
# Are Drugs Made in Emerging Markets Good Quality?

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**Are drugs made in emerging markets good quality?**
A preliminary assessment of product consistency by use of Raman spectra

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Summary

Increasing competition generally decreases product prices. But in the case of pharmaceuticals, this is only beneficial if competitor products are therapeutically equivalent (bioequivalent). One measure of quality control is a consistently made product, examined in detail in this paper. A comprehensive study of drug samples in African and Asian countries--assessed for variability by spectrometer--suggests that registered products perform notably better than unregistered products. As all of the sampled drugs are used to treat potentially lethal infections, this product variability (particularly of unregistered drugs) could prove detrimental to public health.

Future analysis will assess how significant these spectral differences are in terms of drug quality and hence how important changes in policy should be to limit quality variability.

## Background

Demand for pharmaceuticals in mid-income and developing countries is increasing rapidly. Some major western companies now generate 25% of their revenue from emerging markets,[1] up from single-digit percentages only a decade ago. Internationally-traded generic drugs have also moved into these markets. Recently, many nations--sometimes supported by western aid agencies--have developed their own pharmaceutical production capabilities.

In principle, expanded drug production is good for consumers, since increased competition will cause prices to fall, thereby increasing access to drugs and ultimately patients' welfare. More products are only beneficial to the patient, however, if the products are "bioequivalent" (act in the same way in the body) to the approved products which they are copying.

In a previous paper, my research team assessed the basic quality performance of drugs, finding that those procured in Africa performed worse than those in mid-income nations. In addition, registered products, those which had been approved by the national drug regulatory agency of the countries from which the drugs were procured, performed better in every location than those which were not registered or probably not registered. In some instances, medicines were not on approved medicine lists, but the companies informed researchers the products were registered. In other instances products had previously been registered but recently had been delisted for a variety of reasons. [2] This paper builds on that previous analysis.

## Methods

Organic compounds, such as medicines, have a spectral "fingerprint." Each medicine's spectrum can be differentiated from similar products. There are many types of spectra; this paper uses spectra obtained by scanning products with the Truscan Raman spectrometer. Here, I aim to establish whether the raman spectra of products procured in the field varied noticeably from a good quality reference sample.[3] Significant variability is most likely an indicator of production failures, which are likely to undermine drug quality. A spectral profile of a reference sample was established for each product using the Truscan. This entails scanning known good quality (reference) samples of each product in order to establish a spectral profile against which other samples of the product can be tested.

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[1] http://www.allbusiness.com/company-activities-management/financial/14031536-1.html

[2] Bate R, L Mooney and K Hess. Medicine Registration and Medicine Quality: A Preliminary Analysis of Key Cities in Emerging Markets. *Research and Reports in Tropical Medicine.* 2010:1, 89-93 (Dec 2010). DOI: 10.2147/RRTM.S15199

[3] A "pass" measured rapidly by a handheld Raman spectrometer indicates that any variability is within allowable limits, however this does not denote consistent quality (since this method cannot test for whether the trace elements, degradation byproducts, and solubility of the product are acceptable).

Following previous sampling methods,[4] essential drugs were procured by covert shoppers from private sector drug stores and pharmacies in 19 cities across 17 countries. Sampling came from 11 African cities, 3 Indian cities, and in 5 mid-income cities – Sao Paolo, Moscow, Bangkok, Istanbul and Beijing. The essential drugs collected were for the treatment of malaria, tuberculosis and bacterial infections (see Table 1).

