WORKING PAPER

Expanding access to quality medicines: An empirical critique of a new WHO initiative

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Summary

In September of 2015, The World Health Organization (WHO) issued a warning letter to Mumbai-based *Svizera Labs*, part of *Maneesh Pharmaceuticals*, threatening to rescind approval for use of its Tuberculosis (TB) drugs if quality standards were not dramatically improved[1]. A health authority criticizing an Indian drug producer is not news, the US Food and Drug Authority issued dozens of complaints against such companies in the past year alone, however, such action from WHO was unusual as WHO is not a drug regulator.

WHO has taken on the role of a pseudo-regulator in its efforts to increase access to medicine. Products made in markets with limited regulatory oversight are often of unknown provenance and quality. WHO tries to assess these products, approving of the better ones, so buyers can have more confidence in their quality. The WHO prequalification of medicines (PQM) system has likely become the single most important quality metric in emerging markets, especially for the donor community, which buys millions of treatments of WHO approved generic medicines each year.

Yet there has been no independent evaluation of whether WHO is effective in overseeing quality, and whether its assessments are societally beneficial. Moreover, there is a lack of evidence that WHO assessments drive better production quality – WHO may just be approving manufacturers who already make a good product; simply identifying good manufacturers is probably beneficial in and of itself.

Drawing on my team's quality assessments of thousands of samples in 19 emerging countries (primarily large cities), we find that PQM products are far better quality (five times less likely to fail basic quality analysis) than those approved locally that are not approved by WHO. These results echo findings from the few other studies undertaken[2].

Furthermore, an unpublished study by McKinsey, funded and quoted by WHO, stressed the importance of PQM. For a total budget of US$ 13 million in 2013, the manufacturers that achieved prequalification allegedly delivered quality controlled vaccines, therapies and diagnostics worth approximately US$ 3 billion[3]. McKinsey claims that the PQM process also assists emerging market medicine regulatory authorities to increase their own capacity to oversee production standards.

Yet the WHO is not a stringent regulatory authority, and when products we sampled were subjected to more rigorous tests, PQM products were more likely to fail than those products approved by stringent regulators like the FDA (after all WHO has no jurisdiction over any company – some can make a good product and achieve approval, but then do not always make a good product for the market).

[1] http://in.reuters.com/article/2015/09/04/india-pharmaceuticals-svizera-idINKCN0R41JW20150904

[2] ACT Consortium Drug Quality ProjectTeam & The IMPACT2 StudyTeam, 2015. Quality of Artemisinin-Containing Antimalarials in Tanzania's Private Sector—Results from a Nationally Representative Outlet Survey. The American Journal of Tropical Medicine and Hygiene, pp.14–0544.
WHO Expert Committee on Specifications for Pharmaceutical Preparations & World Health Organization eds., 2011. WHO Expert Committee on Specifications for Pharmaceutical Preparations: Forty-ninth report. Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products, Geneva: World Health Organization.

[3] Rago, L., 2014. Added value of WHO Prequalification. Updates from product streams (medicines, vaccines and diagnostics). Available at: http://www.who.int/medicines/areas/policy/PQ_Added_Value_Washington_2014.ppt [Accessed September 30, 2015].

More concerning is WHO's own response to this critique. When confronted by evidence of inferior product quality in their approved products, WHO initially ignored the evidence, then denied any problem in a press release without ever answering the specific questions raised. WHO was acting more like the public relations department for the manufacturers than an independent arbiter of quality.

In principle the PQM system could be beneficial even if more of the products it approves fail quality control than those approved by stringent authorities (like FDA), but there are risks that inferior products, if used by millions of people, could drive resistance across populations, to say nothing of the suffering of those taking those products.

A thorough assessment of products is therefore warranted, yet is unlikely to occur. While WHO staff seek high quality medicines for patients, WHO has no practical interest in assessing quality, when any criticism has been made it has ignored and then denied it. Worse still, some of its staff has pressured researchers not to be involved in independent assessments.

However, encouraging signs are beginning to emerge. With the WHO criticism of *Svizera Labs*, WHO is taking on some of the responsibility of its assumed regulatory function. Additionally, while interactions between regulators in emerging markets and the developed world could deliver a more nimble and better adapted selection of products than a centralized overly-bureaucratic hyper-sensitive UN agency, corruption at the national level in emerging markets ensures that such an outcome is not happening.

