A Risk-Based Resource Allocation Framework for Pharmaceutical Quality Assurance for Medicines Regulatory Authorities in Low- and Middle-Income Countries

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Acknowledgments

Acronyms

DALY	disability-adjusted life year
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTE	full-time equivalent
GMP	good manufacturing practices
ICH	International Council for Harmonization
IT	information technology
LMIC	low- and middle-income country
MQM	medicines quality monitoring
MRA	medicines regulatory agency
PQM	Promoting the Quality of Medicines (program)
QA	quality assurance
QALY	quality-adjusted life year
RBA	risk-based approach
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Glossary of Terms

For purposes of this document, the following definitions are used.

active pharmaceutical ingredient	any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product
disability-adjusted life year	a measure of overall disease burden, expressed as the number of years lost due to ill health, disability, or early death
effectiveness	a measure of the accuracy or success of a diagnostic or therapeutic technique when carried out in a real world environment
falsified	medical products that deliberately/fraudulently misrepresent their identity, composition, or source
perspective	the viewpoint from which economic or other analyses are performed (e.g., societal, governmental, third-party payer, and patient perspectives)
pharmacovigilance	the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem
porous borders	connections between neighboring countries through which goods and persons move without control or regulation
quality-adjusted life year	a generic measure of disease burden, including both quality and quantity of life lived; 1 quality-adjusted life year is equivalent to 1 year lived in perfect health

quality assurance	an integrated system of activities involving planning, quality control, quality assessment, reporting, and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence
risk	the probability of an untoward outcome and the severity of the resultant harm associated with a medicine used under specified conditions in a defined population
risk analysis	the review of the risks associated with a particular event or action, analyzed quantitatively or qualitatively, as part of risk management
stringent regulatory authority	national drug authorities that are members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
substandard	authorized medical products that fail to meet either their quality standards or their specifications, or both
unregistered/ unlicensed	medical products that have not undergone evaluation and/or approval by the national medicines regulatory authority in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation
universal health coverage	a healthcare system that provides healthcare and financial protection to all citizens of a particular country

Executive Summary

Pharmaceutical quality assurance (QA) systems should include strategies for the identification of substandard and falsified medicines, vulnerabilities in the pharmaceutical QA system, and the proportional allocation of appropriate resources to mitigate or manage them. However, allocating adequate resources to build and strengthen pharmaceutical QA systems is a challenge for low- and middle-income countries (LMICs), many of which currently rely to some or a large degree on donor support that is not sustainable. This document proposes a framework for risk-based resource allocation for regulatory QA in LMICs to assist country regulatory agencies in managing and sustainably supporting pharmaceutical QA to achieve maximum health impact and efficiencies. This framework for a risk-based approach to resource allocation for pharmaceutical QA by medicines regulatory authorities (MRAs) is intended as a potential guide to the development of country-specific tools for resource allocation. The framework consists of six core elements: (1) risk analysis, (2) analysis of the pharmaceutical market, (3) analysis of the country characteristics, (4) assessment of the regulatory and QA environment, (5) risk management (including resource allocation for pharmaceutical QA), and (6) assessment of the impact of resource allocation. The framework can be operationalized by identifying: (1) risk-triggering and risk-mitigating factors using attributes of the country itself, (2) attributes of the regulatory and QA environment for medicines within the country, and (3) attributes of the country's pharmaceutical market. Risk-triggering and risk-mitigating factors provide the basis for risk analysis, and risk analysis guides resource allocation. Finally, the impact of resource allocation is subject to impact evaluation. The framework will help countries to prioritize and channel limited resources to the most fundamental and high-impact regulatory functions. When deployed (assuming sufficient resources are available), the risk-based approach should help facilitate the progressive attainment of self-funded and potentially sustainable QA systems, maximizing country investments and enabling responsible graduation of countries away from dependence on donor support for regulatory systems strengthening. This risk-based approach for resource allocation for pharmaceutical QA at MRAs should help improve and maintain public health, achieve efficiencies, and promote public confidence in health systems.

1.   Introduction

1.1   The importance of pharmaceutical quality assurance

Pharmaceutical quality assurance (QA) is critical for health systems performance because of the central role of medicines (drugs and vaccines) in maintaining and improving health. The use of poor-quality medicines in low- and middle-income countries (LMICs) can lead to a number of problems, including treatment failure, disease exacerbation, promotion of antimicrobial resistance, greater morbidity and mortality, waste of resources, and erosion of the public's confidence in health systems [1]. Faced with competing health priorities and limited resources, allocating adequate resources to build and strengthen pharmaceutical QA is an imperative, yet it is a challenge for LMICs.

The World Health Organization (WHO) characterizes poor-quality pharmaceuticals as consisting of substandard, spurious, falsely-labelled, falsified, and counterfeit (SSFFC) medical products and recommends the use of the terms "substandard and falsified" for ease of reference, while avoiding the use of "counterfeit," which is associated with the protection of property rights [2] [3]. This framework therefore uses "substandard and falsified" to align with the WHO terminology. Moreover, in 2014 the 67th World Health Assembly (Resolution 67:20) identified regulatory systems as an essential component of health systems strengthening toward promoting safe, effective, and quality-assured medical products.

The Promoting the Quality of Medicines (PQM) program, a cooperative agreement between the U.S. Pharmacopeial Convention (USP) and the U.S. Agency for International Development (USAID), supports LMICs in strengthening their pharmaceutical QA systems with the ultimate aim of ensuring the quality, safety, and effectiveness of medicines by building capacity in the regulation, analysis, and manufacture of medicines [4]. The generation and appropriate allocation of adequate resources to strengthen medicines QA systems remains a challenge for LMICs, many of which rely on donors for financial and technical support. Donor support can be sporadic and insufficient and may not necessarily contribute to the development of sustainable pharmaceutical QA systems, so there is a need to identify a path to sustainability for efficient pharmaceutical QA systems in LMICs. Use of the limited resources available to establish cost-effective and sustainable pharmaceutical QA systems helps to ensure the greatest public health impact within a country's capabilities and to sustain the public's confidence in health systems.

