Toward a multidisciplinary approach in research on quality of medicines

Highlights from an Informal Online Gathering

on Medical Products Quality and Public Health

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Mailing list, including participants (in alphabetical order)

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Background and objectives

Based on World Health Organization (WHO) estimates, 1 in 10 medical products circulating in low- and middle-income countries (LMICs) are substandard or falsified.[1] A meta-analysis conducted in 2018 by Ozawa and coll. reported similar findings.[2] Not only have substandard or falsified (SF) medicines[3] a major impact on individual patients' health, potentially causing serious illness or even death, but they also have a major public health impact, being a threat to antimalarial and antibacterial resistance, as well as having an economic impact both for individuals and for health systems that purchase or use these products.[4]

Ensuring medicine quality is challenging due to the weakness of regulatory oversight in many LMICs as well as along international distribution channels; and to the plethora of stakeholders involved in supply and distribution of medical products, in the public and in the private sector, and in the private not-for-profit sector (non-governmental organizations (NGOs)), international organizations and faith-based organizations). Furthermore, the informal sector may also play a big role.[5] Due to the complexity of interactions across different mechanisms and stakeholders, the problem of poor-quality medical products cannot be untangled without an interdisciplinary approach. It is of utmost important to promote platforms to exchange knowledge and ideas and to provide opportunities for collaborations. Such platforms can also encourage experts in specific areas to think out of the box and come up with innovative solutions to this problem.[6]

This "informal gathering" was the third of a series of informal events that started in person in 2019 for those interested in the subject working in northern Europe, thanks to the initiative of Paul Newton at Oxford University/IDDO/MORU, with the intent to share research projects, brainstorm on research ideas and identify synergies and collaborations among relevant stakeholders. This specific gathering was convened by Raffaella Ravinetto and Paul Newton with the following objectives:

- To foster a multidisciplinary approach in research on quality of medicines
- To brainstorm on research priorities and collaborations

Some 60 people joined online and participated actively in the discussion, by posing questions and comments in the chat box, or by interacting with the speakers. The event was structured so as to provide several perspectives and experiences in the fight against poor-quality medical products. First, Cécile Macé provided the field insights", highlighting the several practical challenges that LMICs face. Second, Lutz Heide showed how academics working in technical areas such as analytical chemistry and laboratory science can help to assess the prevalence and causes of SF medicines, while building North-South collaborative partnerships to empower local stakeholders. Third, Kate Hampshire and Heather Hamill discussed how social sciences can help other researchers to interpret and contextualize their results, as well as understanding their underlying causes. Fourth, the group engaged in active discussions touching upon all the topics discussed by the speakers. The major points of discussions as well as recommendations are summarized at the end of this report.[1]

The informal online gathering has evolved from a small in-person meeting in the UK in December 2019 to, with the pandemic, a virtual only meeting organized by Dr Harparkash Kaur in June 2020 from London and then the current large event that was focused on northern Europe. With interest in the subject growing and more people wishing to join, at the end of the meeting there was discussion as to how to include more colleagues in other parts of the world, especially in Africa, Asia and the Americas. This is a key aspect, giving the rather unexpected growing popularity of the meetings, to be discussed before the next informal on-line meeting. In the meantime, any suggestions to the organizers are very welcome.

[1] In this report, the focus is on quality of medicines, but most considerations will also apply to quality of medical products.

This open-access meeting report was written by Tiziana Masini and approved by Raffaella Ravinetto, Paul Newton and the speakers. It will be disseminated among participants as well as to all who confirmed interest in the gathering. It will also be published online on the website of the Institute of Tropical Medicine Antwerp, and of other partners if interested.

Quality of health products – Main challenges in LMICs, *Cécile Macé*

Speaker Bio: Cécile Macé is a public health pharmacist with more than 30 years of experience in pharmaceutical policies, procurement and supply chain management, access to medicines and quality assurance of health products. She worked for 10 years in pharmaceutical systems in Chad, Senegal and Cameroon and for 11 years for international Non-Governmental Organizations such as the MSF Access Campaign and the International Union against TB and Lung Disease. She spent 10 years in UN organizations including the WHO Department of Essential Medicines and Health Products and the United Nations Development Program (UNDP), where she was senior health PSM adviser providing support to countries implementing Global Fund programmes. She is currently an independent consultant.

