A MIXED-METHODS FRAMEWORK USING FRAGMENTATION TO ESTABLISH SAMPLING FEASIBILITY OF PHARMACEUTICALS

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ABSTRACT

Substandard and falsified pharmaceuticals substantially increase levels of morbidity, mortality and drug resistance. These problems are most urgent in low- and middle-income countries. In the face of sophisticated counterfeiters, poor international coordination of global supply chains, and limited detection resources, pharmaceutical regulatory agencies in these countries require cost-efficient and systematic approaches to identify and act against substandard and falsified pharmaceuticals.

Existing research has identified critical shortcomings in current surveillance. This paper proposes an iterative, mixed-methods framework that accounts for various factors of the regulatory environment and provides regulatory agencies with guidelines that can help focus limited sampling budgets more effectively. We demonstrate how knowledge of the patterns of substandard and falsified pharmaceuticals affects sampling budget requirements and enables tailoring of sampling plans. The suggested framework leverages risk differences by subdivisions of a pharmaceutical market (referred to here as fragments) to assess if feasible sampling policies exist and how policies can be efficiently tailored. Our work synthesizes existing models and guidelines with local stakeholder knowledge towards a more efficient deployment of valuable sampling resources. A case study applying this framework with the collaboration of the regulatory agency of Liberia is discussed.

***K*eywords** pharmaceutical supply chains · substandard and falsified medicines · mixed methods

1 Introduction

Substandard and falsified pharmaceuticals (SFPs) affect the treatment of a large number of diseases around the world. According to the World Health Organization (WHO), the level of SFPs for particular medical products on the market in different countries ranges from as low as one percent to as high as fifty percent (WHO, 2006). Low- and middle-income countries (LMICs) bear the brunt of these dangerous medicines: at least one in ten medical products in LMICs is estimated to be an SFP (WHO, 2018). According to a review of the literature surrounding SFP products (Karunamoorthi, 2014): "WHO estimates that fake anti-malarials cause up to 20% (200,000 people) of the one million malaria deaths worldwide each year. A recent International Policy Network study estimates the actual burden could lead to 450,000 preventable deaths every year." In addition to causing elevated morbidity and mortality, SFPs are also a key driver of the increasing threat of antibiotic resistance (WHO, 2017a) as well a contributor to the lack of public confidence in public health systems (Cockburn et al., 2005).

Although original producers are sometimes culpable in pushing substandard products to markets, it is believed by the United Nations Interregional Crime and Justice Research Institute (UNICRI) that many falsified pharmaceuticals enter the global supply chain during the procurement, repackaging and reselling operations of intermediary suppliers located throughout the world. Products often experience multiple turns of repackaging iterations – often on the order of twenty to thirty – before arriving at their ultimate distribution points (UNICRI, 2012). During these repackaging iterations, serial numbers are reprinted, making definitive package tracing very difficult, and the original packaging is not always destroyed, leading to further falsification opportunities. Additionally, regardless of origin, these falsified products are often impossible to discern from their authentic counterparts via packaging inspection alone. The falsification of Avastin in 2011, at that time a common cancer treatment, emphasizes the fact that no brand of pharmaceutical is immune to falsification and illustrates the sophistication of falsifier operations (Blair, 2012). Newton et al. (2011) documented a wide array of cases where falsified products were manufactured across the globe using a variety of active pharmaceutical ingredient (API) substitutes. Furthermore, falsifiers went to extreme lengths to fabricate packaging and labeling nearly identical to that of the original manufacturers and regulatory agencies. A WHO report encapsulated the complexity inherent in the modern global supply chain (WHO, 2017b):

> Nowadays, a tablet taken in Germany may be made in Egypt from ingredients imported from India, Brazil and Spain, packaged in foil that came from China, inserted into a box designed for the United Kingdom of Great Britain and Northern Ireland, and shipped to Liverpool by way of Dubai. A trader in the United Kingdom, taking advantage of fluctuations in the foreign exchange rate, might legally repackage the medicines with information written in German and ship it to Munich.

In contrast with attempting to discern falsified products via visual diagnosis, chemical screening technologies are essential for distinguishing authentic pharmaceuticals from their imitators as well as determining if products have degraded to an unacceptable level. Chemical screening tools analyze the reactions of a medicine with reagents to determine if sufficient active pharmaceutical ingredients, or APIs, are present in the sample. Various screening techniques offer different levels of information concerning the detected levels of API. In their review of tools and technologies available for detecting SFPs in LMICs, Kovacs et al. (2014) described paper chromatography and other portable laboratory tools such as PharmaCheck and GPHF-MiniLab as the most cost-effective chemical screening devices available.

Low-cost detection devices have high potential to be effective tools in thwarting SFP propagation in low-resource LMICs. The ideas presented in this work were initiated through a collaboration with a chemistry team at the University of Notre Dame that has been working on paper chromatography for SFP detection. Their paper chromatography tool, also known as a paper analytical device or PAD, has a reported sensitivity of 92-100%, a reported specificity of 88-100%, can cost less than $0.50 to manufacture, and is equipped to detect many of the common fillers utilized by falsifiers, like talcum, chalk, or paracetamol (Weaver et al., 2013).

This paper presents the approach developed by operations researchers and in-country regulatory professionals to implement the PADs in an LMIC context. Given our focus on resource-limited countries, we consider contexts where national medicines regulatory authorities (NMRAs) make decisions regarding the deployment of low-cost SFP detection devices under stringent budgetary constraints. These constraints may reflect a limited number of devices or a limited ability to procure samples throughout the supply chain. Additionally, we focus on a decentralized quality-assurance structure: inexpensive mobile screening tools are distributed at various points in the national pharmaceutical supply chain, and products flagged as SFP suspects are sent to one of a small number of centralized locations for confirmatory diagnosis.

Effective deployment of these innovative detection tools in LMICs poses a challenge from an operations research perspective. SFPs are seemingly everywhere, yet detecting and disrupting the flow of these products is made difficult by the complexity of global supply chains. Obtaining statistical confidence through the general use of these devices in random sampling requires substantial commitments of operational and budgetary resources that are often in short supply in LMICs. A 2017 WHO report contains a key insight into the realization of SFPs that offers hope in attempting to further refine sampling policies (WHO, 2017a):

> Substandard and falsified medical products are likely to be unevenly distributed across therapeutic categories and geographical regions. They tend to cluster in areas or situations where risk factors that favor the manufacture or sale of such products are high.

Knowledge of the characteristics of SFP distributions is crucial in maximizing the effectiveness of limited resources, as stressed in a Promoting the Quality of Medicines (PQM) Program report (Nkansah et al., 2017).

The goal of this work is to develop a mixed-methods framework that synthesizes the capabilities of low-cost detection devices with the limited resource availability of many LMICs towards minimizing the effect of SFPs. This work bridges the operational gap between a novel and useful technological device and the implementation of this device under severe budgetary constraints. We introduce a mixed-methods approach to inform the sampling processes of NMRAs of LMICs who face the combined challenge of high levels of SFPs as well as limited resources to detect such products. Whether the use of such low-cost detection tools can feasibly be used to identify SFPs under a particular pharmaceutical environment is a critical first step in developing a sampling process. Furthermore, knowledge of distributed SFP risk throughout different areas of the supply chain is crucial in strategically allocating valuable testing resources, and stakeholders are an essential resource in defining this knowledge. This paper describes a mixed-methods process of asking and testing questions regarding the prevalence of SFPs, and demonstrates the implementation of this process with a case study in Liberia.