1.2   Minimum regulatory functions required for every country

While the number and scope of regulatory functions may differ among countries (depending on their laws and regulations), according to WHO, medicines regulatory functions include:

- Licensing the manufacture, import, export, distribution, promotion, and advertising of medicines.
- Assessing the safety, efficacy, and quality of medicines, and issuing marketing authorization.
- Inspecting and surveilling manufacturers, importers, wholesalers, and dispensers of medicines.
- Controlling and monitoring the quality of medicines on the market.

- Controlling promotion and advertising of medicines.
- Pharmacovigilance.
- Providing independent information on medicines to professionals and the public.

Countries may differ in the number and scope of the various regulatory functions they prioritize and perform based on factors such as pharmaceutical regulatory laws and regulations, as well as available resources. Many countries do not have the capacity to meet principal regulatory functions, which highlights the need for additional prioritization. Alternatively, countries may want to know what they can do for themselves and what they may have to work with others for. Where information may already exist as a common good, as in pre-market review of medical products by stringent regulatory authorities, it may be that an abridged review may obviate a given country's allocation of resources for full review toward an approval decision for given product(s). Similarly, countries may decide to enter into agreements to share inspection reports of facilities with other countries' regulatory agencies to avoid duplication of effort. Countries should be able to determine what functions and at what scope must be performed for the most efficient use of their limited resources in order to protect their populations.

1.3 Metrics for assessing the impact of a health system-level healthcare intervention

Pharmaceutical QA is a health system-level intervention because it is not limited to a single disease area and may cover entire countries or geographical regions. Pharmaceutical QA can be conceptualized as existing to reduce the loss of medicines-related quality-adjusted life years (QALYs) or, similarly, to reduce the accrual of medicines-related disability-adjusted life years (DALYs) in a given country. Pharmaceutical QA can also be conceptualized as existing to increase efficiency in the medicines regulatory process and other related activities of a given country with the overall aim of improving the effectiveness, safety, quality, and availability of medicines and consequently improving health outcomes.

QALYs and DALYs are globally recognized metrics of choice for assessing the health impact of interventions and for making resource allocation decisions across the health sector. These metrics combine health-related quality and length of life [5]. QALYs and DALYs allow comparison of the value of interventions or the burden of disease for those with predominantly morbidity consequences as well predominantly mortality consequences. QALYs are configured as a positive measure of health gain. Utility estimates, the quality-of-life component of QALYs, are generally available for many health states but less so in LMICs [6]. DALYs are a metric of overall health-related harm and have two advantages: (1) they are configured as a cumulative measure of disease burden in countries, regions, and/or globally, and (2) published disability weight estimates are available for multiple diseases and risk factors [7]. These measures can be applied to examine the scope and impact of regulatory functions and therefore identify those that are most valuable to product public health.

1.4 A risk-based approach to medicines regulation at MRAs

The concept of a risk-based approach (RBA) is prevalent in many sectors of the global economy [8]. Stringent regulatory authorities, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have adopted the RBA for key regulatory functions such as

inspection of production facilities and sampling of products for quality testing [10]. For example, the U.S. Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) directed the U.S. FDA to replace biannual facility inspections with inspections guided by an RBA. The U.S. FDA's RBA uses attributes such as compliance history, history of past recalls, and frequency of previous inspections to allocate inspection resources to higher-risk facilities. With the same goal of preventing duplicative waste, U.S. FDA and EMA recently agreed to mutual recognition of facility inspections in their respective jurisdictions. As another example, the Singapore Health Services Authority adopted an abridged evaluation of medical devices conditional upon approval by at least one of five reference agencies in the United States, Europe, Canada, Australia, and Japan. The rationale of this approach to medical device evaluation is that, given approval by MRAs in these five countries, the Singapore Health Services Authority would gain multiple institutional advantages and those medical devices should pose minimal risk to people in Singapore.

WHO's published guidelines for quality risk management in LMICs recommend certain action by MRAs (reviews and inspections) and by manufacturers of medicines and producers of active pharmaceutical ingredients across the entire product life cycle (design, development, manufacture, and distribution) [11]. Additionally, a previous review described an approach to monitoring of pharmaceutical product quality using risk-based modeling methods and leveraging preexisting data [12]. The stringent regulatory authorities' adoption of the RBA has mainly focused on how to reduce duplication. However, the application use of the approach to support more efficient and rational allocation of regulatory resource has been lacking.

The value of an RBA is in its ability to inform the allocation of regulatory resources proportionately to risk. In pharmaceutical QA, an RBA should identify product quality risks and other vulnerable areas and then allocate proportionate resources to mitigate or prevent them [9]. The RBA can therefore provide a comprehensive framework to construct LMICs' plans to potentially transition from partial or full donor dependence to regulatory self-sufficiency, i.e., to a state of financial sustainability for pharmaceutical QA in the context of sufficient human and technical resources. However, regulatory authorities in LMICs may not have formal frameworks for the application of an RBA to resource allocation for pharmaceutical QA. Given resource constraints and individual country insistence on performing all necessary regulatory functions, an RBA framework is of immediate priority and importance [13]. An optimal regulatory system is one in which regulatory interventions are proportionate to public health risk and sustainable within local government and other available resources. Therefore, an RBA to regulatory activity should help MRAs fulfill the pharmaceutical QA role of minimizing the loss of drug-related QALYs (or the accrual of drug-related DALYs) at the lowest cost, achieving efficiency and ensuring the effectiveness, safety, quality, and availability of medicines.

2.   Objective

This document presents an RBA framework for resource allocation and is intended to assist MRAs in LMICs in proportionately allocating and sustaining levels of resources for key regulatory functions in pharmaceutical QA to maximize public health impact in their countries. This framework identifies pathways for leveraging limited regulatory resources while still protecting public health. MRAs can use an RBA for country management and financing of medicines QA systems such that self-sufficiency and sustainability can be introduced, advocated for, and institutionalized. A country's ability to ensure the quality of medicines in its health system—as a basic public health service that is not dependent on donor funding—should improve the provision of quality essential health services and increase efficiency. These outcomes are particularly critical as countries strive to achieve and finance universal health coverage.