Regulation of medical products, including medicines, is particularly important given the peculiar nature of these products compared to other consumer goods. Indeed, health product consumers – *the patients* – are a vulnerable group of consumers, as they cannot evaluate themselves whether a certain medicine is beneficial for them, nor can they assess themselves the quality of the product – *the medicine* – they are being given. Not only poor-quality medicines have an impact on individual patients, but also a major public health impact, potentially leading to raising of antibiotic resistance or spread of an infection because of the use of substandard products.

Regulation of medical products available by stringent regulatory authorities (SRAs) [7]

In countries with a stringent capacity to regulate pharmaceutical markets (in terms of skills, and of availability of sufficient staff and resources), patients can rely on the assessments done by their NRAs, which regulate the manufacturing, importation and distribution of these products, as well as regularly inspect all the stakeholders along the supply chain. Distribution is equally regulated in the public and private sector; pharmaceutical activities are conducted under the responsibility of qualified pharmacists; and regulatory oversight is equally applied to products that are sold by licensed suppliers on the internet. Pharmacovigilance systems are in place to report side effects, and alert systems are in place to withdraw a product from the market if necessary. However, as highlighted by the COVID-19 outbreak, even countries with stringent regulatory capacity are at risk of encountering substandard products. With the imbalance between the demand and supply for personal protective equipment and medical devices such as ventilators and oximeters, an increase of substandard products has been reported in various countries, including Europe and the US, which had to delist products previously approved under emergency clauses. UN organizations faced the same issue, with one UN agency having to reject up to 45% of the products proposed by suppliers due to wrong specifications or inappropriate documentation received.

Quality of medical products in LMICs

A study carried out by WHO in 2017 on the public health and socioeconomic impact of substandard and falsified medical products, estimated that the aggregate observed failure rate of tested samples of substandard and falsified medicines in LMICs is around 10%.[1] Based on this figure, the model estimated the dramatic impact on death rates for childhood pneumonia caused by SF antibiotics, noting that death rates would increase further in case of SF products with no API at all. The model also estimated that LMICs' expenditures for SF corresponds to 30 billion, highlighting a huge waste of resources for countries with already constrained economic capacities on top of the health impact.[1]

The capacity of NRAs in LMICs varies greatly depending on the country and the context. The WHO Global Benchmarking Tool for evaluation of national regulatory systems of medicines and vaccines, developed to assess the maturity levels of NRAs, shows that most assessed

countries have non-mature regulatory functions to effectively and comprehensively control their markets, due to lack of capacity and resources.[8] Furthermore, SRAs do not have full control of the medicines that are not meant for use by their own population, even if a part of the manufacturing was done in their territory – indeed, medicines "for-export-only" are not strictly controlled by SRAs. This is also the case for NRAs in China and India.

Main challenges in supply and distribution of medical products in LMICs

The difficulty to regulate the pharmaceutical markets in LMICs is further exacerbated by the multiplicity of procurement and distribution channels, and by the plethora of stakeholders that are involved in (or even interfere with) the national supply chain at several levels and to different extent, and which often do not collaborate with one another. These stakeholders include Ministries of Health, NRAs, National Procurement Centre, Hospitals, as well as stakeholders from the private sector such as distributors, wholesalers, importers, private pharmacies, and from the non-for-profit sectors. In some settings, faith-based organizations are in charge for up to 40% of health facilities. In some countries, unfortunately, the informal sector may also be very prominent and active. Given this complexity, traceability of a product from the national level to the peripheral level is challenging, and often totally lacking in LMICs without warehouse management systems and Logistic Electronic Management Systems, especially at peripheral level. This makes it difficult to detect SF products along the supply chain, and to recall a product if and when necessary.

Many procurement strategies and practices in LMICs still use medicine price as the priority criterion when selecting best offers from bidders in national tenders. As long as there is such a pressure to lower medicine prices, quality will always be compromised over lower prices. National procurement agencies should verify if the products imported in their country are those that had received the initial regulatory approval, i.e. with the same specifications and coming from the same manufacturing unit. Importation of unregistered medicines via waivers, which may be necessary in the context of emergencies or to access to life-saving medicines for very severe conditions such as extensively-drug resistant tuberculosis, may also increase the risk of having SF medicines in national markets, if the national regulatory and procurement agencies do not have the capacity to adequately control these importations. Uncontrolled donations from different stakeholders, including external partners, as well as donations negotiated and accepted at political level without consulting the NRA, may carry the same risk.