We consider how data from sampling throughout a supply chain, coupled with qualitative insights from stakeholders, can be tailored to account for underlying risk and maximize the efficient use of valuable resources. Throughout this paper, we use stylized examples to illustrate core concepts that can be extended to the settings of particular countries. The intent of using these simplified settings is to emphasize the key ideas of the mixed-methods approach without venturing into statistical intricacies that might distract from the overall approach. We then conclude this work with a description of an application of our approach currently being undertaken through a collaboration with the Liberia Medical and Health Products Regulatory Authority (LMHRA).

2 Related literature

The past twenty years have seen a greatly heightened interest in the problem of SFPs (Nayyar et al., 2015). Similarly, resource scarcity in global health applications has been attracting increasing interest in the field of operations research. The work presented in this paper fits within two areas: (1) substandard and falsified pharmaceuticals and (2) mixed-methods approaches in operations research. In this section, we review the related literature and highlight the specific context of our study within the intersection of these areas.

2.1 Substandard and falsified pharmaceuticals

An extensive body of work exists concerning SFP studies conducted within a particular country or subset of countries. Ozawa et al. (2018) completed one of the most recent surveys of this body of work, including breakdowns by region, pharmaceutical, and methodology for 265 identified studies of SFPs. The WHO released a pair of reports in 2017 that are fundamental descriptions of the SFP problem as it exists, as well as the mechanisms currently being utilized to combat SFPs (WHO, 2017a; WHO, 2017b). Despite the acknowledgement that SFPs constitute a significant proportion of LMIC markets, significant hurdles exist in the implementation of a successful testing policy. As described by WHO, many NMRAs face a subset of the following challenges: overstretched regulatory frameworks, poorly established reporting cultures, weak responses to SFP incidents, and a "buyer beware" status quo stemming from a low level of

international coordination. Rather than monitor pharmaceutical products at the points of distribution, NMRAs are required to ensure on their own that all internationally and domestically produced products are of good quality and that this quality is guaranteed throughout all echelons of the national distribution network. As noted in Pisani et al. (2019), the goal in many cases is to decrease the profit margins realized by those benefiting from SFPs so that the tendency to do so is decreased. The resulting operational capacity needed to carry out these tasks often far outstrips the regulatory resources available to do so.

Sophisticated technologies such as track-and-trace (Rotunno et al., 2014) and blockchain methods (Sylim et al., 2018) have been introduced or developed to fight SFPs. However, it is not clear if or when LMICs will utilize or have access to these technologies, and as stated by the WHO: "regulatory structures must adapt to existing realities" (WHO, 2017b). Newton et al. (2009) offer ideas for sampling pharmaceutical outlets based on the principles of lot-quality assurance sampling (LQAS). To "facilitate transparent, consistent, and accurate reporting," they suggest a standardized checklist of reporting guidelines for sampling studies of SFPs, known as Medicine Quality Assessment Reporting Guidelines (MEDQUARG). They note that randomized sampling surveys can be stratified by geographic or socioeconomic variables; however, stratification results in a high number of samples required to achieve a high significance level. They describe LQAS as able to determine whether the prevalence of poor-quality medicines or outlets "exceeds a certain threshold," acting as an economical step before moving to fully randomized surveys of a particular region or stratum. In this work, we illustrate that in the presence of restricted sampling budgets, the levels of stratification are crucial in determining the feasibility of sampling plans for detecting SFPs. A PQM report discusses the implementation of a risk-based post-market surveillance program for pharmaceuticals quality assurance in LMICs (Nkansah et al., 2017). They present guidelines for planning a yearly iterative sampling plan that is based on country-specific objectives and sampling capacities. Similar to their identification of the need for approaches tailored to country-specific risk profiles, we define the concept of *fragmentation* to describe leveraging uneven SFP probabilities and tailoring sampling approaches to reflect these underlying risks. We extend the ideas presented in Newton et al. (2009) and Nkansah et al. (2017) to thresholds that can be calculated *a priori* as a function of the regulatory context and resource constraints faced by the NMRA. We propose a dynamic approach to sampling where ongoing switching can be incorporated to maximize limited budgets and enable NMRAs to address their multiple challenges more effectively.

2.2 Mixed-methods approaches in operations research

As NMRAs often face complex environments with limited data on system performance, the value of qualitative insights might drive future strategies such as mixed-methods research (Creswell, 1998). Mixed methods systematically integrate quantitative and qualitative methods to obtain a deeper understanding of a certain phenomenon (Johnson et al., 2007). Golicic et al. (2005) describe a mixed-methods approach to supply chain management with a focus on logistical administration. As they stated, qualitative information is highly essential to achieve a deep understanding of complex supply chains. Further issues that arise from the theory built from the qualitative data can then be addressed through quantitative models. With an analogous goal of building stakeholder theories within dynamic environments, Dubey et al. (2015) use a mixed-methods approach in the context of green supply chain management.

From an operations research perspective, the prevalence of large sets of nearly instantly available data has driven significant developments in online experimentation methods (Burtini et al., 2015). However, within the context of

pharmaceutical regulation in LMICs, extensive amounts of real-time data are often unavailable. This quantitative information gap necessitates the use of expert and stakeholder knowledge. The need for integration of operations research techniques with applicability to real-world settings has been highlighted (Besiou et al., 2018), and this type of integration has been performed with success in similar settings. Gralla et al. (2013) utilize expert preference surveys to develop objective functions for the optimal distribution of humanitarian assistance. Tucker et al. (2020) generate pharmaceutical supply disruption models that provide a basis on which to evaluate different decision-maker policies.

Our work defines a mixed-methods scheme in developing effective sampling plans towards combating SFPs in LMICs. The mixed-methods framework presented in this paper iteratively cycles between qualitative stakeholder information and quantitative sampling policies that account for limited sampling budgets. The resulting policies include sampling plans that are dynamically updated as more information about SFP tendencies is obtained. For instance, an NMRA may realize upon sufficient data collection that the testing of a particular set of products or within a particular region may be an inefficient or ineffective use of resources, and decide to switch to testing a different product type or products within a different area.

The rest of this paper is organized as follows. Section 3 explores how sampling budgets, structures of SFP patterns, and temporal aspects to pharmaceutical regulation can drive the feasibility of testing strategies, i.e., whether required sampling levels exceed a given budget. In Section 4, we illustrate how these ideas can be synthesized into an overarching framework that allows NMRAs to adaptively allocate limited sampling resources as a function of the regulatory environment and the realization of SFPs in their particular setting. Section 5 describes an ongoing case study that applies this framework to the setting in Liberia. We conclude in Section 6 with a discussion of next steps.

3 Feasibility and fragmentation

Two central concepts behind our work are the principles of *feasibility* and *fragmentation*. With a given set of conditions and resource constraints, sampling plan feasibility denotes the possibility, with statistical confidence, that the sampling plan will provide sufficient actionable information about SFPs in order to launch an effective response. Fragmentation refers to the ways in which the market can be partitioned to create clusters with similar characteristics related to the risk of SFPs. These factors can include pharmaceutical class, geographic division, manufacturer, and supply chain echelons and branches, among others, as in the WHO and PQM reports (WHO, 2017b; Nkansah et al., 2017). In Section 3.1, we demonstrate the concept of feasibility with respect to different levels of brands, sampling budgets, and temporal constraints. Section 3.2 explores the concept of fragmentation and its implications for feasibility and sampling policy design.

3.1 Sampling feasibility

Sampling plans can be rendered infeasible in a multitude of ways. In Sections 3.1.1 and 3.1.2 we discuss the concept of feasibility relative to sampling budgets and temporal requirements, respectively.

