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Out of the boxes, out of the silos: The need of interdisciplinary collaboration to reduce poor-quality medical products in the supply chain

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ABSTRACT

In this paper, we argue that understanding and addressing the problem of poor-quality medical products requires a more interdisciplinary approach than has been evident to date. While prospective studies based on rigorous standardized methodologies are the gold standard for measuring the prevalence of poor-quality medical products and understanding their distribution nationally and internationally, they should be complemented by social science research to unpack the complex set of social, economic, and governance factors that underlie these patterns. In the following sections, we discuss specific examples of prospective quality surveys and of social science studies, highlighting the value of cross-sector partnerships in driving high-quality, policy-relevant research in this area.

1. Introduction

Substandard and falsified (SF) medical products have long been acknowledged as a threat to individual and public health.[1–3] They cause unnecessary morbidity and mortality, contribute to antimicrobial resistance,[4,5] and have a negative economic impact for households and health systems.[6] In 2017, the World Health Organization (WHO) estimated that about 1 in 10 medical products in low- and middle-income countries (LMICs) are substandard or falsified.[6] These estimates were later confirmed by other researchers.[7] Furthermore, the COVID-19 pandemic has revealed some key vulnerabilities to SF medical products in high-income countries too.[8–10] For example, more than 140 warning letters had been issued by the United States Food and Drug Administration (USFDA) as of mid-February 2021, concerning the use of unapproved medicines for treatment of COVID-19.[11] In the European Union, almost 33 million face masks, tests, and diagnostic kits, and 70,000 L of sanitizers were seized by Europol through Operation Shield in 2020.[12]

Assuring the quality of essential medical products for all is an important pre-requisite to achieving universal health coverage (UHC).[13] A complex set of coordinated interventions is needed, at local and global levels, to reinforce legislation, regulate supply chains, improve detection and reporting of SF medicines, and raise public awareness.[14,15] The complexity of the problem requires an interdisciplinary approach both for routine activities and for research, as highlighted in 2018 by a group of experts who attended the first-ever international conference on

Abbreviations: SF, Substandard and Falsified; WHO, World Health Organization; LMICs, Low- and Middle-Income Countries; US FDA, United States Food and Drug Administration; UHC, Universal Health Coverage; IDDO, Infectious Disease Data Observatory; NRAs, National Regulatory Authorities; AMA, African Medicine Agency; USP, United States Pharmacopoeia; Ph Int, *International Pharmacopeia*; API, Active Pharmaceutical Ingredient; NGO, Non-governmental organization; GMP, Good Manufacturing Practices; GSMS, *WHO Global Surveillance and Monitoring System.*

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Medicines Quality and Public Health.[3]

Here, we share some reflections on how interdisciplinary research can contribute to fighting poor-quality medical products. They are inspired by the debate of a group of experts in pharmaceutical and social sciences that took place at an online workshop organized by the Institute of Tropical Medicine, Antwerp, Belgium, and the Infectious Disease Data Observatory (IDDO), Oxford, UK, in December 2020.[16]

2. Views from the workshop

2.1. Research to support national regulatory authorities

Well-functioning national regulatory authorities (NRAs) are an essential component of health systems,[17] but the NRAs of most WHO Member States lack the resources and skills needed to thoroughly assess the quality of medical products circulating in their territories.[18,19] The WHO has developed a Global Benchmarking Tool of Regulatory Systems,[18,20] enabling NRAs to undergo self-assessment or external assessment by independent experts. This process includes identification of strengths and weaknesses for each regulatory function (i.e. National Regulatory System, Registration and Marketing Authorization, Vigilance, Market Surveillance and Control, Licensing Establishments, Regulatory Inspection, Laboratory Testing, Clinical Trials Oversight and, for overseeing biological products, NRA Lot Release), and formulation of an institutional development plan for upgrade. Thus far, only a handful of NRAs in LMICs have reached maturity level 3 (out of 4), corresponding to "stable, well-functioning and integrated regulatory systems" able to undertake critical oversight functions: Ghana and Tanzania as importing countries for medicines and vaccines, and India, Indonesia, Serbia, Thailand, and Vietnam as manufacturing countries for vaccines. (The capacity to regulate the production of medicines and vaccines are considered separately, because the latter requires the specific capacity of the NRA to release each manufactured batch).[19]