In LMICs, access to quality-assured medicines is further challenged by the absence of health insurance schemes, with patients paying out of pocket and thus seeking products in unregulated (informal) markets, where they might be cheaper. This behavior may also be prompted by lack of access to certain products in the public health facilities.

Conclusions

To conclude, there is definitely a need to further document the extent of the problem in LMICs, so as to guide the control and post marketing surveillance programmes of NRAs; to guide the establishment or reinforcement of national laws and regulations; and to inform policy makers about measures to be put in place to detect and prevent SF medicines. Furthermore, even though the problem of SF medicines is common to many LMICs, we need to investigate and understand the specificities of each country context, to be able to provide countries with specific and targeted recommendations.

Medicine Quality Studies in Africa *(Lutz Heide)*

Speaker Bio: Lutz Heide is a pharmacist by training. Since 1994 he is professor of Pharmacy at the Pharmaceutical Institute, Tübingen University, Germany. His research focuses on substandard and falsified medicines in African countries, with whom he has established many fruitful collaborations. In 2014-15 he spent two years at the University of Malawi as Professor of Pharmacy working on SF medicines in Malawi. Prior to initiating his academic career, Lutz worked for three years as Senior Pharmacist Adviser for the Ministry of Health in Somalia, responsible for the establishment of a medicines supply system for 700,000 refugees.

Ensuring medicine quality is paramount in providing safe and effective health care and reducing overall health care costs, and even if poor-quality medicines should be *prevented*, it is also crucial to *detect* those that may have reached the market. Access to reliable chemical-analytical methods to analyze medicine quality is an important component of the broader Quality Assurance (QA) system that must be in place to assess medicine quality. This capacity must be built in LMICs and its sustainability can only be ensured by establishing collaborations with country-level institutions and laboratories, and by engaging in training activities to promote capacity strengthening.

Chemical-analytical methods for medicine quality studies

Pharmacopeias give quality specifications which a given medicine must comply with, and methods to prove or disprove compliance with these specifications. Based on Pharmacopeias, medicines samples are tested for several parameters such as the product's identity, the amount of the active pharmaceutical ingredient (API) in the sample, the ability of the sample to dissolve in order for the API to be bioavailable and be therapeutically effective, the sterility (crucial for parenteral formulations) and the stability. By applying appropriate techniques, Schäfermann and co-workers investigated 500 samples of 13 essential medicines in Cameroon and the Democratic Republic of Congo (DRC) according to the U. S Pharmacopeia and detected several samples of Salbutamol and Penicillin V that contained much less API than what was declared, and a few samples of Amoxicillin, Clavulanic Acid, Metronidazole and Penicillin V that did not contain any API at all.[9]

To perform such comprehensive and detailed analysis, fully equipped laboratories are needed, where High-Performance Liquid Chromatography (HPLC) or mass spectrometry (MS) analysis can be run. While some LMICs have this capacity, most LMICs have very few laboratories who can do these analyses, with (very) limited capacity. The development of simple and inexpensive screening methods that can be run directly in the field is utmost important to ensure that some post-marketing surveillance can take place regularly at field level. The Global Pharma Health Fund (GPHF) Minilab® is currently the most widely used screening technology in LMICs, but other screening technologies such as Near Infrared or Raman spectroscopy are also under development, which hold great promise thanks to the fact that they are very easy and fast to use. The GPHF Minilab® was developed to empower local staff to carry out basic quality analysis through a simple, inexpensive screening method based on thin layer chromatography (TLC). It includes test protocols for 100 APIs and a trained person can run approximately 20 analyses per day.[10] By using the GPHF Minilab®, Gnegel and co-workers detected SF chloroquine tablets, among those available from informal vendors and licensed pharmacies in Cameroon and DRC.[11] Subsequent investigation by HPLC and MS, carried out at the University of Tübingen (Germany), confirmed the absence of detectable amounts of chloroquine and the presence of other undeclared APIs in four of the samples.

European-African collaborative research in equal partnership; from research findings to policy and practice improvements.

Many projects from this group, such as the one conducted by Gnegel and co-workers, demonstrate that working in equal partnerships with local partners, including researchers, academics and technicians, is possible and essential. Such collaborations are key to empowering local organizations, thus enabling sustainability of medicine quality research and

analyses in LMICs. Local conferences, platforms for knowledge exchange with all relevant local authorities involved in ensuring quality of medicines, as well as training workshops with technicians in local health facilities, are very helpful to foster capacity building.