3.1.1 Feasibility with respect to sampling budgets

We begin with a stylized setting to illustrate feasibility with respect to sampling budgets. Suppose it is known that falsifiers only possess the operational capacity to convincingly reproduce the packaging and tablets of the brand of a

single manufacturer of a particular pharmaceutical. The NMRA wishes to ensure that the sampling budget allocated to testing this pharmaceutical is sufficiently large to be confident that the falsified brand is detected. Additionally, for the simplicity of illustration, make the following assumptions: 1) The NMRA can randomly sample from each manufacturer's brand of this pharmaceutical without biases of convenience of access, revealing to stakeholders they are conducting sampling, etc. 2) The screening tool being utilized by the NMRA has perfect sensitivity and specificity. 3) Each manufacturer's brand has an equal chance of being the falsified brand.

Let K be the set of brands of a given pharmaceutical product. Suppose some $\hat{k} \in K$ is the brand number being falsified at a rate $\hat{p}$, so that proportion $\hat{p}$ of product $\hat{k}$ available on the market is falsified. Let n be the number of samples required of each brand $k \in K$ to attain $(1-\alpha)$ confidence that $\hat{k}$ is detected. Observe that although only one brand is being falsified, every brand needs to be similarly sampled to find the falsified brand. Assuming $n \cdot \hat{p} \geq 5$, $n \cdot (1-\hat{p}) \geq 5$ permits us to use the normal approximation of the binomial distribution to calculate n as:

$$n \geq \frac{(\Phi_{1-\alpha}^{-1})^2(1-\hat{p})}{\hat{p}} \tag{1}$$

where $\Phi_{1-\alpha}^{-1}$ is the inverse cumulative standard normal distribution value at the $(1-\alpha)\%$ level. The total required sampling budget for this pharmaceutical, B, is then a function of $\hat{p}$ and K, and can be calculated as:

$$B(\hat{p}, K) = \sum_{k \in K} n = |K| \left\lceil \frac{(\Phi_{1-\alpha}^{-1})^2(1-\hat{p})}{\hat{p}} \right\rceil \tag{2}$$

where the ceiling operator ensures that the number of required samples is integer-valued. We refer to (2) as the *Budgetary Base Model*. Note that $B(\hat{p}, K)$ increases linearly in $|K|$, the number of brands, and decreases non-linearly in $\hat{p}$, the proportion of brand $\hat{k}$ that is falsified. While this is a simplified model, it illustrates basic relationships in setting budgets: budgets must be larger with more brands and lower rates of falsification. Table 1 shows how quickly the budget increases with these parameters. For example, with $|K| = 10$, a drop in the falsification rate from 30% to 20% increases the budget from 64 to 109 samples (a change of 45), but a drop from 10% to 1% increase the budget from 244 to $2,679$ samples (a change of $2,435$). Conversely, changes in the number of brands, $|K|$, from 10 to 20 results in a doubling of the budget regardless of the underlying $\hat{p}$. Crucially, $\hat{p}$ is more difficult to estimate than the typically accessible $|K|$, so establishing a correct sampling budget poses challenges. When the simplifying assumptions of this stylized example are relaxed, such as incorporating imperfect screening capacity or interacting factors, the challenges become more pronounced.

Now consider a situation where the budget for sampling is fixed – a common occurrence in many resource-limited settings. Assuming the number of pharmaceutical brands available on the market is known in our stylized setting, the decision becomes: "Is $\hat{p}$ sufficiently high such that it is *feasible* for our budget of B to detect the falsified brand with $(1-\alpha)$ confidence?" For a set sampling budget, the NMRA can complete the inverse of the Budgetary Base Model calculations to determine the $\hat{p}$ threshold below which testing cannot detect falsified brands with the required confidence. (An example of this scenario is given in Section 3.2.) Acknowledging that the testing of certain products or sectors may not contain a feasible sampling plan permits the NMRA to focus its budget on sampling other pharmaceuticals or other activities that improve the quality of the pharmaceutical supply, rather than conduct exceedingly expensive testing.

		$\hat{p}$						
		1%	***5%***	***10%***	***20%***	***30%***	***40%***	***50%***
$\|K\|$	***5***	1,340	258	122	55	32	21	14
	10	2,679	515	244	109	64	41	28
	20	5,357	1,029	487	217	127	82	55
	50	13,393	2,571	1,218	542	316	203	136
	100	26,785	5,141	2,435	1,083	632	406	271

Table 1: *Minimum sample requirements (B) for $(1-\alpha) = 95\%$ confidence of detection of one falsified brand of a pharmaceutical product using the Budgetary Base Model, as a function of the number of brands ($|K|$) and the underlying falsification rate of the affected brand ($\hat{p}$)*

In practice, it is unrealistic that each brand should have an equal chance of being falsified. Falsifiers orient their operations towards maximizing profit (Pisani et al., 2019), so brands or pharmaceuticals capturing larger market shares or charging higher prices will often experience an upwards push in their falsification rates. Knowledge of which brands are more likely to result in SFPs can be leveraged to reduce sampling levels by not sampling brands with lower risk.

3.1.2 Feasibility with respect to time

One of the prime objectives for an NMRA in conducting post-market surveillance is to recall any batches of products found to be falsified, substandard, or otherwise unfit for public consumption. If, by the time a recall has been issued, the public has already consumed most or all of these unsuitable products, however, the resulting positive impact of the recall on public health will be quite limited. Since significant resources are typically required to complete sufficient testing and identify particular batches for recall, it is crucial that NMRAs factor the time required to conduct a recall action, as well as the public's rate of consumption, into their feasibility assessments.

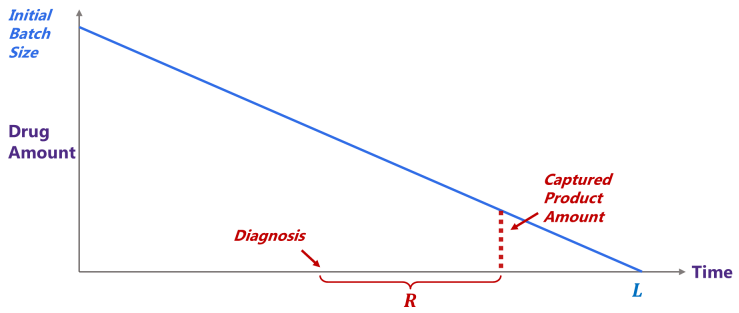

Figure 1: *The feasibility and ultimate efficacy of NMRA recall actions is strongly dependent on the consumption rates of medicines (L) and the speed with which the NMRA can act (R).*

As an extension of the Budgetary Base Model, consider a sampling situation where an NMRA has already ascertained its $\hat{p}$ threshold and possesses a sampling budget, B, sufficient to retain $(1-\alpha)$ confidence that it will

detect an SFP of a given product. Figure 1 depicts a situation where pharmaceuticals are consumed at a constant rate upon the instant the batch is introduced into the market, defined as $t = 0$. Let L be the total time until all doses of a batch are fully consumed. We refer to this batch consumption period as our *Time Allowance*. Let R be the length of time required to conduct a recall of a batch of medicines once the batch is diagnosed by the NMRA as being unfit for public consumption. Clearly, if the point in time where the batch is diagnosed as unfit is greater than $L - R$, the Time Allowance remaining is insufficient to withhold even one dose of falsified product from the market. Conversely, a shorter recall period R, and earlier diagnosis of unsuitability relative to the introduction of the product to the market, results in a higher amount of captured doses. NMRA cognizance of this reality, including efforts to streamline recall actions and calibrate sampling with the introduction of new batches of medicines into the market, minimizes the ultimate impact of these bad products on consumers.