However, improving NRAs capacities and resilience in LMICs will require much greater investment.[21] Under-resourced NRAs can benefit from mechanisms for regulatory reliance, including the assessments by the WHO Prequalification Team,[22] which can reduce duplication of work, thus saving resources for other priority tasks. Furthermore, harmonization initiatives can facilitate the upgrade of regulatory standards while streamlining national processes. For instance, the Medicines Regulation Harmonization Programme of the East African Community (Kenya, Uganda, Rwanda, Burundi, and the United Republic of Tanzania, recently joined by South Sudan), launched in 2012, aims to establish a harmonized regional regulatory system that enables the coordinated approval of medicines through various regulatory pathways. In its pilot phase, it reduced the amount of time to register medicines by about half, aligned the regulatory standards and processes, and built the capacity of all NRAs. Challenges ahead include shifting from donor support to becoming self-sustained, optimizing the cooperation between NRAs with very different levels of resources and experience, and moving toward a more transparent system that is easier to navigate.[23]

Regulatory harmonization is growing in the African context, characterized hitherto by variable regulatory capacities[24] and a high prevalence of SF medicines (estimated at 19%, while 42% of the reports of SF products submitted to WHO between 2013 and 2017 come from this region).[7] In 2009, the African Medicines Regulatory Harmonization initiative was launched to create more effective, efficient, and transparent regulatory mechanisms across the continent. In 2021, the treaty for the creation of an African Medicines Agency (AMA) was ratified. The AMA will coordinate the regional harmonization systems and will create the opportunity to upgrade regulatory standards across the continent.[25] These developments, even if still at very early stage, are important for protecting African health systems from poor-quality medicines, and even more in view of the upcoming local production of COVID-19 vaccines in Rwanda, Senegal, and South Africa, which is hoped to improve global production for fulfilling global the needs.[26–29]

Irrespective of their maturity level, NRAs and regional medicines agencies would benefit from the use of evidence-based strategies and ongoing performance monitoring. Research can play a pivotal role in informing these strategies, including those to prevent and detect SF medical products, and in monitoring their performance. For instance, research on the prevalence of SF medical products in a given region or country can guide the priorities of post-marketing surveillance (e.g., which are the riskier products? and the riskier areas?) and regulatory enforcement (e.g., is it more urgent to reinforce the inspection systems of manufacturers, or along the distribution chain, or at the borders?). Qualitative research can provide important suggestions, e.g.: to shape education and awareness campaigns and identify priority groups for such campaigns (such as prescribers, dispensers, patients).

2.2. Quality surveys

Reliable data on the prevalence of SF medical products, either concerning a specific region or a specific category/type of product, are of utmost importance for informing appropriately-targeted corrective actions, and supporting advocacy toward donors and policymakers. Ideally, data should be generated through prospective surveys, in which medical products are randomly collected for quality testing. Stringent methodological guidelines need to be applied, including adequate sampling and testing techniques, to ensure data quality, representativeness, and reliability.[30,31] The researchers should also carefully consider the ethical implications of the surveys to ensure (among other things) the protection of the surveyors and the surveyed as well as the adequate involvement of local researchers and regulators throughout the research and reporting process.[32] Technical expertise in the fields of pharmaceutical sciences, analytical testing, and epidemiology needs to be partnered with experts in research ethics[33] and with representative(s) of the NRA in the study country(ies) who can bring years of on-the-ground experience to the table. It would also be important to involve social scientists in this research, in order to investigate the perceptions and behaviors of the different stakeholders. Involving health economists could be important in order to combine the findings on the prevalence of SF medical products with price analysis. By triangulating the different datasets, researchers could untangle the link between quality and price, given the unproven, but common assumption, that quality-assured medicines are always more expensive. These mixed-methods studies could also provide useful guidance to Central Medical Stores and other stakeholders across the national procurement systems for improving the quality and price specification of national tenders. Furthermore, they could inform National Programs and prescribers on the determinants of consumers' purchase practices,[34] as further discussed in the section on "Social science studies".