Introduction

In an effort to increase access to medicines, the World Health Organization (WHO) is significantly expanding its Essential Medicines List (EML)[4]. Originally designed to assist developing countries prioritize critical medicines for infectious diseases and other major conditions, it will expand from January 2016 to include drugs for a wider array of diseases and conditions. This paper reflects on the efficacy of the WHO Pre-qualification of medicines program (PQM), which has been verifying the quality of some of the drugs on the EML for the last ten years[5].

To our knowledge, no public evaluation has taken place. WHO reports the consultancy McKinsey claiming that the PQM system covers medicines worth $3 billion and costs $13 million to run[6]. However, these figures are merely descriptive – they are not analysis; they tell us very little. What's more, the study has not been made public, therefore these figures cannot be assessed for accuracy.

The concept of the essential medicines list and the pre-qualification program are arguably sound. With inadequate medical capacity and limited buying power in the poorest nations, WHO expertise in helping these nations prioritize drug procurement for government programs makes sense. WHO expert panels determine which drugs are most efficacious and cost-effective and should be included on the EML; these may be innovator or generic drugs. As the WHO explains: "The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment." The list was first published in 1977, and included 204 pharmaceuticals. The list is updated every two years. The 19th edition was released in April 2015. More than 130 countries have created national essential medicines lists based on the WHO's model list. These lists contain between 334 and 580 medications[7].

The addition of medicines has often followed WHO donor priorities (such as combatting HIV) rather than strictly the highest priorities of emerging nations, however, there is no historic criticism of the list itself[8].

As of April 2015, 95% of all developing countries had published a national EML, of which 86% have been updated in the past five years.

The WHO Model EML serves as a guide for the development of national and institutional EMLs. Each country caters its list to regional factors such as prevalent diseases; availability of medicines; treatment facilities and personnel; affordability; and genetic, demographic and environmental factors.

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[4] http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf

[5] Although there are three other PQ departments covering diagnostics, intravenous devices, vaccines and laboratories, etc. these are not discussed in this paper.

[6] Rago, L., 2014. Added value of WHO Prequalification. Updates from product streams (medicines, vaccines and diagnostics). Available at: http://www.who.int/medicines/areas/policy/PQ_Added_Value_Washington_2014.ppt

[7] Bansal, D; Purohit, VK (January 2013). "Accessibility and use of essential medicines in health care: Current progress and challenges in India." Journal of pharmacology & pharmacotherapeutics 4 (1): 13–8. doi:10.4103/0976-500X.107642. PMID 23662019.

[8] Combatting HIV is obviously a top priority for many emerging countries in Africa, but antibiotics and vaccines for children are arguably more important and were not the driver of the system.

The IMS Institute found a wide variance between the WHO and country EMLs[9]. Only 65% of the drugs on the WHO list appear on the Philippine's list, 59% on Indonesia's list and 31% on China's list. The differences exist for communicable diseases, non-communicable diseases and vaccines alike.

The IMS Institute study seems to suggest that countries follow the Model EML to varying degrees and do not necessarily update their lists immediately following the publication of a new WHO EML. With better communication between regulatory and health authorities across nations a centralized WHO EML would not be required, but given corruption and limited capacity in many emerging nations, the WHO EML model seems to be of benefit.

Traditionally, the EML has contained medicines for infectious diseases, like malaria and TB, however, more recently the WHO list has expanded to include medicines for non-communicable diseases (NCDs), such as hypertension, diabetes and cancer. The list also was expanded for diseases such as hepatitis C with the emergence of new and far more effective treatments have come online[10], as well as new drugs to combat multi-drug resistant versions of malaria and TB.

As some infectious diseases are brought under control in emerging markets, and more importantly as wealth increases in these locations, the relative burden of morbidity shifts from infectious to non-infectious diseases and multi-drug resistant versions of infectious diseases. Therefore, it is natural for WHO to seek to include medicines shifting the attention of its essential medicines list and pre-qualification system accordingly[11].