3. Framework

3.1 Overview

The framework for an RBA to resource allocation for pharmaceutical QA at MRAs is intended to be a country-specific macro-level tool for resource allocation consisting of six core elements: (1) risk analysis (2) analysis of the characteristics of the country, (3) analysis of the pharmaceutical market, (4) assessment of the characteristics of the regulatory and QA environment, (5) risk management (including resource allocation for pharmaceutical QA), and (6) assessment of the potential impact of resource allocation (Figure 1).

Figure 1. A framework for risk-based pharmaceutical QA in low- and middle-income countries
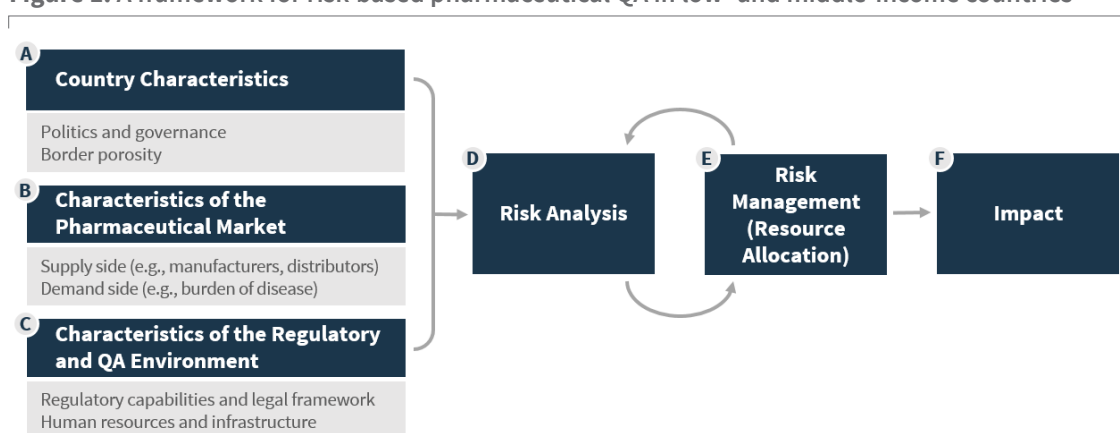
As shown in Figure 1, the characteristics of a country (Box A), its pharmaceutical market (Box B), and its regulatory and QA environment (Box C) are the sources of potential risk for the use of substandard and falsified medicines. The three broad attribute categories all contribute data for risk analysis (Box D). The three types of attributes are classified as risk initiating or risk mitigating. After a risk analysis is completed, the ranked risks inform risk management, which depends, in part, on resource allocation for QA (Box E). The process and results of resource allocation (Box E) may also contribute data for risk analysis (Box D). The final step in the framework is the assessment of the impact of the resource allocation (Box F).

Within each category (Boxes A–F) are subcategories and attributes. For Boxes A–C, different subcategories and attributes contribute data to risk analysis. For Boxes D, E, and F, the subcategories represent different components of risk analysis, risk management, and impact assessment, respectively. The complete framework, including subcategories and attributes, is shown in Figure 2 (Appendix 1).

As an example, characteristics of the pharmaceutical market contribute information for risk analysis by identifying priority (high-risk) pharmaceutical products or therapeutic areas for consideration during risk analysis. The prioritization of pharmaceutical products or therapeutic areas for risk analysis is based on the disease burden in the country, the characteristics of products used in the country, and the volume of medical products of interest consumed in a given country. Medical products for diseases or conditions of high burden in a given country should be prioritized. Medical products with special attributes (such as intravenous or highly potent or high-value products) and

products for which there is a high demand (such as anti-infectives) may also be prioritized. Table 1 illustrates the different attributes of countries, pharmaceutical markets, and the regulatory and QA environment, and possible sources of data to operationalize these attributes in the framework. Table 2 summarizes the different activities involved in risk analysis (Box D), risk management (Box E), and impact assessment (Box F).

Table 1. Risk-triggering and risk-mitigating attributes for risk analysis and selected data sources for their operationalization

Attribute		Possible Data Sources
Country characteristics	Politics and governance	World Bank Worldwide Governance Indicators [14]
		Corruption Perception Index [15]
		Primary data collection
	Border porosity	Published peer-reviewed data
		Publicly available data
Pharmaceutical market characteristics	Supply side*	Published data and country profiles
		Primary data
	Demand side†	Published data (country profiles, pharmaceutical market reports)
		Publicly available data
		Primary data
Regulatory and QA environment‡		Published data
		Publicly available data (MRA websites)
		Primary data
		In-country reports
		World Health Organization data

* Includes manufacturers, distributors, and sellers; multilateral agencies; donors, nonprofits, and philanthropies; home industries and repackaging; and itinerant drug sellers.

† Includes volume of drugs, biologics, devices, and diagnostics sold in the country; characteristics of products (e.g., parenteral versus oral); burden of disease in the country; and priority therapeutic areas in the country.

‡ Includes a legal framework for medicines regulation; a national medicines policy; dedicated financing for regulatory activity; adequate human resources and physical infrastructure; standards, guidelines, and procedures; information sharing; and regional and global regulatory harmonization.

In discussing the framework below, we use personnel or staffing resources as an example. Human resources are a critical component for medical products quality assurance for any country's MRA. Inadequate staffing, low salaries, poor work conditions, and insufficient training are critical weaknesses that can hinder the effectiveness of MRAs.

3.2   Perspective of the framework

The perspective from which this framework is conceptualized and from which it should be operationalized is that of the government through its national MRA. However, it is expected that there will be some shared responsibility with other governmental and nongovernmental organizations, such as manufacturers,

importers, wholesalers, distributors, and dispensers of pharmaceuticals, and that the framework may be conceptualized and operationalized to include these stakeholders' perspectives as well.