Shifting the mindset around pharmaceutical quality towards the feasibility of sampling policies gives NMRAs a quantifiable budgetary argument based on SFP rate thresholds, available screening capacity, and time frames for ensuring effective regulatory action. In the next section, we discuss the concept of fragmentation and how fragmentation knowledge can be leveraged towards establish feasible sampling plans.

3.2 Market fragmentation

Despite the knowledge that SFPs are rampant throughout LMICs, the overall numbers of reported cases remain low relative to the scale of the issue. Identifying a batch of substandard or falsified medicines resembles a "needle-in-a-haystack" problem requiring an efficient deployment of what are often small sampling budgets. These sampling budgets then preclude the general use of machine-learning techniques, as these techniques often require large amounts of data. The 2017 WHO report contains a key insight into the realization of substandard and falsified medicines that offers hope in attempting to further refine sampling policies (WHO, 2017a): "Substandard and falsified medical products are likely to be unevenly distributed across therapeutic categories and geographical regions. They tend to cluster in areas or situations where risk factors that favor the manufacture or sale of such products are high." This insight is emphasized by the work of Pisani et al. (2019) and Nkansah et al. (2017). We refer to the ways that these clusters of risk with similar traits can be formed as fragmentation. Fragmentation can manifest in a variety of ways, such as rural versus urban pharmacy location, domestic versus international product procurement, or geographic divisions (e.g., mountains) that prompt outlets on either side of the division to procure from different sources or carry different types of medical products. For other forms of fragmentation, such as different brands of a particular medicine or different pharmaceutical outlets within an otherwise homogeneous region, we may suspect differences in SFP prevalence, but there might be no clear reason to suspect one specific brand or outlet more than another.

Figure 2 provides an abstraction of a process that splits the overall pool of medicines on a fragmentary basis in order to enable a higher probability of SFP detection. The light circles indicate safe pharmaceuticals, while the larger bold dots depict SFPs. As quantitative and qualitative information regarding the fragments is learned, NMRAs can generate partitions of the overall population - depicted as the solid lines - to isolate fragments with very different SFP rates. Per the Budgetary Base Model, as a result of a much higher $\hat{p}$, testing within these fragments requires lower sampling budgets and translates to larger overall sampling capacity.

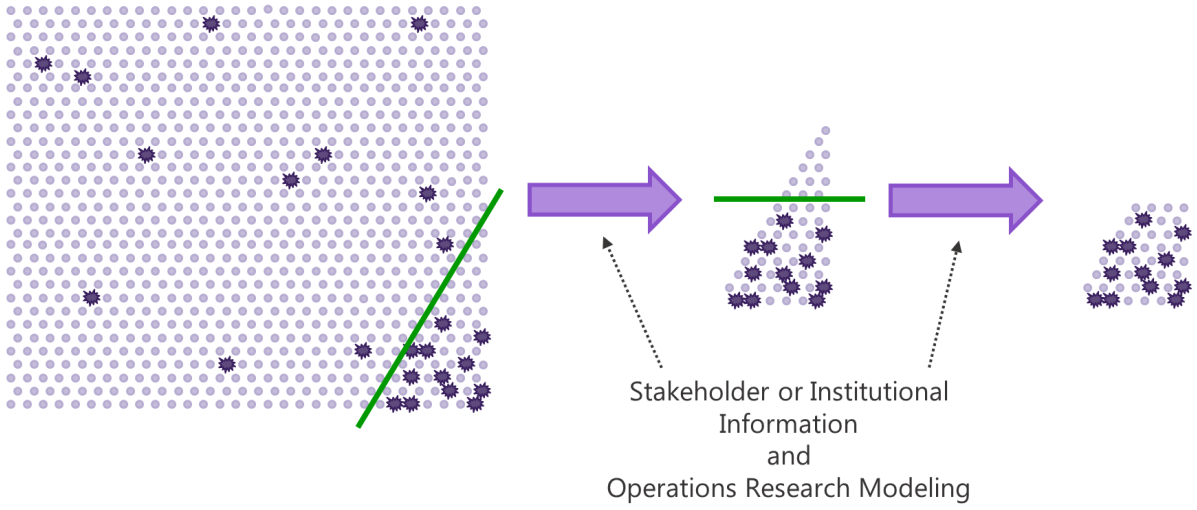

Figure 2: *Illustration of how a combination of stakeholder hypotheses and online experimentation algorithms can maximize the tendency to sample from sub-populations of pharmaceutical products with higher rates of substandardization and falsification.*

Fragmentation understanding is then a crucial element of efficient use of limited sampling budgets. However, upon examining this abstraction, the first question that comes to mind is: how should dimensions and their fragments be generated? We elaborate on this question in Section 4, presenting a mixed-methods approach that utilizes prior institutional knowledge, stakeholder hypotheses, and adaptive switching to maximize information gain and probability of SFP detection and removal. Decisions to switch sampling routines are rooted in resource availability and public health priorities. Once it is known that insufficient resources exist to confidently detect SFPs in one setting, available resources should be immediately pivoted towards finding a setting where they are sufficient.

Knowledge of the true underlying patterns of falsification has a demonstrable effect on required sampling budget requirements. Imagine Figure 2 represents the entire market of a particular pharmaceutical product. Let the SFP prevalence ($\hat{p}$) for this market be 3%. From the Budgetary Base Model, we know that 88 randomized samples are required to identify an SFP product with $(1-\alpha) = 95\%$ confidence. Assume stakeholder knowledge or other evidence enables divisions of the market along the solid lines shown in the figure, and let the SFP prevalence within this sub-population be 25%. Now only 8 samples are required to identify an SFP product within this sub-population.

Crucially, the gain made by dividing the overall pool of pharmaceuticals into smaller units is a function of the unevenness of the SFP distribution. Should the sub-population described above feature an SFP prevalence of only 5%, the resulting sampling budget requirement is 52 samples.

Sampling budgets are ordinarily readily known to NMRAs. Utilizing a framework centered around fragmentation permits NMRAs to complete two critical actions: 1) Hypothesize a dimension (or collection of dimensions) within which SFP prevalence is highly uneven, and 2) Establish $\hat{p}$ thresholds for the highest SFP prevalence of a particular fragment where particular sampling budgets possess feasible prospects for successful SFP detection. Using dimensions with even distributions across fragments leads to oversampling of fragments with low underlying $\hat{p}$, while using

dimensions with large numbers of fragments necessitates higher underlying $\hat{p}$ to maintain feasibility. The correct identification of significant fragmentation factors should then be of particular concern to NMRAs. In Section 4, we propose a mixed-methods framework that uses the fragmentation concept towards maximizing stakeholder information and testing theories surrounding fragmentation for a particular setting.

4 A mixed-methods approach to define fragments and assess feasibility

What makes pharmaceutical regulation difficult is the unknown location, severity, and timing of the manifestation of SFPs. When designing and implementing a sampling plan, operations research methods present avenues through which decisions and trade-offs can be explored more systematically. In this section, we offer an iterative approach that incorporates qualitative stakeholder information and empirical data collection within a mixed-methods framework. Consistent with PQM and WHO recommendations, this approach provides a usable structure on which NMRAs and other stakeholders can implement effective testing policies. Since no two country environments are exactly alike, regulators require strategies they can tailor to their specific contexts. The central idea is to use an empirical paradigm to identify and test hypotheses surrounding important fragmentation factors regarding the prevalence and character of SFPs. More precisely, the framework defines an instrument upon which NMRAs can form ideas about how and why SFPs occur, use empirical evidence to refute or support those ideas, and dynamically synthesize these data into new hypotheses about SFPs.

