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The Danger of Substandard Drugs in Emerging Markets: An Assessment of Basic Product Quality

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Abstract: Background: Increasing competition generally decreases product prices, but in the case of pharmaceuticals, this is only beneficial if competitor products are therapeutically equivalent. This study analyzed drug samples from countries with emerging economies, assessing them for basic quality. **Results:** Removing all obvious and suspected counterfeit products and degraded products, 1912 samples remained. 3.8% failed basic quality control tests performed with the Global Pharma Health Fund e.V. Minilab®. 5.2% failed product authentication by raman spectrometer. Africa has a greater problem with substandard products than any other location. **Conclusions:** Since all of the sampled drugs are used to treat potentially lethal infections, it is important that the threat of these substandard products be more widely recognized.

Key words: Substandard, counterfeit, pharmaceuticals, antimalarial, antibiotic, antimycobacterial, emerging economies

INTRODUCTION

Demand for pharmaceuticals in emerging economies is increasing and pharmaceutical companies are supplying medications to new consumers. Many developing nations, including Kenya, Uganda and Nigeria have recently developed their own pharmaceutical production capabilities and the number of licensed producers in India and China has increased significantly.

In principle, expanded drug production is good for consumers since increased competition will cause prices to fall, thereby increasing drug access and patients' welfare. However, if the cheaper drugs are not bioequivalent (act in the same way in the body) to the approved innovator products which they are copying, this trend could cause significant harm to patients.

Most research on poor quality drugs has focused on counterfeit products or failed to draw a distinction between counterfeit products and legal substandard products (Bate *et al*., 2010b). It concludes that the burden of poor quality drugs is acute in African nations, but also extends in smaller quantities to most emerging markets. However, few studies have addressed the quality of the legitimate drugs sold in these markets. By removing counterfeit drugs, as far as is knowable, from the study sample and subjecting remaining samples to basic quality control tests, this study tentatively evaluates whether legally produced but substandard products are a threat to public health in emerging markets.

MATERIALS AND METHODS

Following previous sampling methods (Bate *et al*., 2008), essential drugs were procured by covert shoppers from randomly selected private sector drug stores and pharmacies in 19 cities across 17 countries. Study agents posing as customers were asked to purchase a sample lot of antimalarial, antibiotic, or antimycobacterial tablets from the formulations available. Treatment packs which were either purchased and stored in the manufacturer's original packaging or loose in paper envelopes, were kept in appropriate conditions until testing. Tests were completed within 40 days of sample collection. Samples came from 11 African cities, 3 Indian cities and 5 mid-income cities-São Paolo, Moscow, Bangkok, Istanbul and Beijing. The essential drugs collected were for the treatment of malaria, tuberculosis and bacterial infections (Table 1).

Over the past three years, 2121 drug samples were procured. Given the extant literature (QAMSA, 2011), we expected to find counterfeit products. In order to focus this research on substandard products, we endeavored to remove counterfeit and degraded products from the sample, 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. Visual inspection revealed 39 samples which were likely counterfeit because the packaging contained spelling errors, incorrect fonts,

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Table 1: Minilab testing results by region of procurement and drug type[a]

	Antimalarials			Antimyco-bacterials			Antibiotics: Ciprofloxacin			Antibiotics: Erythromycin			Total		
Region	Failures	Total	Percent	F	N	%	F	N	%	F	N	%	F	N	%
Africa	33	500	6.6	1	39	2.6	6	102	5.9	0	18	0.0	40	659	6.1
India	7	186	3.8	11	237	4.6	7	192	3.6	3	84	3.6	28	699	4.0
Remaining countries[b]	0	22	0.0	3	222	1.4	2	206	1.0	0	104	0.0	5	554	0.9
Total	40	708	5.6	15	498	3.0	15	500	3.0	3	206	1.5	73	1912	3.8

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

unusual colors or other obvious defects. Of these, 15 were confirmed counterfeit by the legitimate manufacturers. An additional 71 samples were deemed counterfeit since they contained no active ingredient. The fifty-six samples which had expired before they could be tested were also excluded from the analysis.