In the past WHO PQM activities have been funded by short-term grants, however, in an effort to promote sustainability, the WHO is introducing a new financing approach. The new financing model aims to generate at least 50% of the operational funds[12]. WHO will require an annual financial contribution from manufacturers of health technologies to PQM. Contributors will not be consulted on the use of the funds, rather, the program will release a yearly audited financial report. The funding model is expected to be in force by January 2016.

These additional fees equate to one percent of the annual sales value of prequalified drugs. The fees are to be voluntarily provided by the respective companies, in order to expand and improve WHO operations, particularly in training staff at national regulatory authorities.

Claims have been made that the amounts of these extra contributions will be verified by the purchasers, however, this innovative funding model is clumsy, and it will put pressure on accounting staff on all sides; surely any company making these extra voluntary payments in full and without being pursued, will be doing so as a goodwill gesture – and presumably hoping such behavior will be rewarded?

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[9] https://www.imshealth.com/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Insights/IIHI_Essential_Medicines_Report_2015.PDF

[10] http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/

[11] There is also an activist element to WHO, which encourages the health community agenda of combatting western corporations and promoting emerging market corporations

[12] http://www.who.int/medicines/prequal_fin_mode_consultation/en/

Table: Proposed fees to be levied for PQ by funding stream

		Diagnostics	Medicines/ FPP	Medicines/ API	Vaccines	
1 Initial assessment fee (per application)	Simple	$12,000	$8,000	$8,000	$25,000	*Applications follow the same definition as used today, i.e. separate applications submitted for different dosages / formulations of the same compound*
	Complex[1]		$12,000	$12,000	$67,000	
2 Major variation fee (per variation)		$3,000	$6,000	$3,000	$10,000	*Major variations as defined by WHO guidelines on variations to a prequalified product*
3 Annual contribution	Scaled based on eligible sales of PQ products: around ~1% of sales					*Honour-based system (validated with data from donors/procurers)*

API = active pharmaceutical ingredient; FPP = finished pharmaceutical product
[1] Complex products for FPP includes all injectables, implantables or fixed-dose combinations with 3 or more APIs; for APIs defined as injectables.

PQM has an unfortunate history of being forced prematurely into being during the '3 by 5' initiative, which put hundreds of thousands of HIV patients at extremely high risk of developing resistance to first-line antiretroviral drugs as it allowed unproven drugs on its list, did not have the capacity to ensure the necessary supply of quality drugs and imposed a too heavy burden on fragile health systems[13].

The situation at PQM has improved, however, it remains an opaque operation. Manufacturers use PQM as without it, they could not sell to aid agencies.

This is not to say that PQM is not beneficial or a reasonable way forward; simply that we do not know that the system is effective. It may be that WHO's resources could be better focused on building capacity of national regulators, rather than trying to intervene on their behalf. After all, WHO's Constitution states that its aim is: "(c) to assist Governments, upon request, in strengthening health services." Should PQM be seen as a 'stop-gap' solution while national regulatory authorities gain capacity and expertise?

The other questions that should be answered before WHO launches a major expansion of its EML and PQM system are: have the PQM system and the EML provided a material benefit and if so to whom and at what cost? What are downsides of the PQ and EML if any? What is the impact on emerging nations of the EML? What impact on drug resistance will result from an expansion of PQ EML? Is it better than nothing – and is that good enough?

My aim is less ambitious, it is to empirically assess whether the PQM system approves companies that consistently deliver high quality medicines, and if not discuss what impact inferior medicines might have, and what policies might limit any negative effects.

[13] Bate, R. & Mooney, L. (2006) WHO's Comprehensive HIV Treatment Failure: Will We Learn the Real Lessons From 3 by 5? AEI WORKING PAPER #133, NOVEMBER, 2006 www.aei.org/workingpapers www.aei.org/publication25215 #20946 https://www.aei.org/wp-content/uploads/2011/10/20061130_AEIWP133.pdf

Why is the PQM system required?

There are numerous unusual market dynamics and often asymmetries of information in the production, marketing and sale of pharmaceuticals. Most of these are well known, such as that the cost of manufacturing the first pill costs hundreds of millions of dollars, however, the cost of production afterwards is minimal, and therefore fair pricing is always a matter of opinion.