To provide a motivating example for the importance of understanding specific contexts, we can consider what observations we should expect under different opportunity structures for falsifiers. This example is rooted in the work of Pisani et al. (2019), that attempts to identify market risk. From the perspective of a falsifier of pharmaceuticals who is attempting to maximize profit gain, two essential operational parameters are as follows. The first is sunk cost: how much investment is required to produce a sufficiently close replica of a pharmaceutical product available on the market? The second is the availability of injection opportunities: once replicas are fabricated, how frequently and easily do falsifiers have opportunities to insert these replicas into the pharmaceutical supply chain.

The observed patterns of falsification can take different forms as a function of the values of these operational parameters. When sunk costs are high, we should anticipate a low number of falsified brands on the market, as falsifiers look to save on capital investments. When injection opportunities are regular and unimpeded, as might be expected in environments with low regulatory capacity or open borders, the flow of falsified products should then take on a consistent character over time. With more erratic injection opportunities, we should anticipate a more batch-like presentation of such products. This might not always be the case, however, as erratic opportunities earlier in the supply chain may result in a sifting and ultimately regular presentation pattern over time. Knowing the values of these parameters, then, can prove invaluable to those attempting to thwart such actors. Different observations imply different operational constraints of falsifiers attempting to maximize profits, which, as summarized in Table 2, can have significant consequences for NMRAs and their policy decisions.

As detailed in Table 2, we face the possibility that feasible sampling policies do not exist. As a counterpart to the operational constraints like sampling budgets and recall periods that were posed in Section 3, feasibility in this example depends on the overall capacities and opportunities of falsifiers. The variety of implications for regulator actions in each

Sunk Costs	*Injection Opportunities*	*NMRA Observation*	*Implications for Regulators*
High	**Steady**	*Consistent falsification of a small number of brands*	Initial identification of a falsified brand has large returns, as intensive testing of this brand can result in many captured falsified batches. Capturing these batches introduces high costs to falsifiers, as they are forced to move away from this brand and absorb high sunk costs. Consequently, information from sampling batches today strongly instructs approaches to sampling future batches, as the same brands are more likely to be falsified in the future.
High	**Volatile**	*Inconsistent falsification of a small number of brands*	With falsified batches clustered over time, judicial use of the Time Allowance is critical, as a given batch of product may be the only source of falsification over a significant time period.
Low	**Steady**	*Consistent falsification of a large number of brands*	Low sunk costs present largely reactionary scenarios for NMRAs, as capturing one SFP batch does not significantly hurt falsifiers. Attacking a steady stream of falsified products with low sunk costs means that falsification will simply be distributed across a large number of brands. In this environment, NMRAs must likely seek alternative methods to LQAS to address falsifiers' root incentives, such as track-and-trace technologies or subsidies of key products.
Low	**Volatile**	*Inconsistent falsification of a large number of brands*	Effective management of the Time Allowance becomes crucial here, as a recall action against brand X today means a recall action against brand Y tomorrow.

Table 2: *Implications for regulators under various operating environments of falsifiers*

scenario means that it is crucial for NMRAs to have a sense of which scenario is pertinent to them. We next elaborate on a framework that utilizes known system characteristics, captures stakeholder assessments regarding applicable scenarios and SFP prevalence, and empirically tests these hypotheses towards the goals of maintaining feasibility in sampling and maximizing the detection of SFPs throughout the system.

4.1 Generating a framework

Figure 3 illustrates our recommended mixed-methods framework. This framework utilizes two primary inputs. The first input includes those aspects of the medical supply system over which NMRAs have little to no influence. We refer to these aspects as the "external environment." These factors may include, but are not limited to: the complexity of the supply chain, the prevalence and costs for actors to produce or distribute SFPs, the consumption rates of different products, allocated budgets for sampling, and the length of time required for recall actions to be effected. NMRAs may have an impact on some of these factors, but for the purposes of the framework, we do not consider modifying these factors as a tactical or operational decision. The second primary input is the screening tool. Strongly linked to the pharmaceutical regulatory environment are the screening tools at the disposal of the NMRA. As different tools have different advantages and disadvantages (Kovacs et al., 2014), and NMRAs are often left with the decision of which tools

to procure, screening capability can be theorized as its own area. Centralized laboratories are powerful yet expensive to maintain and immobile, while the use of most mobile technologies results in a sacrifice of detection precision.

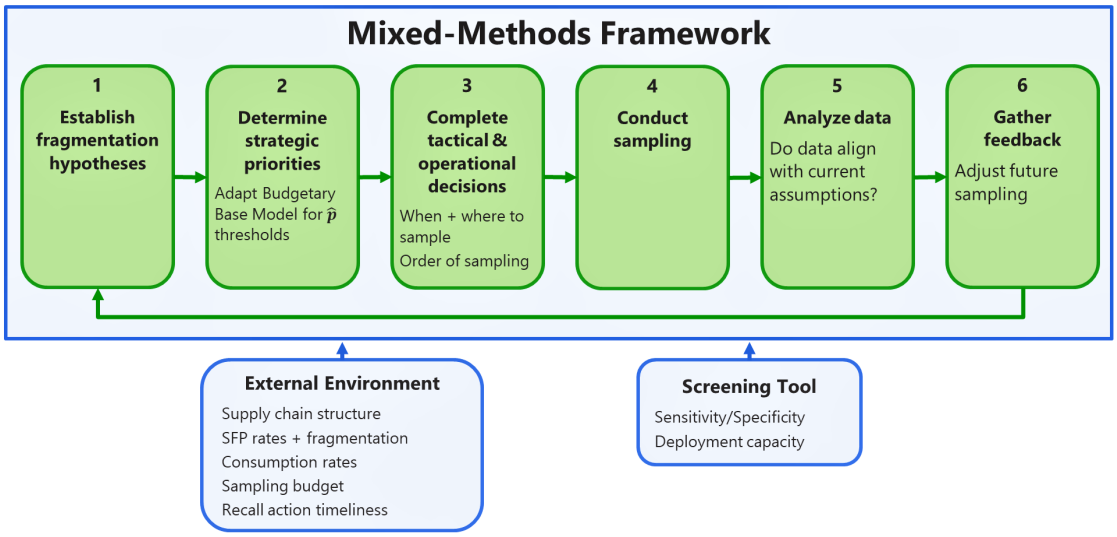

Figure 3: *The mixed-methods framework for adaptive evaluation of hypotheses regarding the fragmentation of substandard and falsified pharmaceuticals*

Under this framework, we propose the following process to establish, test, and analyze hypotheses regarding fragmentation and feasibility:

1. **Establish fragmentation hypotheses**: Any number of potential dimensions of fragmentation might exist for the context of a given NMRA. The insights and hypotheses of all stakeholders should be considered. The results of stakeholder interviews and discussions can be used to structure data collection to ensure hypotheses can be statistically tested later. For example, a hypothesis that rural distribution outlets have distinct SFP rates relative to urban outlets means that an urban/rural measurement should be recorded with each post-market sample collected.