Currently, the bulk of expertise, analytical infrastructure, and funding opportunities for quality surveys are still concentrated in the Global North. Therefore, it is critical to involve and empower local researchers, to help ensure that contextual challenges and needs are taken into account, and to strengthen research capacities in the Global South. The interdisciplinary group should be built around equal partnership agreements, including the co-ownership of datasets and a shared governance of future use of data. The experience of collaborative surveys carried out in Rwanda and Malawi shows that such a collaborative set-up, in addition to ensuring the research relevance for the concerned country (e.g., by prioritizing affordable research tools, easily deployable in LMICs),[35] can prompt regulatory actions to the direct benefit of public health (for instance, research findings may lead to recall of SF medicines) (See Box 1).[36,37]

2.3. Social science studies

Measuring the prevalence of SF medical products in itself cannot disentangle the many complex behavioral and structural issues that influence the production, distribution, and use of SF medical products. For

Box 1
The impact of quality surveys on tackling SF medical products: quality of oxytocin and misoprostol in health facilities of Rwanda[37]

It is well-known that some medicines for sexual and reproductive health may meet major quality and stability problems.[38] Therefore, in 2018, Bizimana and colleagues conducted a cross-sectional study to assess the prevalence of poor-quality oxytocin injections and misoprostol tablets in 40 randomly selected government-owned, faith-based, and private health facilities, outlets, medical stores, and wholesalers across Rwanda. The collected samples were tested at a reference Quality Control laboratory. Oxytocin injections were investigated according to the standards of the United States Pharmacopeia (USP), and misoprostol tablets according to the standards of the International Pharmacopeia (Ph. Int).

The survey findings showed that no oxytocin sample had insufficient content of active pharmaceutical ingredient (API), even if all samples of one batch of a stated Chinese manufacturer showed an excessive API content (117–122% of the declared amount). Conversely, 40% of misoprostol samples showed extremely insufficient content, i.e., only 42.5–48.7% of the declared amount. The substandard brands were reported to the national regulatory authorities and to WHO. These independently confirmed the laboratory findings and issued a recall.

example, how do individuals understand the risks of SF products? How do consumers decide to purchase from the informal market? How do regulators end up granting a marketing authorization for substandard medical products? How are individuals' experiences shaped by interactions within and between social groups and with society as a whole? The decisions made by consumers, retailers, distributors, manufacturers, regulators, and other stakeholders can impact medicines quality in intricate and sometimes counter-intuitive ways. Moreover, some decision-making processes strongly depend on the geographical, historical, and social contexts, as well as on structural constraints, cultural beliefs, and past experiences that can shape communities' trust in health systems and medical products.[39] A better understanding of these aspects, combined with the understanding of factors linked to the structural constraints inherent in local pharmaceutical systems (e.g. limited pharmaceutical budgets, weak regulatory oversight) and individual practices, can help guide comprehensive and contextualized mitigation strategies.

Social sciences can, in particular, help untangle how certain decisions are made under conditions of uncertainty, asymmetry of information, vulnerability, and constrained agency.[40] Asymmetries of information put *consumers of medicines* in a vulnerable position vis-à-vis sellers, who are likely to be better informed about quality or appropriateness of a medicine, or which is a fair price. Furthermore, the fact of being unwell (or having a family member unwell) can increase a sense of urgency to obtain medicines that put consumers or purchasers of medicines in a position of susceptibility to sellers' interests. Vulnerability will tend to be higher for those with limited income, without health insurance, and those who live in areas with few options for accessing quality-assured medicines.[41]

Understanding decision-making processes about SF medicines is not only relevant for consumers. For instance, well-intentioned but unskilled *retailers* in poorly-regulated contexts may be exposed to similar levels of uncertainty when deciding whether a supplier is reliable and whether a product is safe. They may also hesitate to report suspected SF medicines, for fear of reputational and economic consequences, or even physical threats from reprisals.[42] It is equally important to (1) understand why *governmental and international procurement agencies, donors, and NGOs* may implicitly or explicitly accept the risk to buy non quality-assured medicines[43,44] and (2) challenge any hidden assumptions about *regulators'* behaviour and motivations, shedding light on the relationship between apparent 'misconduct' and structural constraints.[44]

