AFRICA FIGHTING MALARIA BULLETIN #5

January 13, 2011

Improving Assessments of Fake and Substandard Drugs in the Field

By Roger Bate

Introduction

Substandard and counterfeit drugs can be lethal to patients and accelerate drug resistance across at-risk populations. This is a major problem for diseases like malaria with few high-quality treatments available. Some African governments, notably Nigeria and Ghana, have responded to this challenge, often with help from donors, and have deployed an array of technologies to assist them.

In 2007, our research team tested anti-malarial drugs collected from six African cities and found that roughly a third of the medicines failed at least one quality control test (see http://www.plosone.org/article/info:doi/10.1371/journal.pone.0002132). In 2010, further research was published on repeat testing of drugs collected from some of the original cities as well as additional cities in different countries (see http://www.malariajournal.com/content/9/1/157 and http://www.dovepress.com/medicine-registration-and-medicine-quality-a-preliminary-analysis-of-k-peer-reviewed-article-RRTM).

This research provided some interesting data about quality differences by location and drug type. It also showed that over time drug quality has probably improved in at least some cities. But the details of the testing results might also point to a potential problem for authorities, which we discuss here alongside potential solutions.

The drugs were tested using the Global Pharma Health Fund e.V. Minilab®, which is a series of tests forming a useful protocol. It begins with a visual inspection of the product, followed by an easy and inexpensive dye test for active ingredient and a disintegration test for basic solubility. A more complicated, but still relatively inexpensive, thin-layer chromatography (TLC) assay for active pharmaceutical ingredient (API), is the next phase. After these tests, suspect products can then be sent to a proper laboratory for more detailed analysis, such as high performance liquid chromatography (HPLC). Following such a protocol, including compendial laboratory analysis, fake and substandard drugs can be identified allowing authorities to take appropriate action.

But in the real world, the entire protocol may not be followed, and even the more complex but more portable parts may not be followed either. Visual inspection is easy in principle but harder than one would expect even for those with patience. Thankfully, disintegration and dye tests are straight forward, but while TLC is not very complex, it does require electricity, a fair number of chemicals and laboratory equipment, and some training. A high school graduate could be trained in a week, and someone with laboratory experience from a university, such as myself, could competently use the Minilab® in a couple of days. But even those with training will attest that it

takes quite a bit longer to truly appreciate this science, which is also something of an art form in interpretation.

So it is possible that in at least some settings, the only tests actually undertaken will be visual inspection and maybe the appropriate dye test. These tests are enough to find the most obvious fakes; but a considerable problem in emerging markets is substandard and degraded products, which, like the "better" fakes, might contain enough active ingredients to pass dye tests. So, one has to wonder how many fakes are missed by just performing the simplest tests?

Methods/Results

In an attempt to answer this question, I went back to our data to see how many of the fake or substandard products we identified would have been missed by only undertaking visual inspection, disintegration and dye tests, and not TLC. It is obvious that more sophisticated techniques, such as Raman spectrometry, which we did undertake, lead to the discovery of more fake and substandard drugs than Minilab® tests, but deploying hand-held spectrometers is even more expensive and unlikely in poor world settings.

Taking just the anti-malarial artemisinin-based products from all samplings, we had 414 samples in testable form, consisting of 276 monotherapies and 138 artemisinin-based combination therapies (ACTs) (See Table 1). Overall, 53 samples failed the Minilab® protocol, of which 26 had zero API, 7 had (approximately) 100% API (these products failed for other reasons, such as obvious counterfeit packaging or failing disintegration testing), and 20 had non-trivial (roughly 15-75%) amounts of API.[1]

Table 1. Testing results by drug type and amount of API[i]

Drug Type	**Zero API**	**100% API**	**Some API (15-75%)**	**Total Failed/ Total Tested**
ACTs	5/138	2/138	4/138	11/138
Artemisinin monotherapies	21/276	5/276	16/276	42/276
Total Failed/ Total Tested	26/414	7/414	20/414	53/414

i. There were a total of 414 samples (276 monotherapies and 138 ACTs), of which 361 had 100% API and passed all Minilab® tests. The remaining 53 samples that failed tests had the above API concentrations (7 samples had 100% API but were failed for different reasons).

[1] Of those that could be tested with a Raman spectrometer, 389 samples remained. From within this subset, 56 samples failed spectrometry testing, and 49 samples failed TLC or other Minilab® tests (all of which failed spectrometry testing; in other words, 7 samples failed spectrometry, which had not failed TLC or other Minilab® tests.)

The 20 samples which contained some API were failed by the TLC assay, but passed the existing rapid red dye test currently deployed by Minilab®. In other words, these products (4.8% of the total sample and 37.7% of those products which failed the full Minilab® protocol) might not have been subject to further testing and would have stayed on the market were TLC not available or not properly undertaken.

Discussion

Given that the Minilab® is not a trivial cost (about $5,000 to start, and more if training is required), it is quite likely that there are many places that could afford to deploy stand alone dye tests (at less than $1/test) but could not deploy TLC, and certainly not more sophisticated techniques. In such circumstances then, at least some poor quality medicines would remain in circulation.

Improving field assessment methods is important because the counterfeiters watch what regulators are doing and have been able to adapt to changes in packaging and content in the past. In Southeast Asia, sixteen different holograms were copied by counterfeiters to pass off their anti-malarial drugs (see http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050032). And prior to the deployment of Minilabs®, counterfeiters, some caught on camera by the BBC for the documentary *Bad Medicine*, added a small amount of API to products. They did so in order to pass rapid dye tests, which had been deployed by anti-counterfeit agencies to find fakes. So the notion that counterfeiters would adapt again and add much more API, whilst still not ensuring a good quality product, is certainly plausible.

Some fake drug investigators in India and China I've spoken with believe that at least some counterfeiters are indeed making a wider array of fakes, including adding far more API for certain markets. Of course, they make less money this way, but avoiding detection while accepting lower profits may be an efficient trade off from their perspective.

In thinking about this problem, I was alerted to a new dye test developed by scholars at the London School of Hygiene and Tropical Medicine (LSHTM) (see http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007270). From speaking with one of the developers of this assay, Dr Harpakash Kaur, and by assessing the above paper, it appears that this dye test is more sensitive to concentration of API than current dye tests. And hence it would have captured most of the 20 samples with non-trivial amounts of API because the result would have been noticeably different than either zero or 100% API. Of those 20 samples, 17 had approximately between 15% and 40% of API, three had between 50% and 75%. It is possible that the final three might have passed, and from inspection, appeared to be degraded products, but the remaining 17 probably would have been identified (none of these products can be tested today since they are past expiry and the results would not be reliable).

While full deployment of the Minilab® did capture these failures, in the real world where the Minilab® might not be fully deployed, reliance may be placed on rapid and probably inferior dye

tests. Having a more informative dye test, like the LSHTM test, might well identify some substandard drugs, and lower risks to patients. Hopefully some entrepreneur will operationalize this test for the field. At the very least, and in the short run, it would be beneficial if the Minilab® could deploy the LSHTM test.

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