Over the past three years, 2121 drug samples have been procured. Given the extant literature, I expected to find deliberate counterfeit or substandard products. In order to focus this research on product variability, all dubious products were removed from the sampling.[5] After removing the obviously expired, degraded, substandard and counterfeit products from the dataset, 1838 samples remained. These samples included 121 brands, 13 different types of drugs, and spanned three therapeutic drug classes.[6]

Samples of each product were tested using the Raman spectrometer, and variations from the spectral profile were assessed for each product. In keeping with standard practice, deviations of up to 5% from this profile were considered to be an acceptable amount of product variation.[7] Any product with a deviation greater than 5% was considered a "failure."[8]

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[4] Bate R, Coticelli P, Tren R, Attaran A (2008) Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa – A Six Country Study. PLoS ONE 3(5): e2132. doi:10.1371/journal.pone.0002132

[5] It was assumed that the most obvious examples of fake, degraded or substandard products could be detected; therefore, the authors attempted to exclude products deemed suspect using the Global Pharma Health Fund e.V. Minilab® protocol. Forty-three of the 2121 samples appeared degraded, containing pills that were crumbling or significantly discolored. An additional 39 samples appeared to be counterfeit by means of visual inspection, with packaging containing spelling errors, incorrect fonts or printing colors, or other obvious defects; of these, 15 were deemed counterfeit by the legitimate manufacturers. An additional 145 samples failed thin layer chromatography testing for active pharmaceutical ingredient and/or simple disintegration, using the Global Pharma Health Fund e.V. Minilab®, indicating they were either counterfeit or seriously substandard. 56 samples were removed due to prior expiration.

[6] Drugs consisted of nine antimalarials, to include chloroquine, sulfadoxine-pyrimethamine, mefloquine, amodiaquine, artemether, artesunate, dihydroartemisinin and two artemisinin-based combination therapies (artemether-lumefantrine and artesunate-amodiaquine); two antimycobacterials, to include isoniazid and rifampicin; and two antibiotics, to include ciprofloxacin and erythromycin.

[7] David E. Bugay and Robert C. Brush, "Chemical Identity Testing by Remote-Based Dispersive Raman Spectroscopy," Appl. Spectrosc. **64**, 467-475 (2010)
http://www.opticsinfobase.org/as/abstract.cfm?URI=as-64-5-467

[8] A failure does not mean the product is definitely substandard, counterfeit or unsafe; it simply means inconsistency with the profile established. In other words, the spectra reflects notably different compounds or compounds in notably different concentrations from those that would be present in the reference sample. Variability implies problems with consistent manufacturing of the product. Indeed, measured variability probably underestimates quality problems since the spectrometer cannot pick up all types of product variability.

Finally, the packaging of the 1838 samples was assumed to be legitimate (e.g. a US-packaged drug was assumed to be manufactured in the US – however, this potentially ignores counterfeits missed during the initial screening).

Results

The 1838 samples were stratified by apparent country of origin and manufacturing class, and, where appropriate, by the size of the company. Generally speaking, there was the most variability in products made in Africa, followed by products made in China, Vietnam and the smaller producers in India.

None of the innovator brands produced in the European Union, Switzerland or the United States failed spectrometry testing; 4% of non-domestically produced generic drugs and 7% of drugs manufactured from within the countries they were also procured failed testing (see Table 2). The failure rate of drugs produced by African companies was 9.3% (ranging from 0% in South Africa and Morocco to 14.3% in Ghana and the Democratic Republic of the Congo); the failure rate of Chinese companies was 7.7%; of Vietnamese companies: 4.9%; of Indian companies: 4.4, and of "western" companies: 0.23%[9] (see Table 3). The failure rate of western companies' generic drugs was higher than that of innovator brands, with one failure as opposed to zero.

It was not possible to compare product variability by drug type in a useful way because not all drugs were procured in every location. It is worth noting that there were relatively more failures among antimalarials than among antimycobacterial drugs or antibiotics (see Table 1). One explanation for this finding is that antimalarials are made and sold in Africa, where drug quality is lower, more often than the other types.[10] Support for this assumption came from the fact that the one drug sold in all sampled countries – ciprofloxacin – did indeed fail more often in Africa than in other markets (mirroring the overall data) – albeit sample sizes were small in some markets for this universally available drug.

Among antimalarials, some products were only available in India, while others were only available in Africa. No antimalarials were available in the cities of Istanbul, Beijing and Moscow, where malaria is non-existent or rare. Some antimycobacterial drugs bought in these mid-income nations were not available in many African cities – making proper comparisons impossible.