However, the main drivers of problems in obtaining access to medicines in emerging markets often result from inefficiencies in registration of products, and the cost of doing business in emerging markets. The efficient (usually very low) pricing in such locations is often cost prohibitive of western companies, where the onerous registration processes and costs are not insignificant[14].

Historically innovator companies sold small amounts of their products at relatively high prices to the elites in emerging markets. Companies made small profits from these sales and did not risk products being illegally sold back (diverted) into their more lucrative markets. These actions are understandable from their perspective; however, they are also neither efficient nor equitable to patients in emerging markets.

Weak, often absent, regulators in emerging markets led to a free-for-all of unproven quality medicine for the masses and small expensive markets of western-approved medicine for elites. To fill this market demand, there was a proliferation of entrepreneurial generic producers (especially from India), manufacturing cheap medicine and taking significant market share. However, much of this production was of unknown quality and major donors refused to purchase such medicines for fear of patient safety.

Only when companies overreached in 1999 and tried to enforce intellectual property rights on HIV medicines in South Africa, to keep supply limited and prices high, did health activists and donors successfully agitate for a new system. The result of those actions yielded the WHO prequalification system.

Empirical Evidence and Political Pressure

Over the past 8 years my research team sampled close to ten thousand medicines from 22 cities in 19 emerging nations. The majority of the medicines procured were to treat infectious diseases, especially tuberculosis and malaria. These medicines were screened for basic content using thin layer chromatography and/or raman spectrometry. A subset of medicines was subjected to far more detailed analyses. And this subset includes medicines that have been prequalified by WHO.

In 2012 a few experts on my team wrote a paper analyzing WHO PQ antimalarials. The results of the paper were not startling, however, the treatment of the *original* authors of the paper, even by people that have no direct connection to WHO or the PQ program, was startling. The impression left by the criticisms of the authors was that public health officials want the PQ system to be above reproach and they assume that any criticism of PQ is either flawed or motivated to undermine WHO.

[14] For and extensive discussion of drug pricing and policy see https://www.aei.org/publication/drug-pricing-and-its-discontents/

In that study, 104 antimalarial medicines, all WHO PQ, were procured from three West African nations – Togo, Nigeria and Ghana. Eight (7.7%) of them did not have sufficient API, the results published in a peer reviewed scientific journal[15]. Such a result is not surprising, other papers with non-PQ products showed far worse results (often 25-35% of the sample failing quality control),[16] however, for WHO it was something of an embarrassment. The HPLC content analysis was done by Harparkash Kaur and her team at the London School of Hygiene and Tropical Medicine. Dr. Kaur was also part of a larger evaluation being undertaken by LSHTM (and partner labs in other nations) on antimalarials. She was internally criticized by LSHTM management for assisting us and pressure was applied by the WHO malaria department as well. In the end Dr. Kaur and the coauthors withdrew from the publication, and since the scientists who had done most of the analysis were no longer on the paper, the Associated Press, which had been due to cover the paper, declined to cover the results[17].

WHO pressure therefore had worked to muzzle the results.

Since our concern was potential threats to patients from poor quality medicines, the authors sent the remaining samples from the failing batches to the WHO PQ program for analysis. WHO failed to confirm that they had analyzed the products we sent them. However, subsequently WHO PQ posted a statement on its website (since removed) to indicate that all batches of medicine were fine, after consulting with the companies that manufactured the medicines. Of course WHO, and regulators like FDA, must maintain relationships with manufacturers and seek clarifications when discussing their alleged quality problems. However, to rely on manufacturer veracity to identify problems of alleged substandard production at their facilities creates a conflict of interest to say the least. Fortune magazine eloquently described the lengths of deception large companies can employ[18].

Since WHO appears never to do post market surveillance, simply ignoring our work is risky for patients.

Hypersensitivity to a small sample does not indicate guilt on the part of WHO, or certainty of problems of quality for the manufacturers, since Dr. Kaur's team may have made laboratory errors and/or products might have degraded and been manufactured adequately. However, our initial evidence was significant enough so that we wanted to know how other PQM products performed. That analysis is presented here for the first time.