2. **Determine strategic priorities**: Discussions within the NMRA should dictate the feasibility trade-off between SFP prevalence thresholds and resource availability for testing. Prioritization of which classes of pharmaceutical products, as well as sectors of the medicine distribution network (e.g., publicly versus privately procured pharmaceuticals), must be established. For example, investigating hypotheses requiring testing across too many fragments, or analyzing batches whose consumption rate is too fast to enable effective recall, should be postponed. These decisions often involve an inherently subjective weighting of the importance of different afflictions or health programs. The "MedRS Tool" for risk assessment, as established by Nkansah et al. (2017), can be utilized. This step is where more sophisticated versions of the Budgetary Base Model would be applied.

3. **Complete tactical and operational decisions**: Operational decisions refer to the actual testing choices an NMRA makes in implementing a sampling policy. These include, but are not limited to: specific outlets from which to obtain samples, a schedule for how frequently to obtain samples, and how many samples to purchase during a visit to an outlet. Another possible decision might be the required number of flagged samples of

a particular product before triggering a recall, quarantine, or more precise laboratory testing. This type of threshold decision becomes especially relevant in the case of testing substandard pharmaceutical products with imperfect screening tools. Design of experiments is covered extensively in the literature, but the general idea is that samples should be distributed randomly such that conclusions can be drawn among different fragmentation dimensions. For example, hypothesizing that differences in SFP prevalence exist between two geographic regions requires reasonably random sample collection across each of these regions.

4. **Conduct sampling**: With thresholds and pharmaceutical priorities in place, combined with the data collection dimensions along which desired hypotheses can be tested, sampling plans can be implemented. The Medicine Quality Assessment Reporting Guidelines for data collection, as established by Newton et al. (2009), should be followed.

5. **Analyze collected data to confirm testing feasibility**: Once sufficient data are collected, the presence of SFP rates above or below feasible prevalence thresholds can be ascertained. Additionally, distinctions in SFP rates across hypothesized fragmentation dimensions can be confirmed or refuted. As in the example described at the beginning of this section, NMRAs can identify which SFP scenario best applies to them.

6. **Perform feedback processing**: As hypotheses are challenged, new rounds of discussions should take place with stakeholders to determine whether to continue present testing strategies, switch sampling plans and screening capacities, or decide that resources must simply be expanded before feasible testing can be performed in the future.

As these sampling iterations progress, possessing descriptive characteristics along hypothesized fragmentation dimensions for all collected samples yields an institutional record of testing data that permits NMRAs to more rigorously evaluate their policies over time. Immediate processing of new data also opens up possibilities for more sophisticated dynamic sampling techniques tailored to particular environments, which we are investigating in ongoing work. The ultimate result is a refining of the policy towards market segments where feasible recalls can be conducted, in addition to quantitative arguments for further resources from funding institutions to meet feasibility in other market segments. Conducting sampling iterations one-by-one, as resources become available, is the simplest version of our approach. Where operational capacity and communicative channels are sufficient, more adaptive "if-then" strategies can be implemented using this framework.

5 Applying the mixed-methods framework

In this section we demonstrate an application in Liberia of the mixed-methods framework presented in Section 4. This mixed-methods framework grew from a collaboration initiated between an operations research (OR) team at [our university] and a chemistry team at the University of Notre Dame. The chemistry team developed inexpensive and scale-able paper analytical devices (PADs) for use in low-resource settings with significant SFP challenges (Weaver et al., 2013). The goal of this partnership is to integrate this novel chemical screening tool with OR methods to provide LMICs with both the screening tools and the decision-making tools for sampling to effectively combat SFPs. It became clear that despite their wide presence throughout the global system, systematically detecting bad products

with reasonable confidence under a stationary sampling budget would be infeasible *a priori* in certain contexts. The mixed-methods framework was developed to ground the deployment of valuable and limited sampling resources in the possibility of infeasibility in testing.

Upon developing the mixed-methods approach described in Section 4, prior relationships with entities based in Liberia permitted the teams to initiate the suggested framework and explore the feasibility of a successful implementation of PADs. According to the World Bank, Liberia ranks 178 of 182 listed countries with regards to GDP per capita (World Bank, 2020), and its low resource levels make it an ideal candidate for attempting to implement our resource-focused approach. Ongoing conversations among the OR and chemistry teams were held remotely from January to June 2019 with research collaborators from the Liberia Medical and Health Products Regulatory Authority (LMHRA), the pharmaceutical regulatory body of the Liberian government. Structured and unstructured discussions were held in September 2019 with LMHRA collaborators by a member of the OR team visiting Liberia. During structured conversations, topics like SFP prevalence or recalls were raised from a list and respondents were asked to provide as much information as possible regarding each topic. Descriptions of the questions asked during structured interviews are included in Appendix A.

To establish the primary inputs for the mixed-methods approach, a member of the OR team conducted a trip to Liberia in September 2019 to build a partnership with the LMHRA, ascertain significant framework parameters, and identify hypotheses for the fragmentation of SFPs in the Liberian market. After initial conversations regarding the overall mixed-methods approach and the feasibility concept, feedback was gathered from multiple stakeholders, including various regional LMHRA representatives, the proprietors of major private importers, and the owners of small urban and rural pharmaceutical outlets. The aim of these conversations was to implement the first step of our suggested framework and generate hypotheses of SFP fragmentation that would later feed sampling decisions under an iterative and adaptive sampling policy. These exchanges presented an interesting array of characteristics and constraints particular to the Liberian setting.

5.1 External environment

First, this process bestowed a deeper understanding of Liberia's pharmaceutical supply chain structure. Figure 4 shows a map of the distribution of medical products throughout Liberia. Sanctioned pharmaceuticals enter Liberia through either a public supply managed by the Ministry of Health as a push system, or through private importers whose products are inspected by the LMHRA. Privately owned licensed pharmacies around the country procure directly through these importers as a pull system. The entire private supply chain consists of about 20 private importers, all headquartered in the capital of Monrovia, and no domestic production, resulting in an overall low-complexity system. This overall constrained number of SFP resources suggests strong prospects for feasible sampling plans.

Based on feedback from outlet owners, we characterized the following general inventory policies for outlet owners and importers. Outlet owners tend to follow a base-stock policy with a low reorder point, only procuring their next batch of a pharmaceutical when the current batch is nearly depleted. During visits to private pharmacy outlets, informal reviews of available stocks revealed only one instance where more than two brands of any particular pharmaceutical product were available, supporting these claims. Per the implications of the Budgetary Base Model, the low number of

Figure 4: *Depiction of the pharmaceutical supply chain in Liberia (Map Library Online, 2020)*

potential available brands (one for each of around 20 importers), $|K|$, translates to low values of B, the overall required sampling budget for a given pharmaceutical. Pharmacy owners also mentioned that they tend to adhere to the same importer when replenishing depleted stocks. However, most outlets reported that even when using the same importer, the manufacturer brands received tend to change from batch to batch, indicating that importers are highly active in lowering their procurement costs on the global market. Other importers reported that they tend to maintain the same set of global suppliers over time. Additionally, different responses were recorded from importers with respect to the use of intermediaries - mentioned in Section 1 as a problematic aspect of the global supply system - as opposed to procuring from manufacturers directly. These inventory policies would suggest the hypothesis that SFP issues at the importer echelon vary from batch to batch, as importers alternate among different global suppliers. As a result, special emphasis should be placed on testing batches of products rather than brands, as SFP issues at the importer echelon will likely change across batches.