Collaborative research partnership can also have a huge public health impact, as research often results in the regulatory recall of substandard medicines from the market.

Collaborations between researchers and NRAs

In a study conducted jointly by the Tübingen University and the Department of Pharmacy of the University of Malawi, "extremely substandard" misoprostol preparations were identified, containing only 13% of the declared content. These tablets, marketed by a UK-based company, had been distributed to the government of Malawi.[12] Following the outcome of this study, the Malawian authorities issued a product recall and the Central Medical Store Trusts of Malawi discontinued the procurement of this brand, replacing it with a quality-assured misoprostol brand. When the findings of this project were shared open access, it was noted that this distributor was located at the same address of another company that had been previously reported to distribute poor-quality propofol to the government of Zambia.[13] The UK Regulatory Authority (Medicines and Healthcare products Regulatory Agency, MHRA) thus started an investigation and confirmed the extremely substandard quality of these misoprostol tablets. The subsequent actions of MHRA were not made public, but both UK-based companies saw their MHRA wholesale licenses 'terminated' and went into voluntary liquidation in January 2019. The same owner family still runs several pharmaceutical wholesale companies, some of these opened shortly after closure of the mentioned companies under slightly different names.

In a study conducted by the University of Tübingen in collaboration with the University of Rwanda, two brands of misoprostol were identified that contained less than 60% of the declared amount of the API.[14] After reporting the findings to the Rwanda Food and Drug Authority, a preliminary recall of these two brands of substandard misoprostol tablets was issued immediately, and a final recall was issued just a few weeks later.

Kate Hampshire & Heather Hamill – the social scientists' perspective

Kate Hampshire is a Professor in the Anthropology Department at Durham University. She is a medical anthropologist and has been conducting fieldwork on health and well-being, mostly in Sub-Saharan Africa, since the mid-1990s.

Heather Hamill is Associate Professor in Sociology, Dean of St Cross College. Heather's research primarily centers on the various ways in which problems related to establishing trust and reputation are solved. These issues are particularly pertinent in the low trust environments of high crime neighborhoods and illegal political and criminal organizations. Her current research focuses on the problems of trust created by the proliferation of sub-standard and falsified (SF) medicines sub-Saharan Africa.

Kate Hampshire and Heather Hamill discussed the social scientists' perspective on the topics presented by Cécile Macé and Lutz Heide

The issue of medicine quality is not a stand-alone phenomenon, but it is a complex network of interlocked phenomena involving many stakeholders at different levels of the provision of health care services. This is why it is so important to work between and across disciplines; and there are several areas where social scientists can come into play.

Understanding how the experience of individuals is shaped by interactions with social groups and the society as a whole can help untangle many of the non-technical issues related with SF medicines. Indeed, the decisions that we make as individuals – being pharmacists, retailers, distributors, governments, or others, and considering that we are all at the same time consumers too, – can scale up to impact medicines quality in ways that we do not understand.

The two questions that sociologists are interested in are:

What do people do? (descriptive question)

and

Why do they do what they do? (explanatory question), with three levels of analysis:

a) the macrolevel – including social systems in general and populations at a large scale. For example, high internal shocks such as big changes in the economy or the impact of the current coronavirus pandemic on public health system and subsequently on medicine quality;

b) the meso level, where we are interested in detailed examination of certain parts of society, patterns of social ties within and between groups, and how those ties might facilitate or prevent the penetration of SF medicines.

c) the microlevel, for the understanding of the behavior of individuals and the decisions they take, and for the understanding of how that interacts with the miso and macro levels. For example, in the face of such uncertainty on medicine quality (i.e., you, as an individual, cannot know what is contained in a certain medicine, how it was manufactured, etc.), patients cannot put their trust in the medicine, thus they rather trust the person who sells the medicine, because they believe this person has good intentions. However, the retailer might also not know anything about the medicine quality or might not have the appropriate information to check that. By focusing on the product only (i.e., the medicine) we would end up overlooking this network of relationships and trust between individuals and groups, which is an essential aspect of the SF medicine issue.