3.3   Country characteristics

For LMICs, pharmaceutical QA is a mandate of the government and is usually conducted through MRAs or similar bodies. MRAs regulate the manufacture, trade, and use of medicines as well as the flow of information pertaining to medicines [1]. The mandate of MRAs is to protect public health by enforcing laws and regulations that keep poor-quality medicines out of the market and to promote public health by enabling access to essential medicines. MRAs' activities in this regard may include adopting and enforcing good pharmaceutical practices and strengthening their capacity to perform dossier review, registration of priority essential medicines, and inspection of pharmaceutical premises.

For this framework, we identify only two of multiple possible characteristics of countries that are risk initiating or risk reducing with regard to substandard and falsified medicines and their potential consequences. They are (1) politics and governance and (2) border porosity. These two factors are related but not necessarily correlated. Stable governments as well as countries with weak governance structures may have porous borders.

Politics and governance

A nation's political stability and governance may affect the availability and consumption of substandard and falsified medicines and their adverse impact on public health. High-income countries are more likely to have higher governance indices and better functioning pharmaceutical legislation, regulation, and enforcement. The presence of corrupt practices and perverse incentives encourages the importation and distribution of substandard and falsified medicines and allows illicit supply chains to thrive.

Operationalization of the risk or protection conferred by politics and governance could be based on published indices (e.g., the World Bank worldwide governance indicators [14], Transparency International's corruption perception index [15], political stability indices [16]) and/or collection of primary data during the hazard identification and risk estimation steps of risk analysis.

As an example from the perspective of human resources, unstable and poorly governed countries have a net loss of skilled personnel, including key MRA personnel. The risk-mitigating or risk-initiating impact of politics and governance could be operationalized through both an index of good governance in general and estimates of personnel turnover.

Border porosity

Porous borders, defined as connections between neighboring countries through which goods and persons move without control or regulation, contribute to the presence and consumption of substandard and falsified medicines, particularly in small and landlocked countries. Porous borders have been cited as contributing to a public health crisis related to falsified and substandard medicines in the Mekong [17, 18] and adverse events in the Democratic Republic of the Congo (epidemic dystonic reaction due to falsified diazepam) [19]. The extent to which border porosity is a risk-increasing or risk-mitigating factor for falsified and substandard medicines can also be assessed during the hazard identification and hazard estimation steps of risk analysis. Data to operationalize the framework as it

pertains to border porosity may be obtained from publicly available sources. Border porosity has no obvious risk-initiating and risk-mitigating implications from the perspective of human resources.

3.4 Characteristics of the pharmaceutical market

Pharmaceutical market characteristics (Figure 1, Box A) can contribute data to identify high-risk or priority pharmaceutical products or therapeutic areas of focus for a given country. For purposes of risk analysis and resource allocation, priority products are a function of their supply and demand. It is important to consider both the supply and demand sides: pharmaceutical products for high-burden diseases may be demanded but not fully or partially supplied, and pharmaceutical products for low-burden diseases may be pervasive in the market on account of, say, lower prices, which may increase their consumption. Attributes of the pharmaceutical market also contribute data that can be used for risk identification, risk estimation, and risk ranking independent of the high-risk priority products in a given country. The supply and demand of pharmaceuticals and the different components therein as shown in Table 1 can act individually or collectively as risk-triggering or risk-mitigating factors as relates to the harms associated with falsified and substandard medicines in a given country.

The supply side

The supply side includes manufacturers, importers, wholesalers, distributors, and dispensers from a multitude of sectors (e.g., public, private, donors, nongovernmental organizations, informal markets). Medicines in any given LMIC market may come from multinational agencies such as GAVI (the Vaccine Alliance); The Global Fund to Fight AIDS, Tuberculosis and Malaria; UNITAID; other donors; and/or other nongovernmental organizations. Suppliers may be prequalified by multilateral agencies such as WHO or by individual countries. WHO prequalification through its Prequalification of Medicines program (or lack thereof) can be used as a risk-mitigating (or risk-initiating) signal.

In addition to licensed manufacturers, distributors, and dispensers, the market may include illicit industries, repackaging groups, and/or itinerant drug sellers. The attributes of the pharmaceutical market—as well as of the specific types of medical products—can provide data on risk initiation and risk mitigation, including information on the number and geographical distribution of the components of the supply chain. For instance, parenteral drugs may be assigned a higher risk-initiation priority score than oral drugs. Additionally, issues of drug resistance may affect the supply side; pharmaceuticals that are substandard or falsified contribute to the emergence of drug resistance, which in turn may increase overall risk to the supply chain.

Data for operationalizing the framework with regard to supply-side attributes may be obtained from published data, unpublished but publicly available sources, and primary qualitative and quantitative studies. From the perspective of human resources, the supply side constitutes one of the largest needs for personnel as a resource. Country MRAs spend a substantial proportion of their personnel resources to perform licensing, surveillance, and monitoring the quality and safety of medical products. Of particular importance on the supply side is that, for the majority of supply entities, delegation of regulatory tasks is not possible.

Table 2. Activities involved in risk analysis, risk management and impact assessment

Risk Analysis	Risk Management/ Resource Allocation for QA	Impact Assessment

• Risk identification
• Risk estimation
• Risk ranking/filtering
	• Pre-marketing
	  – Licensing of premises and persons
	  – Inspection
	  – Evaluation and registration
	  – Quality control testing
	• Post-marketing
	  – Product quality surveillance
	  – Safety surveillance/ pharmacovigilance
	  – Enforcement
	• Advertising and other promotion monitoring
		• Costs and cost savings
		• Health outcomes (QALYs and DALYs)
		• Cost-effectiveness
		• Sustainability
		• Safety
		• Availability

The demand side

The demand side consists of the burden of disease from the standpoint of conditions or diseases that require treatment and/or prevention. Among pharmaceuticals needed for diseases are drugs, biologics, devices, diagnostics, and dietary supplements. Pharmaceutical products for prevention include vaccines, contraceptives, and preventive barriers for sexually transmitted diseases. The nature of these products and the products themselves may provide data on risk initiation and risk mitigation.