Analysis of the Indian drugs procured in this research project showed a marked disparity in product consistency between products of large companies (designated as those with more than $300m annual revenue) and those of small companies (designated as those with less than $300m annual revenue) (See Table 4). Nearly 800 products were made in India, of which 327 were manufactured by smaller companies and 471 were manufactured by larger producers. Overall, 35 products failed testing, equating to 4.4% of the total; however, the failure rate of drugs produced by small companies was 8.9%, while the failure rate of drugs from large companies was 1.3%.

[9] "Western" companies were those located in the EU, Switzerland and the US.

[10] Bate et al Plos one 2008

Perhaps the most interesting result was that larger Indian generic producers performed almost identically (1.3% failed) to smaller western (predominantly European) generic producers (1.2% failed), although the sample size of the latter was relatively small (consisting of one failure out of 82 samples).

For 15 of 19 countries sampled, we could positively identify drugs which were registered in each country, comparing those to drugs which were either not registered or probably not registered. In some instances, up-to-date national drug registration lists were not available so the registration status for some of the drugs could not be confirmed. Many registration websites were incomplete, non-functioning or contained old data. Ultimately, 1707 products were identified, of which 1438 were registered and 269 were either not registered or probably not registered (See Table 5). The failure rate among registered products was 3.3% and 13% amongst products which were not registered or probably not registered.

Of the 269 products which were probably not registered, 135 were from Indian producers, another 26 were from other Asian producers, 104 were from African producers, and two each were from Brazilian and European producers.

Overall, the products with the least variability were originator-branded drugs, followed by those produced by large Indian generics companies and European generic manufacturers – these types of products performed noticeably better than products made by other manufacturers.

## Discussion

The results of this research project show considerable product variability across producers by country and by size of company. India is a case in point: the larger Indian generics companies and western manufacturers, all of which have annual revenues of over $300 million, generally make products with consistent spectra, whereas smaller Indian companies, those from other parts of Asia, and the vast majority of the companies in Africa, have far larger product spectra variability.

More consistent production is also associated with (and perhaps caused by) business environments with stricter enforcement of production regulations. Drugs from EU-based or large Indian-based firms, which sell vast quantities of drugs in Africa, performed better than drugs made in markets where regulatory enforcement is weak, such as some countries of East Africa, notably Kenya.[11]

It is not surprising that where we had sufficient details on product registration (in 15 sampled countries), registered products' spectra failed noticeably less than unregistered or probably unregistered products. This provides support for the importance of the process of product

[11] See Bate R, Putze E, Naoshy S, McPherson A, Mooney L. Drug registration – a necessary but not sufficient condition for good quality drugs – a preliminary analysis of 12 countries. Africa Fighting Malaria. 2010 October 1. Available from: http://www.fightingmalaria.org/pdfs/productregistration.pdf. Accessed October 1, 2010.

registration. Approval is not just a matter of formality, instead involving assessment of product quality and stability.

This also lends support to efforts being made by the international community, such as the USAID-funded Promoting the Quality of Medicines (PQM) project. PQM helps regulators in mid-income and developing countries register products, conduct post-marketing surveillance, form consistent Good Manufacturing Practice (GMP) requirements, and even assist some companies achieve GMP status.[12] These efforts appear to be necessary since, as this research project found, the products of local African firms and many from Asia are more variable than (and hence probably not interchangeable with) their more "reputable" western and Indian counterparts.

Again we look at India, which provides an interesting location for study since its companies make products with differing degrees of variability. It is beyond the remit of this research project, but it would be useful to analyze whether the regulations are the same, or enforced to the same extent, in the various production locations. For example, while it is true that the larger Indian companies performed better than the smaller ones, it is also true that the best performing companies came from two states – Maharastra and Andra Pradesh,[13] which report having better enforcement of laws than other states in India. So perhaps the companies have made high-quality products, won market share and attained large revenues today as a direct result of the rules enforced in those states. Furthermore, study of the companies' histories might provide valuable insight as to whether law enforcement has a bearing on how long it takes before product variability is reduced by inculcating GMP into the ethos of the company.