There are several areas where social scientists can contribute to the work that other scientists carry out in the context of SF medicines. However, it is of utmost important that the collaboration is established upfront, and that all partners involved are open-minded and ready to be challenged in a positive way, being open to other ways of seeing the same problem and to think outside their “academic silos”. By studying different components of the same problem, or the same component of the problem with different tools and perspectives, we can understand the problem in its complexity, as a whole.

Possible, specific areas for collaboration with social scientists were mentioned:

- Some barriers to identifying and reporting SF medicines go beyond the technical aspects. For instance, a study carried out by Hampshire, Hamill and co-workers based on 31 in-depth interviews with key stakeholders in Tanzania, identified some of these barriers.[15] These range from lack of human resource capacity particularly at local levels, to the reputational and economic risks of reporting, especially for small-scale retailers, to the very real threat of physical danger from reprisals.
- Particularly in LMICs, medicine procurement and distribution systems can be incredibly complex as well as opaque, owing to: (a) the often very large numbers of actors involved, spanning public/private and formal/ informal sectors; (b) the ways that medicines move within and between these sectors in ways that are difficult to trace; and (c) the fact that, typically, no individual or agency has full oversight of the process. Social scientists can help unpick and unravel such complex supply chains and help to understand how and why certain practices happen along the supply chain. An example was given of the current StreAMS project (Strengthening African Medicine Systems, funded by MRC and partners under the Health Systems Research Initiative), being carried out by Hampshire and Hamill with an inter-disciplinary team of researchers from Ghana, Tanzania and the UK.
  This project entails three main elements: (1) using survey and GIS techniques to map the *actual* routes that medicines in Ghana and Tanzania take from the point of retail upwards to manufacture or import; (2) understanding, through careful ethnographic research, how decisions are made at each point and the role that assessments of quality plat; and (3) agent-based empirical modelling of the supply system to identify key points of intervention and to highlight possible unintended consequences. Preliminary results tend to confirm findings from earlier work carried out by the same researchers: that economic interests,

moral imperatives and socially obligations interact in complex ways that may perpetuate the presence of poor-quality medicines in certain supply chains.[16,17]

- The supply and demand gap and, in particular, situations whereby economic constraints, inadequate access to public-sector facilities and/or stock-outs can limit the options available to people who need medicines. As also stressed by Macé and Heide, patients are particularly vulnerable group of consumers, because of various asymmetries of information (patients are less likely to be able to assess the quality or utility of a medicine than the provider), economics (especially where patients have limited income/resources) and need (when the urgency of a situation requires a rapid response). In this sense, many patients in LMICs are continuously exposed to uncertainty, which affects and influences the decisions they take. Social scientists can help to understand how, under these conditions of uncertainty, people decide what medicines to buy and why, by connecting macro-level uncertainties with micro-level decision making. A project currently ongoing with the WHO in four countries (Ghana, Nigeria, Sierra Leone and Uganda), for instance, is investigating how medicine purchasing decisions and practices come about; specifically, a structural equation modelling is being used, to try to disentangle the effects of information gaps (which could be addressed through communication campaigns) *versus* actual structural constraints (i.e., lack of resources and/or availability of quality-assured options).

Highlights from the discussion

Does high pressure on low prices risk undermining medicine quality?

As noted by Cécile Macé, many procurement strategies or practices in LMICs still use medicine price as the priority criterion when selecting best offers from bidders in national tenders; and as long as there is such a pressure to lower medicine prices, quality might be compromised over lower prices.

The reason offered as a justification not to purchase quality-assured medicines is often the perception that they are more expensive than non-quality-assured medicines. However, this is not always necessarily true. It was pointed out that SF products may in some cases even be more expensive than corresponding quality-assured ones, as price-setting mechanisms may be based on other criteria than the production costs. There is the urgent need to de-mystify this perception, as well as the inaccurate belief that while every product procured from EU or the US is of good quality, what is procured from India, China or Africa is automatically labeled as poor-quality product. The pharmaceutical market is characterized by a huge complexity, which does not allow to make such generalizations.

There are many indications that the same perception of a correlation between price and quality (i.e., high price corresponding to high quality) is present among customers, which leads to several problems including people with economic constraints ending up spending more money than they need to.

> "The challenge is to communicate clearly that 'most substandards are cheaper' is NOT the same as 'most cheaper meds are substandard'" (quote)

Regrettably, there are very few studies comparing medicine quality and price and this was identified as a major research gap.[18] Such studies are urgently needed. They should be able to capture the complexity of this issue, and also select adequate quality indicators, depending on the characteristics of market and regulation in each country.