After removing these obviously expired, degraded and counterfeit products from the dataset, 1912 samples remained. The packaging of these samples was assumed to be legitimate. For example, a US-packaged drug was assumed to be manufactured in the US. This potentially ignores more sophisticated counterfeits which had excellent packaging, contained significant quantities of API and passed initial screening. The sample included 123 brands and spanned three therapeutic drug classes[1].

All 1912 samples were subjected to tests under the Global Pharma Health Fund e.V. Minilab® protocol in order to assess their likely efficacy and compliance with the most basic of pharmacological regulatory standards. The Minilab® was used to run semi-quantitative Thin-Layer Chromatography (TLC) and disintegration tests on each sample to determine the presence and relative concentration of active ingredients and conduct the most basic assessment of solubility. Each test was run in duplicate, with the generous assumption that the result more consistent with the reference was recorded. The Minilab® protocols award products a pass if they have 80% or more of the labeled active ingredient(s) (note there is no upper-bound limit). For fixed-dose combinations and SP, a pass was awarded only if both active ingredients met this standard.

The samples were also analyzed with the TruScan® raman spectrometer. Medicines have a unique spectral fingerprint which can be used to detect minor differences in the drug's chemical make-up. Each product was authenticated by examining the sample's spectrum against a verified original. Variations of greater than 5% from the spectral profile were considered substandard, in line with previous studies (Bugay and Brush, 2010). While this is a more exacting standard than the Minilab test, the spectrometer still is unable to test for trace impurities and other small but potentially dangerous defects.

RESULTS

Minilab® testing revealed that 73 (3.8%) of the total 1912 samples did not pass minimal quality requirements. The spectrometer yielded a failure rate of 5.2% (100 failures). The spectrometer's more exacting standard caught a larger number of failures in the sample of Chinese-produced drugs and in all products made and bought in Africa. Apart from this discrepancy, the difference between the Minilab results and the spectrometry results is slight. In compliance with general practice and the wide use of the Minilab in other studies, the Minilab results are those discussed in this section. Comparisons are available in the tables at the end of this study (Table 5-8).

The 1912 samples were stratified by apparent country of origin and manufacturing class. Additionally, since our samples contained large quantities of Indian companies' products, these were also broken down by the company's size. A total of 3.4% of generic drugs imported and 5.5% of drugs produced and purchased in the same country failed testing (Table 2). The failure rate of drugs produced by African companies was 8.3% (ranging from 0% in South Africa and Morocco to 14.3% in Ghana); Chinese companies: 5.1%; Vietnamese companies: 4.7%; Indian companies: 3.9% and western companies[2]: 0.21% (Table 3, 4).

None of the innovator brands produced in the European Union, Switzerland or the United States failed Minilab testing. Large generic producers in Europe and India also performed very well with only 1.2 and 0.8% failures respectively.

It is worth noting that there were relatively more failures among antimalarials than among antimycobacterials or antibiotics (Table 1). This probably

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

[2]Western companies were those located in the EU, Switzerland and the US

Table 2: Minilab testing results by country and city of procurement and manufacturing class[a]