Sample sizes of drugs produced in the mid-income nations of Brazil, Turkey, Russia, and Thailand were small, and so must not be looked at in isolation. Overall, 8 of 70 products made in these countries failed variability tests, which is a failure rate similar to African producers. Yet it is interesting to note that these countries had very few products (either domestically produced or imported) that were removed from the dataset because they were obviously counterfeit, degraded, expired, or substandard products. This suggests that these countries have generally higher product standards than African nations, but considerable variability in some drugs indicates that quite a few products do not appear to be up to western GMP standards.

Analysis of the regulatory structures in each of these countries points to generally well-performing institutions, but each country has flaws, which vary by location. Brazil allows "similars" to be sold; these are products not established as being bioequivalent to innovator brands.[14] Russia's regulatory officials seem to turn a blind eye to a common practice in Russia, whereby legitimate local companies produce poor-quality versions of medicines to make money on the side.[15] Thailand has had political problems with its government-owned pharmaceutical

[12] http://www.usaid.gov/press/releases/2009/pr091026_1.html
[13] http://www.policynetwork.net/sites/default/files/Safe_Medicines_Chest_2010.pdf
[14] "Frequently Asked Questions," *ANVISA Official Website* Available at: http://www.anvisa.gov.br/eng/generic/faq.htm#02 Accessed 15 August 2010
[15] "New Russian Pharmaceutical Bill passed on final reading," *Global Insight Perspective* (26 March 2010) Available at: http://www.ihsglobalinsight.com/SDA/SDADetail18459.htm Accessed 2 August 2010

company, which has produced substandard medicines as in the case of GPO-vir, an HIV treatment.[16]

China has the reputation of producing many, perhaps most, of the world's fake drugs,[17] as well as allowing sloppy production of many products which have killed an indeterminate number of people.[18] Thus it is not surprising that some of its legitimate products have some variability, given the apparent lack of production oversight. In 2008, prior to the Beijing Olympics, China began tightening its production standards by enforcing more rigorous licensing requirements for drug manufacturers. Like India, however, China still has unevenly enforced quality control, notably in certain states, such as the Shenzhen free trade zone.[19]

For now, it is enough to say that based on anecdotal evidence from numerous product seizures and this more systematic research project, products in global demand (e.g. ciprofloxacin) cannot be assumed to be made to the same standards across the globe.

## Conclusions

This research project demonstrated that although some domestically made products may be of good quality, their spectra are certainly not as consistent as either originator brands or internationally traded Indian or European generics. By comparison, the spectra of products from mid-income countries do worse than these generics but better than African products. Registered products notably perform better than those not registered or probably not registered.

Variability in product consistency is greatest in products made by small companies targeting their home market; the inevitable conclusion is that many producers are not complying with western GMP standards and hence their products are not interchangeable with either internationally traded generic products or brands.

This means that many patients in Africa and some in mid-income nations are taking legitimate products, which have not degraded but may still endanger their lives. My ongoing research is trying to assess how dangerous this situation is, and how it can be improved.

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[16] 'Safe at any cost? Thailand's generic AIDS drugs don't meet international standards and so questions about their efficacy linger' Daniel Ten Kate WEDNESDAY, 24 JANUARY 2007 http://www.asiasentinel.com/index.php?option=com_content&task=view&id=351&Itemid=392 Accessed 17 August 2010.

[17] China's Counterfeit Medicine Trade is booming, Canadian Medical Association Journal, Nov 10 2009, 181, 10, available at http://www.cmaj.ca/cgi/content/full/181/10/E237

[18] One example is the fatal melamine contamination of milk, see http://news.bbc.co.uk/2/hi/asia-pacific/7843972.stm

[19] Office of the U.S. Trade Representative (USTR), "Special 301 Report," (2007) Available at: http://www.ustr.gov/sites/default/files/asset_upload_file230_11122.pdf Accessed 15 August 2010