For recall actions by the LMHRA, the recall process for SFPs is initiated by any "Suspicious" screening result. This result triggers an immediate quarantine of the product and places it on a list of medicines used by inspection officers that are distributed throughout the country and who conduct surveys of the outlets within their purview. The time necessary to conduct this quarantine was estimated to be one week. Confirmatory testing of suspicious products is then conducted at the central laboratory in the capital, Monrovia, or sent abroad to a regulatory agency partner within the West Africa region.

5.2 Screening tools and deployment capacity

Post-market surveillance (PMS) of the private supply chain by the LMHRA occurs when budgets are available, with sample procurement signifying the largest obstacle to extensive sampling. Testing of only one common class of pharmaceutical product, such as amoxicillin or doxycycline, carries a monetary requirement on average of $2 per post-market sample. When facing trouble procuring funds from the government, the LMHRA often receives its PMS

budgets from various external organizations, but these budgets are often received in a piecemeal fashion and priorities for testing can sometimes be dictated by the donors as opposed to the LMHRA. As illustrated in Section 3.1, intermittent quantities of testing resources may impact which batches of medicines permit feasible recall actions, depending on the time elapsed since the batch entered the market, and these constraints must be considered within the mixed-methods framework when deploying sampling resources with an ultimate goal of SFP detection and removal from the market.

With respect to screening tools and deployment capacity, reagent availability at the lab is more constraining than laboratory testing time or technician capacity. A significant laboratory burned down in 2017 (Front Page Africa, 2019), and funding for a replacement is still a in process. As a result, inexpensive and deployable screening devices such as the PAD can occupy an important role in the overall surveillance paradigm. As part of the visit to Liberia, selected LMHRA staff were trained in how to use the PAD and catalog its results. Owing to its ease of deployment, a non-chemistry researcher was able to conduct a training-of-trainers module in a single day, with all participants passing the PAD certification test.

5.3 Hypotheses regarding fragmentation

Although the prevalence of SFPs was acknowledged to be a problem, estimates of the severity of the issue were difficult to obtain. As is common in many contexts, gaining reliable estimates of the value of $\hat{p}$ in each country is extremely difficult (Ozawa et al., 2018). All stakeholders affirmed that substandard manufacture and storage were serious problems throughout the entire supply chain. Multiple stakeholders of varying types were convinced that falsification is only a problem with respect to the unlicensed street vendors who sell pharmaceuticals illegally from makeshift market stands or wheelbarrows. These declarations that falsified products are primarily found in the informal sector aligns with high occurrences of stockouts at registered outlets. The inspection officer for one region reported receiving monthly reports from border-control officials regarding the disruption of the smuggling of falsified products across checkpoints. It was reported by many that actors in a particular neighboring country possess some of the more sophisticated replication technology. Broadly speaking, the borders of Liberia with its neighbors Sierra Leone, Guinea, and Cote d'Ivoire are porous, translating to little movement difficultly for smugglers should they wish to bring falsified medicines into Liberia. It is also conceivable that these products could be brought through the ports of Monrovia. Another observation is that rainy-season conditions often drive considerable stock-out rates in the southeastern counties of Grand Gedeh, River Gee, Maryland, Grand Kru, Sinoe and Rivercess. According to Pisani et al. (Pisani et al., 2019), it should be highly suspected that these extended periods of stock-outs drive up the prevalence of falsified medicines in these counties. As a whole, this feedback suggests that sampling plans should account for the possibility of significant regional differences in terms of falsification prevalence, but should also maintain expectations of substandardization issues throughout the entire country.

5.4 Pharmaceutical classes to test

Overall, conversations with the LMHRA yielded a variety of different hypotheses with respect to the presence and fragmentation dimensions of SFPs. Many described the previously mentioned smugglers originating from Liberia's neighbors, others felt that certain outlets were more prone to distributing unfit products, and others thought the manufacturer home countries were more indicative of poor or good quality. Analysis of ampiclox samples collected for

the chemistry team, as shown in Appendix B, lends some credence to the hypothesis that manufacturer home country plays a role in SFP tendencies.

Because of the limited size of the Liberian market and the resulting degrees of fragmentation, relatively small amounts of sampling can yield empirical data sufficient to test these hypotheses. Outlet owners consistently reported stockouts of amoxicillin, paracetamol and anti-malarials. They cited amoxcillin, paracetamol, anti-malarials, ampicillin, ampiclox and doxycycline as the most valuable products they carried. The consistency of these reports across outlets indicates that SFP tendencies might be most likely with respect to these products, and that sampling plans should focus on some subset.

6 Discussion and next steps

In this paper we developed ideas surrounding the feasibility of sampling plans for SFPs in low-resource settings. We proposed a mixed-methods framework for capturing and leveraging SFP fragmentation knowledge and illustrated how the process within this framework was initiated within Liberia. Although our models were developed keeping low-cost and deployable technologies such as the PAD in mind, the mixed-methods approach we propose can be applied to any form of sampling resource with a limited budget. Our work synthesizes existing models and guidelines with local stakeholder knowledge towards a more efficient deployment of valuable sampling resources. Knowledge of supply chains and their structures is a key tool for addressing the challenges posed by identifying SFPs in LMICs.

In looking forward to expanded collaboration, the OR and chemistry teams, along with the LMHRA, are currently engaged in a pilot project to determine the operational constraints of the implementation of an adaptive switching strategy in a very low-resource setting such as Liberia. Once the initial testing phase of the pilot reveals characteristics critical to the Liberian setting, the collaborative team will develop more extensive sampling strategies in a wider roll-out in accordance with the mixed-methods framework. These expansions will focus on hypothesis testing with respect to SFPs and will include adaptive switching to other pharmaceuticals or market sectors once previously established $\hat{p}$ thresholds have been reached. We anticipate that stepping through mixed-methods iterations will consist a multi-year process. Additionally, possible scenarios of the SFP tendencies within Liberia will be tested using computer simulations of the supply chain in conjunction with realized post-market sampling results. Examples of these scenarios include reception and masking of SFPs at the port of entry, replication and smuggling of medicines from bordering countries, and poor storage conditions at pharmaceutical outlets.

A central principle of this paper is that initiating planning from resource capacities can help governments and organizations effect better outcomes. All too often, policies are formulated with the correct aspirations in mind but without an eye towards how to act should insufficient resources exist to attain these objectives. Quantifying sampling plan feasibility in budgetary terms gives NMRAs the ability to directly tie sampling budgets to lower thresholds and tolerance of SFP prevalence in the pharmaceutical supply chain. Additionally, a current lack of international coordination around pharmaceutical regulation is a central aspect to the challenges now facing NMRAs in LMICs. Until these agencies are properly equipped and global planning enhanced, additional work in resources-oriented policy-making will be necessary.

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A Appendix: Stakeholder Feedback Regarding Substandard and Falsified Pharmaceuticals

A.1 General questions

1. What are some of the most commonly treated afflictions in your country/region?
2. Do you think pharmaceutical substandardization and/or falsification is a serious problem in your country? Do you have any anecdotes or personal experiences regarding these issues?
3. How effective is pharmaceutical regulation, in your opinion? What is done well, and what could be improved?
4. Which pharmaceutical products, in your experience, are most subject to substandardization and/or falsification?
5. What patterns do you notice (if any) with respect to substandardization and/or falsification? Are there patterns with respect to manufacturer, country of origin, medicine type, or time of year? Are there noticeable changes in quality from batch to batch of the same manufacturer?