		Originator branded drugs			Non-domestic generic drugs			Locally manufactured generic drugs			Total		
Country	City	F	N	%	F	N	%	F	N	%	F	N	%
Ghana	Accra	0	15	0.0	1	47	2.1	3	18	16.7	4	80	5.0
Ethiopia	Addis Ababa	0	15	0.0	1	17	5.9	1	8	12.5	2	40	5.0
Egypt	Cairo	0	19	0.0	0	23	0.0	1	13	7.7	1	55	1.8
Tanzania	Dar es Salaam	0	10	0.0	1	17	5.9	1	6	16.7	2	33	6.1
Uganda	Kampala	0	10	0.0	1	29	3.4	2	18	11.1	3	57	5.3
Rwanda	Kigali	0	8	0.0	0	0	0.0	0	0	0.0	0	8	0.0
Nigeria	Lagos	0	19	0.0	8	98	8.2	12	94	12.8	20	211	9.5
Angola	Luanda	0	13	0.0	0	25	0.0	0	10	0.0	0	48	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	17	0.0	1	26	3.8	2	25	8.0	3	68	4.4
Kenya	Nairobi	0	16	0.0	1	18	5.6	1	8	12.5	2	42	4.8
India	Delhi	0	4	0.0	0	9	0.0	13	238	5.5	13	251	5.2
	Chennai	0	2	0.0	0	11	0.0	8	232	3.4	8	245	3.3
	Kolkata	0	4	0.0	0	7	0.0	7	190	3.7	7	201	3.5
Thailand	Bangkok	0	40	0.0	2	61	3.3	1	8	12.5	3	109	2.8
China	Beijing	0	29	0.0	1	32	3.1	1	45	2.2	2	106	1.9
Turkey	Istanbul	0	56	0.0	0	41	0.0	0	6	0.0	0	103	0.0
Russia	Moscow	0	47	0.0	0	38	0.0	0	26	0.0	0	111	0.0
Brazil	Sao Paolo	0	42	0.0	1	42	2.4	0	28	0.0	1	112	0.9
Total		0	373	0.0	19	559	3.4	54	980	5.5	73	1912	3.8

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

Table 3: Minilab testing results by apparent country of manufacture

Country	Producers	Total samples failing Minilab	Total samples tested	Percent failed
India	Large[a]	4	500	0.8
	Small[b]	28	331	8.5
China		9	177	5.1
Vietnam		3	64	4.7
European Union[c]		1	173	0.6
Switzerland		0	155	0.0
United States		0	128	0.0
Nigeria		12	125	9.6
Kenya		2	31	6.5
Tanzania		2	31	6.5
Uganda		2	23	8.7
Ghana		3	21	14.3
Zambia		2	24	8.3
12 samples or fewer collected country of manufacture[d]		4[e]	73	5.5
Brazil		0	30	0.0
Russia		0	26	0.0
Total		73	1912	3.8

[a]More than $300 million in annual revenue. [b]Less than $300 million in annual revenue. [c]Countries include United Kingdom, Belgium, Denmark, France, Germany and Italy. [d]Countries include Egypt, D. R. Congo, Ethiopia, South Africa, Morocco, Thailand and Turkey. [f]One sample from each of the following cities failed-Cairo, Addis Ababa, Lubumbashi and Bangkok

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

Producers	Total samples failing Minilab	Total samples tested	Percent failed[f]
Large Indian[a]	4	500	0.80
Small Indian[b]	28	331	8.46
Chinese	9	177	5.10
Southeast Asian[c]	4	72	5.56
Western[d]	1	456	0.22
African	26	314	8.30
Producers in Mid-income Nations[e]	1	62	1.61
Total	73	1912	3.82

[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 the European Union, as well as Switzerland and United States [e]Countries include Brazil, Turkey and Russia

reflects the location of purchase, as more antimalarials were procured in Africa where drug quality is lower overall (Bate *et al*., 2008). An analysis of ciprofloxacin, the one drug sold in all sampled countries, supports this assumption. Ciprofloxacin samples procured in Africa did indeed fail more often than when procured in other markets, mirroring the overall data.

It was not possible to compare product quality by drug type in a useful way because not all drugs were procured in every location. Some antimalarials were only

Table 5: Spectrometry testing results by region of procurement and drug type[a]

	Antimalarials			Antimycobacterials			Antibiotics: Ciprofloxacin			Antibiotics: Erythromycin			Total		
Region	F	N	%	F	N	%	F	N	%	F	N	%	F	N	%
Africa	48	500	9.6	5	39	12.8	9	102	8.8	1	18	5.6	63	659	9.6
India	9	186	4.8	12	237	5.1	8	192	4.2	3	84	3.6	32	699	4.6
Remaining countries[b]	0	22	0.0	3	222	1.4	2	206	1.0	0	104	0.0	5	554	0.9
Total	57	708	8.1	20	498	4.0	19	500	3.8	4	206	1.9	100	1912	5.2

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

Table 6: Spectrometry testing results by country and city of procurementand manufacturing class[a]