Tables

Table 1: Testing results by region of origin and drug type[a]

| | Antimalarial drugs | Antimycobacterial drugs | Ciprofloxacin | Erythromycin | TOTAL |
|---|---|---|---|---|---|
| Africa | (34/485) 7.0% | (1/35) 2.9% | (7/99) 7.1% | (0/16) 0% | (42/635) 6.6% |
| India | (7/179) 3.9% | (12/229) 5.2% | (8/188) 4.3% | (3/79) 3.9% | (30/675) 4.4% |
| Remaining countries[b] | (0/21) 0% | (7/212) 3.3% | (6/198) 3.0% | (3/97) 3.1% | (16/528) 3.0% |
| TOTAL | (41/685) 6.0% | (20/476) 4.2% | (21/485) 4.3% | (6/192) 3.1% | (88/1838) 4.8% |

a. Percentages are supported by (total that failed testing/total samples tested)
b. Countries include Thailand, China, Turkey, Russia, Brazil

Table 2: Testing results by country and city of origin, and manufacturing class[a]

| | | Originator branded drugs | Non-domestic generic drugs | Locally manufactured generic drugs | TOTAL |
|---|---|---|---|---|---|
| Ghana | Accra | (0/14) 0.0% | (1/45) 2.2% | (3/18) 16.7% | (4/77) 5.2% |
| Ethiopia | Addis Ababa | (0/15) 0.0% | (1/16) 6.3% | (1/8) 12.5% | (2/39) 5.1% |
| Egypt | Cairo | (0/19) 0.0% | (0/21) 0.0% | (1/12) 8.3% | (1/52) 1.9% |
| Tanzania | Dar es Salaam | (0/7) 0.0% | (1/15) 6.7% | (1/6) 16.7% | (2/28) 7.1% |
| Uganda | Kampala | (0/10) 0.0% | (1/26) 3.8% | (3/16) 18.8% | (4/52) 7.7% |
| Rwanda | Kigali | (0/8) 0.0% | (0/0) | (0/0) | (0/8) 0.0% |
| Nigeria | Lagos | (0/19) 0.0% | (9/93) 9.7% | (13/90) 14.4% | (22/202) 10.9% |
| Angola | Luanda | (0/13) 0.0% | (0/22) 0.0% | (0/10) 0.0% | (0/45) 0.0% |
| D.R. Congo | Lubumbashi | (0/7) 0.0% | (1/18) 5.6% | (1/7) 14.3% | (2/32) 6.3% |
| Zambia | Lusaka | (0/15) 0.0% | (1/24) 4.2% | (2/25) 8.0% | (3/64) 4.7% |
| Kenya | Nairobi | (0/14) 0.0% | (1/14) 7.1% | (1/8) 12.5% | (2/36) 5.6% |
| India | Delhi | (0/4) 0.0% | (0/9) 0.0% | (14/230) 6.1% | (14/243) 5.8% |
| | Chennai | (0/2) 0.0% | (0/11) 0.0% | (9/228) 3.9% | (9/241) 3.7% |
| | Kolkata | (0/4) 0.0% | (0/7) 0.0% | (7/180) 3.9% | (7/191) 3.7% |
| Thailand | Bangkok | (0/40) 0.0% | (3/61) 4.9% | (1/8) 12.5% | (4/109) 3.7% |
| China | Beijing | (0/27) 0.0% | (1/30) 3.3% | (4/45) 8.9% | (5/102) 4.9% |
| Turkey | Istanbul | (0/52) 0.0% | (0/41) 0.0% | (1/6) 16.7% | (1/99) 1.0% |
| Russia | Moscow | (0/44) 0.0% | (0/36) 0.0% | (3/26) 11.5% | (3/106) 2.8% |
| Brazil | Sao Paolo | (0/42) 0.0% | (1/42) 2.4% | (2/28) 7.1% | (3/112) 2.7% |
| TOTAL | | (0/356) 0.0% | (21/531) 4.0% | (67/951) 7.0% | (88/1838) 4.8% |

a. Percentages are supported by (total that failed testing/total samples tested)

