

Medicine registration and medicine quality: a preliminary analysis of key cities in emerging markets

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Background: The medicine registration process is not just a matter of formality but involves assessment of medicine quality and stability. It is perhaps the most important as well as the simplest aspect of medicine regulation. This study attempts to ascertain whether registered medicines perform better in simple quality tests than those that are either not registered or not known to be registered.

Methods: Over the past 30 months, 2065 essential medicines (for treatment of malaria, tuberculosis, and bacterial infections) were procured by covert shoppers from 11 African cities and from eight cities in a variety of middle-income nations. All samples were assessed using the Global Pharma Health Fund e.V. Minilab[®] protocol, which includes visual inspection, semiquantitative thin-layer chromatography, and disintegration testing, to identify whether they were substandard, degraded, or counterfeit.

Results: Where medicine registration data were available, 1940 medicines were identified, of which 1589 were registered and 351 were either unregistered or not known to be registered. The failure rate among registered medicines was 5% (79/1589) and 37.3% (131/351) amongst medicines that were either unregistered or not known to be registered. African cities had fewer medicines registered (71%, or 488/687) than Indian cities (86.9%, or 610/702) or other middle-income cities (89.1%, or 491/551). Samples from African cities performed far worse in quality tests (18.6% failed, or 128/687) than either samples from Indian cities (8.7% failed, or 61/702) or other middle-income cities (3.8% failed, or 21/551). There was also a notable disparity in failure rates by medicine type; 14.2% (101/710) of antimalarials failed testing, 10.1% (70/693) of antibiotics failed, and 7.3% (39/537) of antimycobacterials failed.

Conclusion: The results strongly indicate that medicine registration is an important component of better-quality medicines. Registered medicines performed better than unregistered medicines, and the result was strongly statistically significant.

Keywords: antimalarials, antibiotics, antimycobacterials, Africa, India

Introduction

One of the critical roles of any medicine regulatory agency, such as the United States Food and Drug Administration (FDA), is to register medicines available for sale to citizens. The registration process for new chemical entities, for agencies like the FDA, generally consists of evaluation and assessment of quality data, preclinical studies, clinical trials, and the product information document; however, smaller agencies may only be able to undertake some of these tasks.^{1,2}

There are obviously good-quality medicines in the United States that are not registered by the FDA; they can be brought in by individuals without explicit approval from the FDA. For example, until April 2009,³ the malaria medicine Coartem[®] (Novartis)

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was not registered by the FDA, but some malaria researchers had personal supplies. There may also be large amounts of medicines, possibly smuggled into the US, that are less likely to be of consistently good quality. These circumstances also exist in other countries and probably to a greater extent. In China, for example, the State Food and Drug Administration reported that in 2007 there were 329,613 cases of unlicensed medicines, most of which were manufactured by “fly by night” firms.⁴

In 2007, Kenya’s Ministry of Health, the World Health Organization (WHO), and Health Action International undertook an assessment of medicine availability and quality in Kenya. The study found that 42% of malaria medicines found on the market in Kenya were not registered, and 16% failed quality control tests, but it was not clear whether registration was associated with poor quality.⁵ As a result of the study, the authors of this paper investigated whether registration was a problem in other countries, particularly in Africa, and what impact registration status might have on medicine quality. This study attempts to ascertain whether registered medicines perform better in simple quality tests than those that are either not registered or not known to be registered.

Material and methods

Over the past 30 months, 2065 medicines were procured by covert shoppers from private pharmacies in 19 cities across 17 developing and middle-income countries (Table 1). Samplings took place in 11 African cities, three Indian cities,

and five middle-income cities, to include São Paulo, Moscow, Bangkok, Istanbul, and Beijing.

All collected samples were from the WHO’s essential medicines list, including antimalarials, antibiotics, and antimycobacterials. In October 2007, when the collections began (in six African cities), the primary aim was to analyze only malaria medicines; therefore, the samples from African cities are biased towards antimalarials, with fewer antibiotics and antimycobacterials procured (Table 2). Additionally, no antimalarials were available for purchase from the cities of Istanbul, São Paulo, and Moscow.

All medicines were assessed using the Global Pharma Health Fund e.V. Minilab[®] protocol to identify substandard, degraded, or counterfeit medicines. This includes visual inspection of packaging and pills for correctness, disintegration for basic solubility, and semiquantitative thin-layer chromatography (TLC) to determine the presence and relative concentration of active ingredients. Each test was run in duplicate, with the generous assumption that the result that was more consistent with the reference was recorded. Quality control of the Minilab was performed daily prior to testing and consisted of performing TLC on Minilab reference samples for the medicine classes being analyzed. In addition, Minilab reagents were quality control tested using reference samples when a new lot was introduced. The Minilab protocols award medicines a “pass” if they have 80% or more of the labeled active ingredient(s). For fixed-dose combinations and sulphadoxine–pyrimethamine, a “pass” was awarded only if both active ingredients met this standard.