There also remains a substantial gap in our knowledge and understanding of the motivations and practices of *manufacturers* of medical products, from large multi-national companies to small 'back-street' operations.[45] There are significant barriers to carrying out meaningful research with manufacturers; even those fully compliant with Good Manufacturing Practices (GMP) have been wary when two of the authors requested interviews. There are obvious fears about protecting intellectual property and the risk of any reputational damage that may come from the scrutiny of even the most compliant practices. However, the owners and employees of manufacturing companies generally do not have any background in social science and so may struggle to understand the relevance of the research. Social scientists may benefit from collaboration with experts from the pharmaceutical sciences, with similar backgrounds to those in the manufacturing industry, who may help "translate" the aims of the research and allay any fears manufacturers might have about participating. Similar considerations pertain with respect to national regulators and other key stakeholders in pharmaceutical systems (for example, pharmacists' professional associations, procurement officers, and health insurers).

Another possible role of social scientists, not yet sufficiently explored, is helping pharmacists, supply officers, and regulators to optimally engage with the public if cases of SF medical products occur during outbreaks or other public health emergencies. A clear and balanced communication is critical to alert people about risks of SF medical products and to provide appropriate advice on identifying and avoiding risky products, without causing generalized fears and mistrust that may lead to disengagement from health services and suspicions about medicines in general.

Pharmaceutical supply systems are often complex and opaque, with large numbers of stakeholders, overlapping roles and limited coordination, spanning both public/private and formal/informal sectors. The economic interests, moral imperatives, and social obligations of each stakeholder interact in complex ways that may perpetuate the presence of poor-quality medical products.[46] Understanding the social and behavioral aspects of decision-making can orient corrective measures, and researchers in pharmacy and analytical methods should consider joining forces with social scientists for a more comprehensive approach to understanding the roots of SF medical products. Ideally and if feasible budget-wise, analytical and social science research should not only happen in parallel, but they should be framed under a coherent research project that allows triangulation of data obtained through different collection methods (See Box 2).

3. Conclusion

The COVID-19 pandemic has increased the vulnerability of global supply chains to poor-quality medical products, but it also brought the issue under the spotlight.[9] This may provide a favorable environment to promote interdisciplinary research collaborations for a comprehensive investigation of the roots, prevalence and features of SF medical products, aimed at suggesting general and contextualized corrective actions at regulatory, policy and societal level.

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Box 2
Monitoring, reporting and regulating medicine quality: tensions between theory and practice in Tanzania[42]

The impact of a monitoring and reporting mechanism such as the WHO Global Surveillance and Monitoring System (GSMS) for SF medicines[47] depends on the willingness and ability of stakeholders "on the ground" to use it. Hamill and colleagues conducted in 2016 a qualitative research project to understand how regulators and local pharmaceutical companies in Tanzania engage with the GSMS. By using a qualitative, interpretative methodology based on semi-structured interviews, the authors identified and discussed challenges linked to monitoring and reporting SF medicines at various levels of the national regulatory system.

The study revealed challenges related to the lack of adequate human resources, infrastructure, and vehicles to reach out to remote locations; the lack of laboratory equipment's and field screening technology; and the inappropriate mix-up of skills, with pharmaceutical inspections in rural areas often carried out by trade officers instead of qualified inspectors. Furthermore, the authors observed that there are strong economic disincentives to reporting suspected SF medicines, and that when cases are reported, they are unlikely to be (adequately) sanctioned. Other factors that hamper the regulatory response include the fear for personal security when denouncing or investigating irregular or illegal practices, internal disagreements, and concerns of information leaking. Last, ethical dilemmas may arise: for example, closing a medicine outlet because of poor practices may leave some rural communities without any other pharmaceutical suppliers.

Overall, these findings shows that various economic, legal, psychological, and ethical aspects should be considered and addressed, concomitantly to the lack of technical resources, in order to reinforce a country's capacity to effectively detect and report SF medicines.

Declaration of competing interest

The authors declare that there are no competing interests.

CRediT authorship contribution statement

Tiziana Masini: conceptualization, writing first draft. Raffaella Ravinetto: conceptualization, review & in-depth editing. Cécile Macé, Lutz Heide, Heather Hamill, Kate Hampshire, Paul N. Newton: review & editing. All co-authors approved the final version of this manuscript.

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