Data for operationalizing the framework (staffing levels, for example) with regard to demand-side attributes may be obtained from published data, unpublished but publicly available sources, and primary qualitative and quantitative studies.

Priority pharmaceutical products and therapeutic areas

The framework allows for operationalizing the risk status of substandard and falsified medicines by selecting high-risk or priority pharmaceutical products, the products for which risk analysis would be conducted in a given country. It is neither practical nor advisable to allocate limited resources equally across all regulated pharmaceutical products. Data-driven knowledge of the composition patterns of the pharmaceutical market enables the selection of high-risk, priority products or therapeutic areas of focus for purposes of risk analysis and potential regulatory action. The choice of these priority products is a factor of supply (products that are available for prescription and use) and demand (products that reflect the burden of disease for which pharmaceutical products exist) in the pharmaceutical market, as well as the risk status of different products obtained through published reports of poor-quality medicines in LMICs.

The supply side's input into the selection of priority products may be independent of burden of disease, which represents the potential demand for pharmaceutical products. Some pharmaceuticals, such as chemotherapeutic agents, may be in high demand based on burden of disease but may exhibit low actual demand due to high cost or lack of health system capacity for their effective use. For certain pharmaceutical products, such as antimalarials and antibiotics, their actual demand may be closely correlated with the burden of disease.

When demand is correlated with the burden of disease, the burden of disease can be used as an input into the selection of priority products for risk analysis. For example, an analyst might select the top 10 causes of disease burden in a given country measured in DALYs. This may be followed by refinement of the disease burden into the top three therapeutic categories for quantifying risk at different sites in the medicines supply chain.

Personnel resources are important in this regard in order to assist with selection of priority pharmaceutical products and therapeutic areas or interest. This step involves such activities as obtaining estimates of disease burden, described as DALYs or QALYs and estimation of affordability and availability of medical products. These are activities that require a certain level of expertise and training.

3.5   Characteristics of the regulatory and QA environment

The regulatory and pharmaceutical QA environments in a given country are key to risk triggering or risk mitigation with regard to substandard and falsified medicines. Multiple aspects of the regulatory environment (Table 1) individually or collectively contribute to the risk of harm from substandard and falsified medicines. In general, the presence or absence of a given attribute will indicate whether the attribute is a risk initiator or a risk mitigator. For instance, the presence or absence of an effective MRA, as objectively measured by presence or absence of physical infrastructure, personnel, a dedicated budget, and a legal remit to perform regulation, may be risk mitigating and risk initiating, respectively.

Other aspects of the regulatory environment that might be considered as risk triggering or risk mitigating with regard to the regulatory and QA environment include the presence or absence of the following:[1]

- Current regulatory capabilities
- Legal framework for medicines regulation
- National medicines policy
- Dedicated financing for regulatory activities
- Sufficient human resources
- Physical infrastructure
- National medicines control laboratories
- Information technology systems and infrastructure
- Standards, specifications, guidelines and procedures (e.g., adherence to good manufacturing practice (GMP))
- Willingness to share information and information sharing agreements
- Level of participation in regional and global regulatory cooperation and harmonization

Current regulatory capabilities

An assessment of current regulatory capabilities is key to assessing the regulatory and pharmaceutical QA environment. At minimum, countries should be able to account for the medical products and

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[1] This list is not exhaustive or intended to be exhaustive.

regulated organizations involved in the supply chain within their borders. The licensure function is critical, as is surveillance and enforcement of product quality and safety. These are activities that the countries themselves must perform: no other country can perform these functions for them, and little to no information may exist elsewhere that they can rely on for decision-making. Current regulatory capabilities are likely highly correlated with current personnel capacity and, therefore, personnel would feature prominently in the operationalization of this dimension of the framework.

The national medicines regulatory agency

Virtually all LMICs have a national MRA or similar body. For a given country analysis, the risk-initiating or risk-mitigating nature of the MRA dimension would require data on attributes such as the MRA's autonomous nature (or lack thereof) and functioning level [20, 21]. Central to the operationalization of the framework as it relates to national MRAs is an analysis of the organization, constitution, resources, and personnel available to the MRA for a given country. Personnel are the key resource that determines whether an MRA exists and is effective in performing essential medicines regulatory functions.

Legal framework for medicines regulation

Relevant laws and regulations are the foundation of medical products regulation. For a given country analysis, the risk-initiating or risk-mitigating nature of the legal dimension requires data on the existence of legal provisions establishing the MRA's powers and responsibilities, legal provisions for declaring conflicts of interest, legal provisions for whistle-blowing to raise concerns about issues in the pharmaceutical sector, transparency, and legal provisions for monitoring the legal and illegal private market and the public market for pharmaceuticals (e.g., licensing and registration of facilities and people across the supply chain, compliance with GMP guidelines and good distributing practices, and control and promotion/advertising of prescription drugs) [20]. An analysis of the legal dimension from the perspective of human resources could be to assess whether laws include references to maintaining minimum staffing levels to achieve given standards of regulatory quality assurance.

National medicines policy

The risk-initiating or risk-mitigating nature of the policy dimension would need country-level data on the existence of a national medicines policy document and whether national pharmaceutical policy and guidelines are monitored and enforced. An analysis of the policy dimension from the perspective of personnel could be to assess whether the policy includes specific best practices for recruiting, maintaining, and remunerating personnel.

Dedicated financing

The risk-initiating or risk-mitigating nature of the financing dimension would need country-level data on whether the MRA receives dedicated funds from the national budget. For instance, there is evidence that less than half of a large sample of LMICs publicly funded one of the key aspects of drug regulation, namely pharmacovigilance [22]. An analysis of the financing dimension from the perspective of personnel could assess whether policies exist for allocating specific resources to personnel and whether there is a coherent and fair structure for payment and reimbursement.

Human resources

For a given country analysis, the risk-initiating or risk-mitigating nature of the human resources dimension would need data on whether the MRA has the sufficient level of qualified human resources

to perform essential regulatory tasks, including implementation of the risk-based framework. Human resource capacity is independent of the ability to pay wages; even when personnel with appropriate training are available to carry out regulatory tasks, the MRA must have a mechanism for providing sustainable funds for wages and other required resources.