		Originator branded drugs			Non-domestic generic drugs			Locally manufactured generic drugs			Total		
Country	City	F	N	%	F	N	%	F	N	%	F	N	%
Ghana	Accra	0	15	0.0	3	47	6.4	3	18	16.7	6	80	7.5
Ethiopia	Addis Ababa	0	15	0.0	1	17	5.9	1	8	12.5	2	40	5.0
Egypt	Cairo	0	19	0.0	1	23	4.3	1	13	7.7	2	55	3.6
Tanzania	Dar es Salaam	0	10	0.0	2	17	11.8	2	6	33.3	4	33	12.1
Uganda	Kampala	0	10	0.0	2	29	6.9	4	18	22.2	6	57	10.5
Rwanda	Kigali	0	8	0.0	0	0	0.0	0	0	0.0	0	8	0.0
Nigeria	Lagos	0	19	0.0	10	98	10.2	15	94	16.0	25	211	11.8
Angola	Luanda	0	13	0.0	2	25	8.0	1	10	10.0	3	48	6.3
D.R. Congo	Lubumbashi	0	7	0.0	2	18	11.1	2	7	28.6	4	32	12.5
Zambia	Lusaka	0	17	0.0	2	26	7.7	4	25	16.0	6	68	8.8
Kenya	Nairobi	0	16	0.0	2	18	11.1	3	8	37.5	5	42	11.9
India	Delhi	0	4	0.0	0	9	0.0	14	238	5.9	14	251	5.6
	Chennai	0	2	0.0	0	11	0.0	10	232	4.3	10	245	4.1
	Kolkata	0	4	0.0	0	7	0.0	8	190	4.2	8	201	4.0
Thailand	Bangkok	0	40	0.0	1	61	1.6	1	8	12.5	2	109	1.8
China	Beijing	0	29	0.0	1	32	3.1	1	45	2.2	2	106	1.9
Turkey	Istanbul	0	56	0.0	0	41	0.0	0	6	0.0	0	103	0.0
Russia	Moscow	0	47	0.0	0	38	0.0	0	26	0.0	0	111	0.0
Brazil	Sao Paolo	0	42	0.0	1	42	2.4	0	28	0.0	1	112	0.9
Total		0	373	0.0	30	559	5.4	70	980	7.1	100	1912	5.2

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

Table 7: Spectrometry testing results by apparent country of manufacture

Country	Producers	Total samples failing Spectrometry	Total samples tested	Percent failed
India	Large[a]	5	500	1.00
	Small[b]	29	331	8.76
China		15	177	8.47
Vietnam		7	64	10.94
European Union[c]		1	173	0.58
Switzerland		0	155	0.00
United States		0	128	0.00
Nigeria		18	125	14.40
Kenya		4	31	12.90
Tanzania		4	31	12.90
Uganda		4	23	17.39
Ghana		4	21	19.05
Zambia		4	24	16.67
Brazil		0	30	0.00
Russia		0	26	0.00
12 samples or fewer collected per country of manufacture[d]		5[e]	73	6.85
Total		100	1912	5.23

[a]More than $300 million in annual revenue. [b]Less than $300 million in annual revenue. [c]Countries include United Kingdom, Belgium, Denmark, France, Germany and Italy. [d]Countries include Egypt, D.R. Congo, Ethiopia, South Africa, Morocco, Thailand and Turkey. [e]Samples from each of the following cities failed-Cairo, Addis Ababa, Lubumbashi and Bangkok

available in India while others were exclusive to Africa. No antimalarials were available in the cities of Istanbul, Beijing and Moscow, where malaria is non-endemic. Some antimycobacterial drugs bought in these mid-income nations were not available in many African cities.