A.2 Procurement (for pharmacy outlets, importers, or NGOs)

1. In general, what are the different sources of pharmaceuticals? Do different products come from different sources? How frequently do these sources change?
2. Can you describe the procurement process and/or supply chain in your country/region? If possible, we would appreciate a sketch of this process.
3. What is the size and packaging of a typical shipment of pharmaceuticals? How consistently do shipments arrive as full/complete? Do shipments typically arrive on time?
4. How are different manufacturers chosen? Are specific brands of a given product requested by the pharmacy/hospital/NGO, or is it left to the distributor/importer? How important is price in making procurement decisions among different options?
5. To what degree do stockouts occur? Do they happen for individual distributors/sources, or do they tend to happen across multiple sources at the same time? What do you do in such situations?
6. How consistently do you see the same manufacturers for particular pharmaceuticals? Do source manufacturers seem to vary over time?

A.3 Regulation (for National Medicines Regulatory Authorities)

1. What are some of the biggest problems facing your agency in doing its job? What hurdles exist for finding substandard and/or falsified pharmaceuticals?
2. Please give a detailed description of your current approach to handling a report of falsified or substandard pharmaceuticals. What possible actions are taken, and how long do they take? (A detailed Statement of Procedure would be very useful.)
3. What is your best estimate for the rate of substandardization and/or falsification in your country/region?
4. Where in the supply chain can the NMRA best implement testing? Why or why not?
5. Do substandard and/or falsified pharmaceuticals tend to appear all at once, or do they seem to be distributed over time?

B Appendix: Laboratory Analysis of Ampiclox Samples

During the September 2019 visit, the collaboration team collected twenty-one samples of ampiclox, a anti-bacterial combination of ampicillin and cloxacillin, from a variety of outlets in Monrovia to aid the chemistry team in establishing PAD methodology for this product. Full laboratory analysis, rather than PAD testing, was conducted on these samples to determine the API percentages of these samples relative to the amounts stated on the packaging. All samples were collected within a two-day period. Figure B.1 provides descriptive plots of the ampicillin and cloxacillin content of these samples by their stated countries of manufacture. Although ampicillin levels hover near 100% for all samples, we note considerable discrepancies with respect to cloxacillin content. This is not totally surprising as cloxacillin has demonstrated sensitivity to tropical conditions in accelerated stability studies, reaching 37% degradation after three days of exposure to tropical settings (50°C and 100% relative humidity), and 94% degradation after 10 days in such settings (WHO, 1986). In further analysis, the chemistry team will be able to provide additional analytical resources for root-cause analysis, such as distinguish whether cloxacillin is low due to improper storage or poor manufacture.

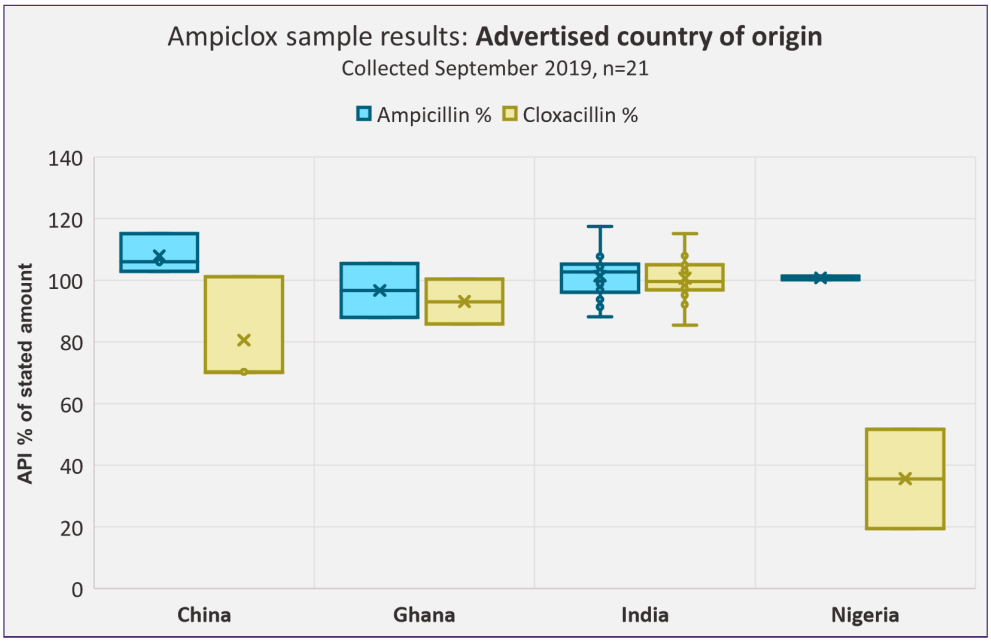

Figure B.1: *Illustration of API percentages versus manufacturer country for ampiclox samples collected from Monrovia outlets in September 2019*

Alternatively, this particular set of samples did not illustrate any strong SFP changes with respect to purchasing price. It is reasonable to expect that outlets charging lower prices than their competitors for identical products might be spending less on proper storage condition in order to make up the difference. However, Figure B.2 does not offer any clear evidence of this phenomenon taking place, and undercuts the hypothesis that price is an indicator of quality.

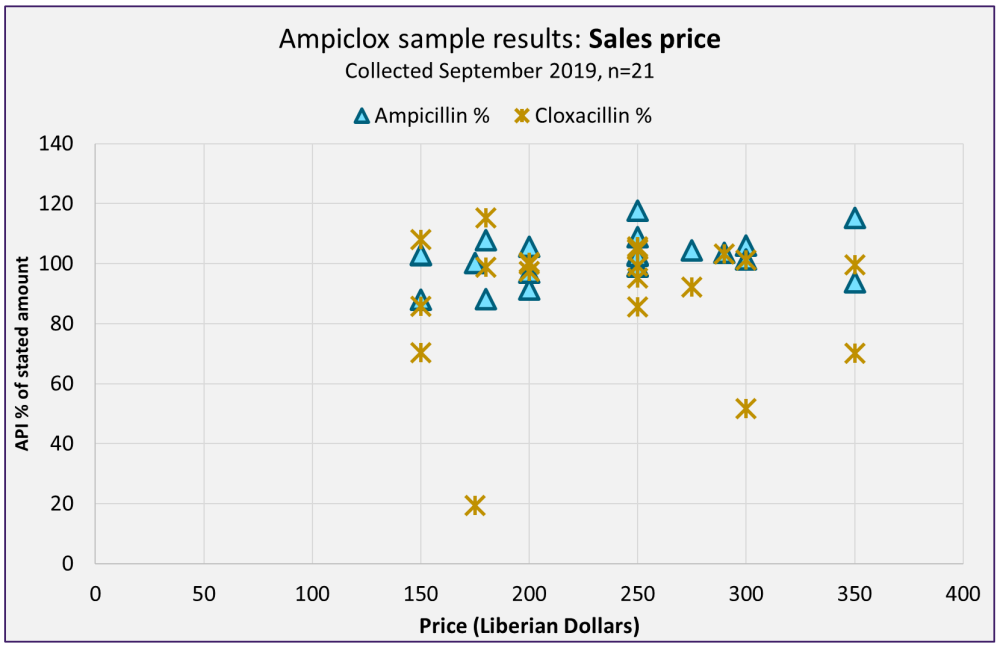

Figure B.2: *Illustration of API percentages versus sales price, in Liberian Dollars, for ampiclox samples collected from Monrovia outlets in September 2019*

That samples originating from other countries did not demonstrate nearly the same amount of degradation indicates a likelihood that fragmentation with respect to manufacturer country may drive significantly different SFP tendencies. It is notable that even this small data set ($n = 21$) offers some support for those hypothesizing manufacturer country as a significant source of SFP fragmentation, and provides viable avenues for future sampling iterations.

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