Table 1 Testing results (failures recorded) by country and city of origin and registration status^a

| Country of origin | City of origin | Registered samples | Unregistered (and not known to be registered) samples | Total |
|-------------------|----------------|---------------------|-------------------------------------------------------|-------------------------|
| Ghana | Accra | 6.6% (4/61) | 63.6% (21/33) | 26.6% (25/94) |
| Tanzania | Dar es Salaam | 9.7% (3/31) | 56.3% (9/16) | 25.5% (12/47) |
| Uganda | Kampala | 20% (8/40) | 44.4% (16/36) | 31.6% (24/76) |
| Nigeria | Lagos | 4.1% (9/221) | 44.2% (23/52) | 11.7% (32/273) |
| Angola | Luanda | 4.9% (2/41) | 38.1% (8/21) | 16.1% (10/62) |
| Zambia | Lusaka | 3.4% (2/59) | 31.6% (6/19) | 10.3% (8/78) |
| Kenya | Nairobi | 11.4% (4/35) | 59.1% (13/22) | 29.8% (17/57) |
| India | Delhi | 10% (23/229) | 21.2% (11/52) | 12.1% (34/281) |
| | Chennai | 3.9% (9/228) | 9.4% (3/32) | 4.6% (12/260) |
| | Kolkata | 5.9% (9/153) | 75% (6/8) | 9.3% (15/161) |
| Thailand | Bangkok | 2% (2/100) | 38.5% (5/13) | 6.2% (7/113) |
| China | Beijing | 2.4% (2/84) | 11.5% (3/26) | 4.5% (5/110) |
| Turkey | Istanbul | 0% (0/97) | 0% (0/6) | 0% (0/103) |
| Russia | Moscow | 1% (1/99) | 27.3% (3/11) | 3.6% (4/110) |
| Brazil | São Paulo | 0.9% (1/111) | 100% (4/4) | 4.3% (5/115) |
| Total | | 5% (79/1589) | 37.3% (131/351) | 10.8% (210/1940) |

Note: ^aPercentages are supported by total that failed testing/total samples tested.

Table 2 Testing results (failures recorded) by location of origin, registration status, and medicine type^a

| Registration status | Antimalarial | | Antimycobacterial | | Antibiotic | | Total |
|---------------------------------------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|-----------------------------------|
| | Yes | No ^c | Yes | No ^c | Yes | No ^c | |
| African cities | 6.6% (25/376) | 48% (60/125) | 3.2% (1/31) | 55.6% (5/9) | 7.4% (6/81) | 47.7% (31/65) | 18.6% (128/687) |
| Indian cities | 6.2% (10/161) | 22.7% (5/22) | 7.5% (15/199) | 20.6% (7/34) | 6.4% (16/250) | 22.2% (8/36) | 8.7% (61/702) |
| Cities of remaining countries ^b | 3.8% (1/26) | 0/0 | 0.87% (2/229) | 25.7% (9/35) | 1.3% (3/236) | 24% (6/25) | 3.8% (21/551) |
| Total | 6.4% (36/563) | 44.2% (65/147) | 3.9% (18/459) | 26.9% (21/78) | 4.4% (25/567) | 35.7% (45/126) | 10.8% (210/1940) |
| Total for both registered and unregistered^c | 14.2% (101/710) | | 7.3% (39/537) | | 10.1% (70/693) | | |

Notes: ^aPercentages are supported by total that failed testing/total samples tested; ^bCountries include Thailand, China, Turkey, Russia, and Brazil; ^cIncludes samples not known to be registered.

An aggregate “fail” was assigned to medicines failing at least one of the three quality tests (visual inspection, TLC, or disintegration). Some of these data have been previously published in the literature.^{6–8}

Registration status was determined after quality testing to eliminate possible bias. Not all medicines were procured from countries where it was possible to ascertain whether they were registered by the local competent authority. For more detailed information on medicine registration, see Africa Fighting Malaria’s working paper.² For 15 of 19 cities sampled, the authors were able to positively identify medicines registered in that country or either unregistered or not known to be registered. In some instances, up-to-date registration lists were not available, so the registration status for some of the medicines could not be confirmed. Many registration websites were incomplete, nonfunctioning, or contained old data. For those with reasonable data, 1940 medicines of 113 brands were identified, of which 1589 were registered and 351 were either unregistered or not known to be registered.

A basic paired *t*-test for mean failure rates was performed to determine whether there was a statistically significant difference between registered and unregistered medicines.

Results

The vast majority (81.9%, or 1589/1940) of medicines were registered in the countries from which they were procured. Of the remaining 18.1% (351/1940), some of the medicines may have been registered, but this was impossible to confirm, due to incomplete records.