Is no medicine better than a poor-quality medicine?

The pressure on low prices is a real issue in medicine procurement, as well as in UHC campaigns. Indeed, scaling up UHC without scaling up funding for pharmaceutical QA/NRA

strengthening bears the risk to lose the balance between making medicines available and affordable while ensuring their quality (thus, their efficacy and safety).[19]

Most pharmacists, researchers and clinicians agree that from the point of view of patients and their health, there is always some level of risk associated with using a non-quality-assured medicine; and they also agree that lack of awareness by concerned stakeholders can result in insufficient attention for quality assurance. This is an issue also at health-care provider and retailer level in LMICs. Customers may be very socio-economically vulnerable individuals or households, paying out of pocket, who risk incurring catastrophic health expenditure, and will be pushed towards the informal market to find affordable products there. Local retailers may be very well intentioned but might not have reliable information (for example on which suppliers are reliable or not), making it challenging for them to advise their customers in the best way. Also, small-scale retailers can be poorly regulated. Some research found that many registered over-the-counter shops were selling medicines that they shouldn't be selling; but, on the other hand, they had become the only source of antibiotics for their communities. This resulted in moral dilemmas for retailers: either to leave patients with no antibiotics at all, or risk to sell antibiotics that they are unsure about in terms of the quality.

From this point of view, is '*no medicine worse than a SF medicine*' from the patient's perspective? As far as we know, the majority of poor-quality medicines contain a lower percentage of API, rather than being actively toxic. Patients taking a medicine with reduced API or bioavailability may still experience or perceive a therapeutic benefit compared with taking no medicine at all, although there may be a public health cost in terms of increased anti-microbial resistance and impaired patient outcome. In the majority of cases, without access to testing equipment, neither the retailer, nor the patient, nor the prescriber will be able to ascertain accurately a medicine's quality, and therefore the associated risk. But from the patient's perspective, it may look like a risk worth taking, even given this uncertainty.

"The bioavailability of an unaffordable medicine is zero percent" (quote)

Research on SF medicines should, in addition to *measuring* their prevalence, also *understand* what guides patients, prescribers and retailers' decisions in situations of uncertainty, and *suggest* possible corrective measures (e.g., for some contexts or products, to encourage retail outlets to join certification/franchise programmes where they are given access to buy and sell quality-assured products). To do so, research must be multidisciplinary. Similarly, social sciences can also help understanding why governmental procurement agencies, donors and other entities responsible to implement donors' funding, may decide to take the risk to buy non-quality assured medicines.

"An advantage for multi-/interdisciplinary work is that more and more funders are realizing that it's not possible to do good quality work without social science expertise on many public health issues, and they include a need for qualitative/social science work in the funding calls for clinical and other types of research that might traditionally have ignored the broader context" (quote)

How to engage with Pharmacovigilance (PV) and Post-market surveillance (PMS), and how to connect them?[b]

Normally, PV is part of the country's regulatory functions, being one department within the NRA. In some countries, PV activities are delegated to universities or other stakeholders, but they still report to the NRA. A strong connection is needed between the PV and the NRA,

[b] The WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medicines and vaccines (https://www.who.int/medicines/regulation/benchmarking_tool_version_vi/en/) includes definitions of indicators for each regulatory functions, including indicators defined for PV systems and descriptions on what they mean with post-market surveillance.

particularly concerning PMS. When PMS detect quality problems, the PV team needs to be informed, as adverse drugs reactions may follow; and when (clusters of) adverse drug reactions are detected by PV, they must be communicated to PMS teams, so as to trigger targeted controls.

In many LMICs, unfortunately, PV systems have very low capacity. Moreover, the focus of PV is generally put on reporting adverse drug reactions, while lack of efficacy, which is a major issue linked to poor-quality medicines, is usually not reported. More research is warranted on the potential role of PV in detecting poor-quality medicines.