Analysis of the Indian drugs procured in this research project showed a marked disparity in product quality between products of large companies (designated as those with more than $300m annual revenue) and those of small companies (designated as

Table 8: Spectrometry testing results by region (and size if appropriate) of apparent manufacturer

Producers	Total samples failing Spectrometry	Total samples tested	Percent failed
Large Indian[a]	5	500	1.00
Small Indian[b]	29	331	8.76
Chinese	15	177	8.47
Southeast Asian[c]	8	72	11.11
Western[d]	1	456	0.22
African	42	314	13.38
Producers in Mid-income Nations[e]	0	62	0.00
Total	100	1912	5.23

[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 the European Union, as well as Switzerland and United States [e]Countries include Brazil, Turkey and Russia

those with less than $300 m annual revenue) (Table 4). 831 products were made in India, of which 331 were manufactured by smaller companies and 500 were manufactured by larger producers. Overall, 32 Indian products failed testing, equating to 4.4% of the total. However, the failure rate of drugs produced by small companies was 8.5%, while the failure rate of drugs from large companies was only 0.8%.

Perhaps most interestingly, larger Indian generic producers performed better (0.8% failed) than western (predominantly European) generic producers (1.2% failed), although the sample size of the latter was relatively small, consisting of only 83 drugs.

Overall, the best quality products were innovator-branded drugs, followed by those produced by large Indian generics and European generics manufacturers. Their products performed noticeably better than products made by other manufacturers.

N.B. Recall that none of the samples' solubility or trace impurities were assessed, so the overall substandard rate is likely higher, perhaps significantly, than that detected by the Minilab®. The outcome of the spectrometer testing substantiates this result: where there was any variation between the two methods of testing, the spectrometer detected a greater number of failures than the Minilab. Further or more sophisticated testing would likely have revealed an even greater number of failures than our initial testing.

DISCUSSION

This research project demonstrates that a small but significant percentage of legal pharmaceuticals in emerging markets do not meet basic quality standards. The spectrometry results from drugs made in Africa and China are noticeably worse than the Minilab resultswhich we suggest may be interpreted in two possible ways. One possibility is that Minilab did not detect the more sophisticated fakes which should be removed from the sample. Alternatively, the additional failures may be legitimate products which are still substandard. Further research may lead us to a more robust explanation. In both cases, these products are dangerous and should not be prescribed to patients.

Indian producers provide an interesting study in company size. Large Indian generics companies, with revenues over $300 million, produce drugs of comparable quality to western manufacturers (less than one per cent failure rate). In stark contrast, some smaller Indian companies produce medicines of lower quality whose failures rates are similar to those produced by African manufacturers (greater than eight percent).

Quality production is probably associated with (and encouraged by) business environments with stricter regulatory enforcement. We further suggest that the size of the problem varies, probably influenced by the producer's home country or, as in India's case, local state oversight requirements, the consumer nation's regulatory strength and the company's size. Unsurprisingly, poorer nations are less effective at monitoring drug production and import and smaller companies perform worse than their larger counterparts (Bate *et al*., 2010a).

While sample sizes of drugs produced in the mid-income nations of Brazil, Turkey, Russia and Thailand were small, this study suggests that these countries also have higher product standards than African nations.

China has the reputation of producing many, perhaps most, of the world's counterfeit drugs (Lewis, 2009), as well as allowing sloppy production of other products, such as melamine contaminated milk, which have killed an indeterminate number of people. Thus it is not surprising that some of its legitimate products have significant quality concerns (USTR 2007, Special 301 Report).

This research project used chromatography and spectrometry analysis to demonstrate that product quality is not uniformly good in poorer markets, most notably in Africa, even once illegal counterfeit and obviously degraded products are removed from the sample.

Although most domestically-produced drugs in poorer nations are good quality, overall, originator brands or internationally-traded Indian or European generics are superior.

In emerging markets, our study suggests that companies targeting their home market produce the highest percentage of substandard drugs. In these cases, the inevitable conclusion is that many producers are not complying with GMP standards and hence their products are not always interchangeable with either internationally-traded generic products or innovator brands.

Even if governments in the developing world were able to eliminate all fake and degraded products from their pharmaceutical markets, our research suggests that some of the remaining legitimate products could still endanger a patient's life. This danger is most pronounced in Africa, where the combination of poor oversight of the manufacturing process and of imported medications allow low-quality drugs to infiltrate the supply chain.

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