Overall, 5% (79/1589) of registered samples failed testing, whereas 37.3% (131/351) of unregistered (or not known to be registered) samples failed testing (Table 1). African cities had fewer medicines registered (71%, or 488/687) than middle-income cities, 86.9% (610/702) of medicines

from Indian cities were registered, and 89.1% (491/551) of medicines from the remaining cities were registered. Samples from African cities also performed far worse in quality tests (18.6% failed, or 128/687) than either samples from Indian cities (8.7% failed, or 61/702) or other middle-income cities (3.8% failed, 21/551). The failure rate of registered medicines in African cities (6.6%, or 32/488) was similar to that of Indian cities (6.7%, or 41/610), but the failure rate of nonregistered medicines was far worse, at 48.2% (96/199) and 21.7% (20/92) respectively.

Across countries, the range of failure rates for registered medicines (0%–20%) was far smaller than the range for non-registered medicines (0%–100%). There was a statistically significant difference in the mean failure rates by city for unregistered medicines (mean = 41.3%, standard deviation [SD] = 26.7) and registered medicines (mean = 5.7%, SD = 5.3, paired *t*-test [*df* 14] = 5.25, *P* < 0.001).

There was a notable disparity in failure rates by medicine type. Antimalarials performed the worst (14.2%, or 101/710), followed by antibiotics (10.1%, or 70/693), and antimycobacterials performed best (7.3%, or 39/537) (Table 2). In general, Africa had higher failure rates regardless of medicine type or registration status, with the exception of antimycobacterials from India, which had the highest failure rate for registered antimycobacterials (although the African sample size was small for this subset). The remaining middle-income cities performed best for registered antimycobacterials.

Failure rates were highly associated with registration status (Table 2), although location, medicine type, and time of collection could also be associated.

Discussion

The results strongly indicate that medicine registration is an important component of better-quality medicines. For every

medicine type in every location (where both registered and unregistered samples were procured), registered medicines performed better than unregistered medicines, and the result was strongly statistically significant.

It is not surprising that Africa performed worse than middle-income nations in terms of quality control testing; this is nothing new and has been established in the literature.^{9,10} But a possible testable cause, such as registration status, has not been measured empirically until it was attempted in this study. African cities had far more unregistered medicines than Indian cities, and unregistered medicines from Africa performed much worse than those from India. However, medicines registered in African cities performed slightly better than those from Indian cities. Medicine types, specific brands, and the locations of manufacturers could be causes, and future research is being done to assess this further.

The remaining middle-income, wealthier cities had slightly fewer unregistered medicines than Indian cities, and registered medicines from these cities performed considerably better than those from India. It is not established in this paper, but it is quite plausible that greater wealth is associated with more medicines being registered and better performance of those registered medicines.

The causes for lack of registration require further investigation. In some countries, this may be due to a problem with the medicine regulator itself. Regulatory agencies may lack financial and other resources, particularly lack of competent staff, and as a result they may be unable to keep pace with new medicine demands and registration of imported medicines. Another explanation is that the borders of some countries, notably Africa, are poorly enforced, and numerous medicines are being smuggled into these markets.

The finding of this paper lends support to efforts to register medicines. In the poorer parts of the world, notably Africa where this study found that over a quarter of medicines procured were not registered, it also provides a reminder of the importance of the process of medicine registration. Approval is not just a matter of formality but involves assessment of medicine quality and stability. It appears that many manufacturers, perhaps the majority counterfeiters, would fail to meet these requirements and hence are avoiding registering their medicines.

Antimalarials failed more often than other medicine types; however, more antimalarials were procured in Africa than other medicines. It is not the purpose of this paper to try to empirically assess whether location or medicine type is more important in explaining failure, once the obvious explanation of registration status is accounted for in

the analysis. The authors suggest that it is the location and the general regulatory environment that is a more powerful explanatory factor than the medicine type, but this has not been established in this paper or elsewhere. Indeed, this would be problematic because 113 brands were procured, some available in one location but not available in others, and it is possible that results are indicative of brand-specific effects and not just medicine type. The brand effects could reflect certain poor-quality manufacturers or the location of manufacture (as many of the medicines procured were not domestically produced). Furthermore, medicines collected in 2007 in Africa performed worse than those collected in 2010,⁷ and improved performance could reflect more medicines being registered; this temporal effect will be analyzed in future research. As the earlier collection consisted of only antimalarials, this could be another reason for poorer performance of this medicine type. Assessing whether location, medicine type, or time of collection is a more important cause of failure may be hard to disentangle, because it is suspected that they are often interrelated.

Conclusion

Given the expected importance of competent medicines agencies overseeing and registering approved medicines, it is of little surprise that registered medicines failed noticeably less often than unregistered or not known to be registered medicines. This fact is exemplified most obviously by the performance of medicines procured in African cities. Indeed, the authors conclude that Africa's poorer performance in medicine quality can at least partly be explained by the fact that African nations have proportionally relatively fewer medicines registered than the other locations.

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Disclosure

The authors report no conflicts of interest in this work.

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