Physical infrastructure

For a given country analysis, the risk-initiating or risk-mitigating nature of the physical infrastructure dimension would need data on whether the MRA has necessary facilities, working space, other capital goods, and/or other assets (such as vehicles and laboratory equipment), as appropriate. An analysis of the physical and infrastructure dimension from the perspective of personnel could be to assess whether personnel are available and trained to utilize necessary equipment related to pharmaceutical QA.

Information technology (IT) systems and infrastructure

For a given country analysis, the risk-initiating or risk-mitigating nature of the information technology dimension would need data on whether the MRA uses a computerized information management system that meets the needs for pharmaceutical QA [20]. Other IT-related attributes include the use of standardized software and systems for medicines registration and licensing as well as communication technologies. An analysis of the legal dimension from the perspective of personnel might be to assess whether IT personnel have adequate training and staffing levels are sufficient.

Standards, specifications, guidelines, and procedures

For a given country analysis, the risk-initiating or risk-mitigating nature of the standards and guidelines dimension would need data on whether the countries and their MRAs have and utilize standards and guidelines such as GMP, good distribution practices, and good pharmacy practice. An analysis of the standards and guidelines dimension from the perspective of human resources could be to assess whether standards and guidelines specify the roles and responsibilities of different types of trained personnel.

Information-sharing

For a given country analysis, the risk-initiating or risk-mitigating nature of the information-sharing dimension would need data on whether the country's MRA has information-sharing agreements with relevant agencies and stakeholders within the country, as well as whether the country or the country's MRA has bilateral or multilateral information-sharing agreements in place with other MRAs. An analysis of the information-sharing dimension from the perspective of personnel might be to assess whether the personnel structure of the MRA has adequately trained and experienced personnel to actively participate in information-sharing forums of relevance.

Regulatory harmonization

For a given country analysis, the risk-initiating or risk-mitigating nature of the harmonization dimension would need data on whether the country participates in regional and international harmonization initiatives (e.g., the International Conference on Drug Regulatory Authorities, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Pan American Network of Drug Regulatory Harmonization) and various pharmacopeias across the world. An analysis of the harmonization dimension from the perspective of human

resources could be to assess whether the MRA has adequately trained and experienced personnel to participate in harmonization initiatives.

3.6   Risk analysis

As shown in Figure 1, risk analysis is at the core of the RBA for resource allocation for pharmaceutical QA. Risk analysis involves three distinct activities: (1) risk identification, (2) risk estimation, and (3) risk scoring/risk ranking. Risk analysis uses a combination of quantitative and qualitative methods to describe risk and depict an informative risk picture [23].

Risk identification

The first step, risk identification, involves an assessment of risks (negative) and opportunities (positive), as well as an estimate of their causes and consequences [23]. In this framework, risks are defined as a direct result of the use of substandard and falsified medicines and other practices, such as the level of performance of MRAs. The consequences of these risks are ideally described in terms of their health effects of loss of QALYs or accrual of DALYs.

Risk identification involves the identification of risk triggers or causes of risk as well as risk-mitigating factors or barriers to risk. Risk-mitigating factors are attributes that exist or steps that are taken to reduce the probability of occurrence of risks. In the framework (Figure 1), the risk triggers and risk-mitigating factors are categorized as being a result of the inherent characteristics of countries (Box A) as emanating from the pharmaceutical market (Box B) and as occurring in the regulatory or QA environment (Box C). For example, if a vaccine to prevent a given disease were obtained exclusively from a UN agency known to procure all the vaccines from WHO prequalified manufacturers, this is a risk-mitigating factor. As another example, the identification of repackaged antimalarials within a given LMIC qualifies as a potential risk trigger. It should be noted that the risk triggers and risk-mitigating factors overlap in the sense that, for many of them, the presence of an attribute in, say, the regulatory regime of a given country, will be risk mitigating, while its absence will be risk triggering. For instance, the lack of a legal basis for the enforcement of good distribution standards in a given country is a risk trigger for vaccines requiring a cold chain, while the presence of a legal basis for such standards is a risk-mitigating factor.

Risk identification uses multiple data sources to elicit information on a broad range of factors, system concepts, and other information pertinent to risk analysis. Risk identification is a process of identifying and listing risk triggers and risk-mitigating factors as possibilities independent from the probability or likelihood of their causing harm. The aim is to generate a list of factors that contribute to or initiate risk, including objective and quantitatively supported factors, as well as more subjective factors, such as whether practitioners think that a given medicine is more likely to be repackaged or overprescribed or misused. The result of risk identification is a listing of multiple quantitative and qualitative risk triggers and risk-mitigating factors arranged in order of importance [10].

To operationalize risk identification, analysts within countries' MRAs might perform a survey among key experts—including regulators, prescribers, pharmacists, and other policymakers—to elicit a listing of risk-initiating and risk-mitigating factors as they relate to a given medicines category. The survey (or other means of obtaining input) could focus on the extent to which different attributes of the nation's regulatory and legal environment and pharmaceutical market act to trigger or mitigate the risk of

consumption of substandard and falsified medicines. Other ways of obtaining necessary information for risk identification include the use of focus groups and data from a variety of preexisting sources, such as published literature and relevant field reports of poor-quality medicines.

Risk estimation

During risk estimation, estimates are calculated for the magnitude of each risk on the list of risks generated during risk identification. Risk estimation can be performed using methods that allow for estimation of probabilities of adverse events of a given severity conditional upon the existence of the risk. For example, an analyst might have access to estimates on the probability that people with malaria receive a substandard antimalarial medicine in a district located near a porous international border.

Existing methods of risk estimation include probabilistic risk analysis (which may be performed by fault trees, event trees, or frequency and probability estimation), failure mode and effects analysis, and surveys of experts [10]. Decision tree modeling, a method of probabilistic analysis, can be used to identify drug-related risks (given their severity) and their likelihood of occurrence [3]. Given that traditional decision tree modeling is constrained to having a choice to make, individual country analyses can be configured as choices among categories of regulatory spending or levels of spending within categories.