Table 3: Testing results by apparent country of manufacture

| | Total samples tested | Total samples failing Raman spectrometry | Percent failed |
|---|---|---|---|
| India | 798 | 35 | 4.4% |
| China | 169 | 13 | 7.7% |
| Vietnam | 61 | 3 | 4.9% |
| European Union[a] | 168 | 1 | 0.6% |
| Switzerland | 151 | 0 | 0.0% |
| United States | 119 | 0 | 0.0% |
| Nigeria | 121 | 13 | 10.7% |
| Kenya | 30 | 2 | 6.7% |
| Tanzania | 30 | 2 | 6.7% |
| Uganda | 22 | 3 | 13.6% |
| Ghana | 21 | 3 | 14.3% |
| Zambia | 24 | 2 | 8.3% |
| Brazil | 30 | 3 | 10.0% |
| Russia | 26 | 3 | 11.5% |
| 12 samples or fewer collected per country of manufacture[b] | 68 | 5[c] | 7.4% |
| TOTAL | 1838 | 88 | 4.8% |

a. Countries include United Kingdom, Belgium, Denmark, France, Germany and Italy
b. Countries include Egypt, D.R. Congo, Ethiopia, South Africa, Morocco, Thailand and Turkey
c. One sample from each of the following cities failed - Cairo, Addis Ababa, Lubumbashi, Bangkok and Istanbul

Table 4: Testing results by region (and size if appropriate) of apparent manufacturer

| | Total samples tested | Total samples failing Raman spectrometry | Percent failed |
|---|---|---|---|
| Large Indian Producers[a] | 471 | 6 | 1.3% |
| Small Indian Producers[b] | 327 | 29 | 8.9% |
| Chinese Producers | 169 | 13 | 7.7% |
| Southeast Asian Producers[c] | 69 | 4 | 5.8% |
| Western Producers[d] | 438 | 1 | 0.2% |
| African Producers | 302 | 28 | 9.3% |
| Producers in Mid-income Nations[e] | 62 | 7 | 11.3% |
| TOTAL | 1838 | 88 | 4.8% |

a. More than $300 million in annual revenue
b. Less than $300 million in annual revenue
c. Countries include Thailand and Vietnam
d. Countries include those within European Union, as well as Switzerland and United States
e. Countries include Brazil, Turkey and Russia

Table 5: Testing results by country and city of origin, and national drug registration list status[a]

| | | Registered samples | Unregistered (and probably not registered) samples |
|---|---|---|---|
| Ghana | Accra | (2/57) 3.5% | (2/20) 10% |
| Ethiopia | Addis Ababa | Registration list unavailable | |
| Egypt | Cairo | Registration list unavailable | |
| Tanzania | Dar es Salaam | (1/22) 4.5% | (1/6) 16.7% |
| Uganda | Kampala | (2/37) 5.4% | (2/15) 13.3% |
| Rwanda | Kigali | Registration list unavailable | |
| Nigeria | Lagos | (13/167) 7.8% | (9/35) 25.7% |
| Angola | Luanda | (0/35) 0% | (0/10) 0% |
| D.R. Congo | Lubumbashi | Registration list unavailable | |
| Zambia | Lusaka | (2/50) 4.0% | (1/14) 7.1% |
| Kenya | Nairobi | (1/28) 3.6% | (1/8) 12.5% |
| India | Delhi | (8/202) 4.0% | (6/41) 14.6% |
| | Chennai | (5/211) 2.4% | (4/30) 13.3% |
| | Kolkata | (4/144) 2.8% | (3/47) 6.4% |
| Thailand | Bangkok | (3/98) 3.1% | (1/11) 9.1% |
| China | Beijing | (1/82) 1.2% | (4/20) 20.0% |
| Turkey | Istanbul | (1/97) 1.0% | (0/2) 0% |
| Russia | Moscow | (3/98) 3.1% | (0/8) 0% |
| Brazil | Sao Paolo | (2/110) 1.8% | (1/2) 50% |
| TOTAL | | (48/1438) 3.3% | (35/269) 13.0% |

a. Percentages are supported by (total that failed testing/total samples tested)