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[15] https://www.dovepress.com/subsidizing-artemisinin-based-combination-therapies-a-preliminary-inve-peer-reviewed-article-RRTM

[16] See www.searching forsafety.net for examples

[17] See http://www.aei.org/publication/substandard-drugs-are-an-even-greater-danger-than-fakes/ for a my presentation of the story at the time

[18] http://fortune.com/2013/05/15/dirty-medicine/ WHO is not equipped to follow-up and investigate any wrongdoing from companies whose medicines it qualifies for the PQ list. Specifically, in the Ranbaxy case, the whistleblower gave extensive documentation of wrongdoing to the WHO along with the US FDA. While the FDA eventually prosecuted the company for data falsification and manufacturing adulterated medicines, there is no public record of the WHO ever having acted upon the information it received.

New Data

A further 229 samples of PQ medicine to treat malaria, bacterial infections and TB was assessed using more advanced techniques (including HPLC) than those used screening all the samples. Of those 229, 103 were also approved by a stringent regulatory authority. None of those 103 failed any quality test. Of the remaining 126 samples, three (2.5%) failed for insufficient content. If we add these three failures to those found in the published 2012 analysis we have 11 failures out of 234 samples (4.7%) of medicines approved by WHO but not SRA approved failing.

Drug to treat	**Sample size**	**Failed quality control**
Malaria	139	9 (6.5%)
TB	48	1 (2%)
Bacteria	47	1 (2%)
Total	**234**	**11 (4.7%)**

As acknowledged in the 2012 study, some of these medicines could have degraded (the content assay showed at least 50% API for all samples failing), however, that is unlikely as none of the SRA approved products bought in the same locations failed. Additionally, none of our samples were likely to be falsified medicines since there were no obvious packaging errors and most (but not all) falsified medicines contain no API.

While the results are statistically significant, the sample size is too small to conclude much from the results with high levels of confidence. However, since none of the SRA approved products fail content assay, it seems reasonable to conclude one point – WHO-approved products are generally good (as confirmed from our previous analysis at least five times better than products approved by local regulators), but probably not always as good as SRA approved versions.

What does slightly inferior WHO approved products mean?

Given that all the WHO PQM failing products contain at least 50% API, there is a chance that they will work adequately in patients and cause no ill effect. However, there is also the chance that they would fail or increase population level resistance (medicines with no API, such as falsified medicines, are far less likely to drive resistance). As a result, occasional post-market surveillance of products on the market, and sanctioning of manufacturers breaking reporting rules, a bit like WHO is beginning to do with *Svizera*, is likely to keep them honest enough that clinical failure remains low and resistance pressure is limited.

Assuming our data are broadly accurate and WHO-approved products are far better than non-WHO approved locally registered products, which themselves are better than unregistered products, encouraging more patients to access WHO-approved medicines will on balance increase positive clinical outcomes and likely also lower resistance pressure.

However, there is a further caveat to this analysis. In 2013 Harvard Medical School scientist, Preston Mason, presented a study at a cardiology conference, which highlighted that many versions of the drug atorvastatin contained an impurity that undermined, either partially or totally, the cholesterol-lowering impact of the medicine[19]. These medicines, widely considered to be generic medicines, were available in numerous countries around the world, notably in Asia, and several of them were made by firms that have either some or multiple PQ products. Are such impurities confined to atorvastatin or could they apply to other medicines (some PQ) made by the same companies?

We don't know.

Incidentally, none of the SRA products approved that were tested by Dr. Mason had any content or impurity problems. And to be clear, an impurity that prevents correct release of the drug, may lead to the kinds of problems with under-dosed medicines (clinical failure and resistance).

So while the PQM program is likely currently beneficial for both clinical outcomes and limiting resistance, that may not always be true, and it may not be sustained over time. As the experiences of Ranbaxy's whistleblower and our own research team, where WHO entirely ignored evidence respectively of wrongdoing and poor quality, and Professor Mason's research finding of impurity flaws in WHO approved medicines, indicate, under a worst case scenario, WHO products might both fail patients and drive resistance. What is most worrying is that presented with problems WHO is not transparent and is loathe to criticize member states, so if the worst case were to happen, it is unlikely to be found by WHO.

[19] http://www.lipidjournal.com/article/S1933-2874(13)00157-8/abstract