Risk ranking and filtering

The combination of probabilities of risks and priority risk triggers and risk-mitigating factors is used for risk ranking, also referred to as risk filtering [24]. Risk ranking seeks to scale or filter the list commensurately with available resources for risk management, in this instance for regulatory and other QA activities. When adequate resources are available, risk ranking addresses the highest priority risks first. However, in limited resource settings, as we would expect in LMICs, it is likely that the country MRA and other stakeholders will be unable to mitigate all the risks on the list, and a prioritization process will need to be established and followed.

3.7 Risk management: resource allocation for regulatory activity

Risk management

Risk management refers to the measures and activities that are conducted to manage risk. This involves a balance of opportunities or benefits on the one hand and losses or costs on the other hand [23]. Risk management by MRAs is performed by use of different financial and non-financial resources, including trained personnel. These resources are targeted at different regulatory activities according to the needs and priorities identified during risk analysis.

Premarketing regulatory activity

Regulatory activities can be divided into premarketing and post-marketing activities. Premarketing activities include licensing of premises and persons, inspection, evaluation and registration, and quality control testing (although quality control testing can also occur in the post-marketing period). These premarketing activities are central to ensuring that individual medicines licensed and registered in given countries are efficacious, safe, and of high quality [1]. Licensing also ensures that the information needed for use of the medicines is available and usable by clinicians [1]. Although many countries insist on the right to conduct licensing for each individual product regardless of resource requirements and the potential for public health benefit on account of sovereignty, there is potential

for mutual country benefit in the use of regional or bilateral approaches to regulatory harmonization and information sharing.

Post-marketing regulatory activity

In the post-marketing phase, regulatory activities include medicines quality monitoring and surveillance, pharmacovigilance, enforcement of pharmaceutical laws and regulations, and monitoring and enforcement of drug promotion and advertisements. Quality surveillance includes screening and testing of medicines, laboratory inspections, and the operation of both regional and central quality control laboratories. Portable technologies are used in field settings (e.g., ports of entry, healthcare settings, or locations in rural towns), and they complement laboratory-based technologies. Post-marketing quality surveillance can be performed using risk-based methods, and guidelines have been developed for this [25].

Pharmacovigilance activities are a mandate of MRAs and should involve continuous post-marketing safety surveillance of medicines. In many countries, the MRA also has the mandate of monitoring the advertising of medicines.

Mapping risks to resource allocation

As shown in Figure 2 (Appendix 1) and Table 2, the dimensions of regulatory action, which include different pre- and post-marketing activities, are the pathways through which risk management is performed for targeted allocation of resources. Although risk management is organized by activity in the framework, many of the necessary resources, whether available or unavailable, act as risk initiating or risk mitigating and therefore also provide data for risk analysis. This is the reason why the arrow runs from risk management (Box E) back to risk analysis (Box D) in Figure 1 and Figure 2 (Appendix 1). The analysis is aimed at quantifying the extent to which the presence, absence, or level of resources are risk initiating or risk mitigating. During resource allocation, resources are targeted to activities of the highest priority given the priority ranking generated from the risk analysis process, independent of whether a given resource provided input into the risk analysis.

To align priorities as identified during risk analysis, policymakers must map them to different areas of regulatory action and spending. For a given set of priority medicines, risk ranking can produce a list that can be mapped to regulatory action through a consultative process with stakeholders at the MRA. This process includes an appraisal of different available resources—financial, physical and infrastructure, human resource, and technical—and deciding how to eliminate, substitute, or supplement different activities.

As an example, a given MRA might generate a list of risk triggers after risk ranking that does not include attributes related to premarket licensing and registration because the majority of the commodities identified are from WHO prequalified manufacturers. This suggests that staffing and other resources may be shifted from premarketing activities to post-marketing activities. Stakeholders could go through a similar appraisal and resource allocation process for post-marketing activities.

3.8   Evaluation of the impact of regulatory resource allocation

The RBA for resource allocation for pharmaceutical QA is proposed as an ongoing process that needs to be flexible in its response and adaptation to the changing risk environment and pharmaceutical

market. Critical to its ability to adapt is the ongoing evaluation of the impact of regulatory activities as they relate to regulatory resource allocation. The metrics of impact include costs, health outcomes, efficiency, and other outcomes.

Costs and cost savings associated with regulatory activities

The costs of providing regulatory activities can be tracked at the MRA by developing and maintaining an inventory of types and volume of resources used as well as their unit costs. The costs of regulatory activity from the perspective of the regulator may be available at the MRA level. However, the costs of regulatory activity from the perspective of society overall should be offset to some degree by the cost savings from the prevention of risk (i.e., prevention of medicine-related problems) [3]. These include costs of outpatient visits and hospitalization. Costs of outpatient visits and hospitalization for medicine-related problems include direct medical costs (e.g., health workers' time, other medications or antidotes, and laboratory tests), direct nonmedical costs (e.g., patient transportation and upkeep), and indirect costs (e.g., opportunity cost of lost productivity during illnesses and convalescence related to medicines' adverse events).

Health outcomes

Health outcomes can be estimated by using commonly accepted metrics, such as QALYs or DALYs. As described in section 1.2, DALYs and QALYs allow comparison of interventions across the health sector.

Cost-effectiveness

Cost-effectiveness arises when benefits (QALYs) are maximized or DALYs are minimized and opportunity costs are minimized for a given level of activity. Cost-effectiveness could be achieved if the RBA for resource allocation for pharmaceutical QA is at least as effective as before a RBA was implemented but is less costly. If the RBA for resource allocation for QA led to cost increases, the assessment of cost-effectiveness would include a valuation of whether the extra cost is worth the extra benefit.

Sustainability

Sustainability is a key issue for pharmaceutical QA in LMICs and can be considered as a dynamic efficiency, i.e., efficiency sustained over long time periods.