Ad hoc research could also help to define the role of existing and future field screening methods for surveillance and research. Importantly, they should not be used to make purchase decisions, nor to draw general conclusions about a supplier being reliable or not, as they only provide some snapshots of the reality in the field.[20]

Strengthening countries' capacity to address SF medicines: the importance of marketing authorization

> "If a medicine is registered by the NRA, then there can be an assumption from pharmacists and healthcare providers in that country that the product is of good quality" (quote)

Regulatory authorities may allow the importation of an unregistered product, if it fills an urgent public health need. In many LMICs, SRA approval or WHO prequalification is a prerequisite for granting import waivers. However, importation of unregistered medicines via these waivers may also increase the risk of SF medicines, if the national regulatory and procurement agencies do not have the capacity to adequately control these importations.

On a different note, it may happen that some essential medicines are simply not registered in some LMICs. The initiation of all regulatory processes hinges on manufacturer's willingness to file for regulatory approval, but the markets in some LMICs may not be attractive from a commercial perspective, and manufacturers will not apply for registration.

On the other hand, the limited capacity of many NRAs in LMICs may dramatically slow down the registration process. Mechanisms such as the WHO Collaborative Registration Procedure (CRP)[21] and harmonization initiatives to standardize registration procedures[22] can help streamline national regulatory approval processes and ensure that medical products available on the market are quality-assured.

The role of WHO and the WHO Prequalification Programme (PQP)

Multidisciplinary research groups could help disentangling the complex set of determinants around the WHO Prequalification. Since its creation in 2001, the WHO PQP has been playing a key role to improve the quality of life-saving medicines used by millions of people in LMICs.[2324] However, its scope remains limited to only certain types of medicines. It is unsure whether extending the scope of the WHO PQP would automatically lead to more quality-assured products being on the market in other disease areas. Manufacturers of other essential medicines that are already on the market would only invest in the quality assurance upgrades needed to achieve the WHO PQ, if they see any commercial benefits, i.e. if getting the WHO prequalification would open up to broader markets or more commercial opportunities.

Another challenge is whether a manufacturer would pursue WHO Prequalification for all its eligible products. There is a risk that, once a manufacturer has obtained WHO pre-qualification for some products, it would not submit other products, because it would already be happy with the good reputation gained. Moreover, many manufacturers and/or distributors supplying WHO prequalified products have rather high Minimum Order Quantities (MOQ), which makes it challenging for small/medium purchasers to place their orders, or to get them prioritized.

Recommendations

Even if this was a short gathering, with a limited set of topics, it was enriched by the active participation of about 60 researchers and experts in the field of quality of medicines. Therefore, it is worthwhile to draw and share a few general recommendations. We have not checked whether all who attended the online gathering agree with this text and we hope that they will prompt further discussion.

(1) Research studies are needed to investigate the relationship between medical products' price and quality, in several settings, so as to counter the perception that high-priced medical products are always of better quality than low-priced ones.

(2) Research studies are needed to answer some key questions for all stakeholders, e.g. governments, regulators, manufacturers, distributors, prescribers, healthcare-providers, health funding agencies etc..[25]

(a) Do they purchase/prescribe/fund non-quality-assured medical products? If so, why?

(b) What are their perceived and actual roles and ethical responsibilities in the selection and procurement of medicines?

(c) How do stakeholders working in pharmaceutical supply and research interact -or not- with each other? What are the barriers to better collaboration?

Such studies should be carried out as multidisciplinary projects, as they require combining pharmaceutical, economic and sociological expertise. Answering these questions will hopefully help to translate research findings into policies and practices, and to develop and put in place mitigation strategies at several levels of the pharmaceutical systems.

(3) Research on SF medicines is necessary to produce reliable information that can feed advocacy strategies targeting high-political levels and decision-makers; and that can guide policy decisions on SF medicines, based on (general and contextual) evidence.

(4) Coordination with access-to-medicine stakeholders, including NGOs advocating for UHC, should be sought, so as to ensure that access to quality-assured medical products is well-explained, and included in their agendas.

(5) The role of universities and academia in strengthening the capacity of NRAs, especially for PV and PMS activities, should be further investigated.

(6) The role that local production of medicines could / could not play in reducing poor-quality medical products in LMICs should be explored.

(7) Researchers could help designing strategies to improve the quality and efficiency of medicines registration in LMICs, and of waivers' processes in case of public health emergencies. For instance, they could investigate the reasons for current barriers and shortcomings, and ways to encourage countries to establish or join international/regional medicine harmonization initiatives.

Prof. P. Claver Kayumba

In grateful memory of Prof. Pierre Claver Kayumba, who contributed greatly to overcoming major pharmaceutical challenges and ensuring good quality medical products in Africa

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