The uniformity of dosage units (UDU) test is specified for tablets, but the procedure varies depending on the tablet subtype [81]. Similarly, the disintegration test differs for uncoated tablets compared to gastroenteric form, which must resist the acidic pH environment of the stomach [82]. For intravenous pharmaceutical dosage forms that will be administered directly to the blood (e.g., solutions, emulsions, or suspensions for injection or perfusion), the sterility test must be carried out to avoid any potential sepsis on the patient [83].

One critical aspect to consider is the appropriate performance of the UDU test, as studies sometimes focus solely on evaluating the quantity of APIs without assessing

| Pharmaceutical dosage form | Tests to be performed | Reference |
|---|---|---|
| Solid dosage form | | |
| Tablets | • UDU<br>• Content uniformity<br>• Uniformity of mass<br>• Dissolution<br>• Disintegration<br>• Fineness of dispersion* | Chapter 2.9.40, 2.9.6, 2.9.5, 2.9.3, 2.9.1 |
| Hard capsules | • Disintegration<br>• UDU<br>• Content uniformity<br>• Uniformity of mass<br>• Dissolution | Chapter 2.9.1, 2.9.40, 2.9.6, 2.9.5, 2.9.3 |
| Soft capsules | • Disintegration<br>• UDU<br>• Dissolution | Chapter 2.9.1, 2.9.40, 2.9.3 |
| Powders for injection | • Content uniformity<br>• Uniformity of mass<br>• Sterility | Chapter 2.9.6, 2.9.5, 2.6.1 |
| Implants | • Release of API<br>• Content uniformity | Specific test for implants, Chapter 2.9.6 |
| Liquid dosage forms | | |
| Solutions for injection or infusion | • Particulate contamination: sub-visible particles<br>• Particulate contamination: visible particles<br>• Sterility<br>• Bacterial endotoxins | Chapter 2.9.19, 2.9.20, 2.6.1, 2.6.14 |
| Emulsions for injection or infusion | • UDU<br>• Sterility<br>• Particulate contamination: visible particles | Chapter 2.9.40, 2.6.1, Specific chapter |
| Suspensions for injection or infusion | • Particulate contamination: sub-visible particles<br>• Particulate contamination: visible particles<br>• Content uniformity<br>• Sterility | Chapter 2.9.19, 2.9.20, 2.9.6, 2.6.1 |
| Concentrates for injection | • Particulate contamination: visible particles<br>• Sterility | Chapter 2.9.20, 2.6.1 |
| Oral solutions, emulsions, suspensions | • UDU<br>• Content uniformity<br>• Uniformity of mass | Chapter 2.9.40, 2.9.6, 2.9.5 |

| Pharmaceutical dosage form | Tests to be performed | Reference |
|---|---|---|
| Oral drops | • Dose and uniformity of dose | Chapter 2.9.27 |
| Syrups | • UDU<br>• Content uniformity<br>• Uniformity of mass | Chapter 2.9.40, 2.9.6, 2.9.5 |
| Gels | | |
| Gels for injection | • Release of API | Specific test for gels |

*UDU: Uniformity of dosage units. API: Active Pharmaceutical Ingredient.*

**Table 2.**
*Pharmacopeial tests according to the pharmaceutical dosage form.*

the deviation between units. Such deviations can be significant, potentially leading to overdosing or underdosing in patients [62, 84–88]. Furthermore, as mentioned it should be necessary to evaluate the specifications over time when they are stored at similar climatic conditions of the countries where they are commercialized.

## 7. Conclusions

A robust and adaptable regulatory framework is crucial for ensuring the global quality of medicines, particularly considering the disparities in regulatory capacity and enforcement between HICs and LMICs. While HICs benefit from more stringent regulations and well-established institutions, LMICs often struggle with the limited resources and fragmented oversight, making the development of coordinated and efficient regulatory structures more critical for addressing the global issue of poor-quality medicines. The regulatory framework should be always adapted to their particularities such as the climatic conditions that affect considerably the quality of medicines.

Furthermore, portable devices should be authorized by the NRMAs because they are qualitative and semiquantitative techniques to detect falsified or substandard medicines, which are commonly used to conduct research in Africa particularly for rural areas where the buildings and the capabilities of the staff could be not suitable for laboratory analysis.

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