Assessment of other pharmaceutical outcomes

We use the term pharmaceutical outcomes to refer to overall pharmaceutical effectiveness, safety, quality, and availability within a given country. It is through these outcomes that an RBA to resource allocation for pharmaceutical QA can have broader impacts on public health, including such important but intangible benefits as restoring or maintaining public trust in health systems.

4.   Discussion

Pharmaceutical quality assurance is an ongoing endeavor for LMICs. The callout boxes below present some examples of ongoing pharmaceutical QA activities designed to mitigate the risk of consumption of falsified and substandard medicines. We also present some examples of how an RBA for resource allocation for pharmaceutical QA might operate in an LMIC, as well as some limitations of the framework for an RBA to resource allocation for pharmaceutical QA.

> **Examples of reducing the availability of falsified and substandard medicines in sub-Saharan Africa [26]**
>
> - In partnership with the USP PQM program, the Ghana Food and Drug Administration performed medicines quality monitoring (MQM) of uterotonics, leading to the destruction of falsified and substandard products in various health centers.
> - In partnership with the USP PQM program, the Kenya Pharmacy and Poisons Board performed MQM of antimalarial medicines, which led to the jailing of sellers of falsified and substandard products, recall of poor-quality products, and destruction of expired products.
> - The USP PQM program also supports MRAs in Mali and Senegal to perform MQM for anti-malarial medicines and increase their capacity for both MQM and medicines regulation in general.

4.1   Example of potential effects of a risk-based approach to allocation of resources at a country medicines regulatory agency

Potential effects of a risk-based approach to resource allocation for personnel at an MRA

As an example, consider a given MRA in an LMIC whose mandate includes performing premarket licensing, inspection, and evaluation of foreign manufacturers of pharmaceuticals. The MRA, insisting on its sovereign right to assess each individual manufacturer, allocates 50 percent of its annual personnel full-time equivalents (FTE) on inspections of foreign facilities.

Upon using an RBA for resource allocation for personnel, it is discovered that the majority of facilities inspected by the personnel at the MRA have previously been inspected by other MRAs in the region or by those in high-income countries and found to be of sufficient quality to pass inspections. The facilities that have previously been inspected are, therefore, deemed to pose minimal risk to patients in the LMIC.

As a result of the RBA for resource allocation, MRA leadership decides to enter into agreements with regional and selected high-income country MRAs to share results of facility inspections in a commonly accessible database and to conduct inspections of facilities only when they do not appear in this database.

During the subsequent fiscal year, the percentage of FTE dedicated to foreign facility inspections reduces by half to 25% FTE and the other 25% FTE of the original 50% FTE is now redirected to priority post-marketing activities such as field-based quality of medicines surveillance and enforcement.

Potential effects of a risk-based approach to resource allocation for pharmaceutical quality evaluation at an MRA

Consider a given MRA in an LMIC with a mandate to assess the quality of vaccines imported into its country by performing laboratory-based testing on vaccine batches. This approach is determined to be costly and time consuming.

MRA leadership decides to utilize an RBA for allocating an appropriate level of resources to the quality control laboratory. The analysis reveals that the manufacturers of all vaccines imported into that country are designated as WHO prequalified and pose minimal risk to people in that country. Therefore, a full quality control analysis is performed only on vaccines that are imported from manufacturers that are not WHO prequalified. For vaccines imported from WHO prequalified manufacturers, the head of the MRA commissions a local expert to assess only the vaccines' thermostability for use in the tropical weather setting.

4.2 Operationalizing the framework

Building on previous work in which analysts proceeded from a proposed framework to performing a primary analysis [3, 27], we propose to operationalize multiple aspects of the framework in selected countries as a way to demonstrate the potential utility of the framework as a country-level resource allocation tool. Such activities could be the precursor of the development, ultimately, of a web-based tool for use by country MRAs in LMICs to allocate resources using an RBA.

4.3 Limitations

This framework for a risk-based approach for resource allocation for pharmaceutical quality assurance was designed to be broad and covers multiple aspects of pharmaceutical quality assurance. This means that it would be challenging to operationalize as a complete framework in actual practice. Our proposed approach to operationalization is that it can be adopted "piecemeal" to identify components of the framework that can be subjected to field analysis as a step toward understanding the potential utility and applicability of the complete framework.

Examples of pharmaceutical quality assurance activities in LMICs [28]

- In 2016, the USP PQM program supported Nigerian manufacturers of oral rehydration salts, zinc sulfate, and chlorhexidine digluconate gel. The manufacturers subsequently supplied quality-assured products in Nigeria and around the region.

- In 2016, the USP PQM program enhanced Liberia's ability to monitor medicines quality at sentinel sites, ports, and other places using Minilab™ technology.

- The USP PQM program supported the Ethiopian Food, Medicine and Health Care Administration and Control Authority to ensure that condoms used in the country were of adequate quality.

5.   Summary

We herein present a framework for risk-based resource allocation for pharmaceutical QA in LMICs. This framework is proposed as a resource allocation tool, anchored by risk analysis, i.e., the assessment of risks within the pharmaceutical sector and their causes and consequences. The framework is operationalized by identifying risk-triggering and risk-mitigating factors using (1) attributes of the country itself, (2) attributes of the regulatory and legal environment for medicines within the country, and (3) attributes of the pharmaceutical market. The pharmaceutical market, in particular, informs the identification of high-risk priority products for risk analysis and regulatory spending. Regulatory spending is guided by a ranking of specific risks inherent within a given market as identified during risk analysis. Targeted regulatory spending can lead to better system-wide impact, including potential cost savings, improved health outcomes, system efficiency and cost-effectiveness, and a greater likelihood of availability of effective, safe, and high-quality medicines within the country. Continuous assessment of the impact of regulatory spending allows the RBA for resource allocation for pharmaceutical QA to respond to changes in the risk environment and pharmaceutical market, thereby improving and maintaining public health as well as promoting public confidence in the health system.

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Annex 1: Framework

Figure 2. A framework for risk-based pharmaceutical QA for MRAs in LMICs showing subcategories and attributes