

The role of pre-shipment batch testing in ensuring good medicine quality

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Abstract

Background. Most donor agencies only procure drugs approved by a Stringent Regulatory Authority or the World Health Organization (WHO) Prequalification Programme in an effort to ensure high quality. However, the US President's Malaria Initiative has occasionally had to return approved drugs with quality issues to the manufacturer. This study compares the quality of artemisinin-based combination therapies (ACTs) produced by WHO-approved manufacturers with non-approved manufacturers and suggests policy changes to improve quality of donor-procured drugs.

Materials and Methods. Over the past five years, covert shoppers procured 1203 samples of ACTs from private pharmacies and drug stores in 16 cities across 14 developing countries. Samples were assessed using the Global Pharma Health Fund e.V. Minilab® protocol to identify substandard, degraded or counterfeit products, and a large number of suspect products were further analysed using high-performance liquid chromatography.

Results. Out of 1203 ACTs, 684 were produced by WHO-approved manufacturers and 519 were produced by non-WHO approved manufacturers. 2.6% (18/684) of ACTs of WHO-approved manufacturers had insufficient active pharmaceutical ingredient (less than 75%), while 12.5% (65/519) of ACTs of non-approved manufacturers had too little active pharmaceutical ingredient, and were considered substandard.

Conclusions. The results of this study suggest that ACTs produced by WHO-approved manufacturers perform nearly five times better than those of non-approved manufacturers, but some approved ACTs have too little active pharmaceutical ingredient. The US President's Malaria Initiative tests every batch of every drug it procures before distribution to recipient countries. Other donors should follow suit to ensure that drugs purchased with taxpayer dollars are of the highest quality.

1 Introduction

Drug approval by a Stringent Regulatory Authority (SRA) or the World Health Organization Prequalification Programme (WHO PQP) is an important determinant of drug quality [1]. An SRA, as defined by the WHO, is a national drug regulatory authority that is a member, observer or associate of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [2]. Most major multilateral and bilateral donor agencies only procure drugs approved by an SRA and/or the WHO PQP [3-5].

The Affordable Medicines Facility - malaria (AMFm), which is a donor financing mechanism designed to expand access to artemisinin-based combination therapies (ACTs), procures only ACTs that are approved by an SRA and/or the WHO PQP. Despite this, however, previous research by the authors of this study suggests that the quality of some WHO-approved ACTs may not be universally good, as over 7% of them were found to have too little active pharmaceutical ingredient (API), as compared to nearly 40% for drugs not approved by the WHO PQP and/or an SRA [6].

The inferior quality of small amounts of WHO-approved medicines is supported by statements from the US President's Malaria Initiative (PMI), a significant donor to malarious countries, indicating that it occasionally returns approved drugs to manufacturers when they fail quality control [7].

Expanding on earlier research, this study compares the quality of ACTs approved by the WHO PQP (and in some cases also approved by an SRA), and hence produced by WHO-approved manufacturers, with non-WHO approved manufacturers, and suggests two policy changes to improve quality of drugs being donated to emerging markets.

2 Materials and Methods

Over the past five years, covert shoppers procured 1203 samples of ACTs (co-blisters and fixed-dose combinations) from private pharmacies and drug stores in 16 cities across 14 developing countries. Sampling took place in 11 African cities (Accra, Addis Ababa, Cairo, Dar es Salaam, Kampala, Kigali, Lagos, Luanda, Lubumbashi, Lusaka, Nairobi), three Indian cities (Delhi, Chennai and Kolkata),

Table 1. ACT test results by country of manufacture and World Health Organization approval status.

Country of manufacture	Percent samples with <75% API* from WHO-approved manufacturers	Percent samples with <75% API from non-WHO-approved manufacturers	Percent total ACT samples with >50% and <75% API
China	12.3% (7/57)	13.5% (15/111)	13.1% (22/168)
India	4% (8/198)	12.5% (13/104)	7% (21/302)
EU/USA	0.7% (3/429)	5.4% (2/37)	1.1% (5/466)
Other countries**		13.1% (35/267)	13.1% (35/267)
Total	2.6% (18/684)	12.5% (65/519)	6.9% (83/1203)

* Active Pharmaceutical Ingredient ** Includes Vietnam, Nigeria, Kenya, Thailand, Tanzania and Uganda, in decreasing order of number of samples (all countries have at least 10 samples).

and two mid-income cities, Bangkok and Beijing, following previous methodology [6, 8-12]. Study agents posed as customers and were instructed to stay within a single neighbourhood and to select pharmacies at first sight on a random walk, and were blind as to the purpose for which they were collecting samples. They purchased a sample lot of ACT, available without a prescription. Once purchased, all drugs were stored at ambient temperature, with low humidity and no sunlight, until testing. Although the pharmacies in these cities were considerably different from each other, every effort was made to ensure that the sampling protocol was as similar as possible in order to provide comparable results. However, even following the same protocol, it is possible that with different shoppers in each of the cities, unknown biases may have occurred.

Samples were assessed using the Global Pharma Health Fund e.V. Minilab® protocol to identify substandard, degraded or counterfeit products via visual inspection, disintegration and semi-quantitative thin-layer chromatography (TLC). A large number of suspect products were further analysed using high-performance liquid chromatography (HPLC) for deviations from API standards. With the exception of 48 newly collected samples, this study is largely a re-analysis of data compiled in other studies described elsewhere, the reader is referred to those publications for a more detailed description of methods [1, 6, 9-12].

Under the WHO International Pharmacopoeia, generally the acceptable range for current artemisinin-based antimalarials and their companion drugs is to contain 90% to 110% of the active ingredient stated on the label, although allowances are made for losses in testing such that an average of 75% may be considered acceptable [13]. We therefore use a lower bound of 75% API in this study to determine whether the samples are of acceptable quality.

3 Results

Out of a total sample size of 1203 ACTs, 684 were produced by WHO-approved manufacturers and 519 ACTs were produced by non-WHO approved manufacturers (Table 1). 2.6% (18/684) of ACTs of WHO-approved manufacturers had insufficient API (less than 75%), while 12.5% (65/519) of ACTs of non-approved manufacturers had too little API. Products with insufficient API are considered substandard. These findings suggest that ACTs produced by WHO-approved manufacturers perform nearly five times better than those of non-approved manufacturers.

The largest number of ACTs of WHO-approved manufacturers came from the United States (US) and European Union (EU) at 62.7% (429/684), as did the lowest number of ACTs with too little API at 0.7% (3/429) (See Table 1). China had the highest number of ACTs of WHO-approved manufacturers with too little API at 12.3% (7/57), followed by India at 4% (8/198). China also had the highest number of ACTs of non-approved manufacturers with less than 75% API at 13.5% (15/111), while India had 12.5% (13/104).

We did not systematically contact manufacturers to confirm whether the drugs were substandard versus counterfeit, as previous attempts to do so were only partly successful. However, in further efforts to only identify truly substandard ACTs and not counterfeits or substandard drugs caused by degradation due to poor storage or transport, those identified as having less than 75% API in this study also had at least 50% API, with no obvious tablet degradation or packaging flaws (such as package discoloration possibly caused by excess sun exposure). It is still possible products designated as substandard were actually degraded or counterfeit, but the chances of this are probably low. For the purposes of this study, counterfeit refers to drugs that appeared to be deliberately and fraudulently mislabelled with regard to

identity or source [14], while substandard refers to drugs that appeared to be poorly manufactured or degraded.

4 Discussion

There is a definite difference in quality between manufacturers of SRA and/or WHO PQP approved ACTs and manufacturers of non-approved ACTs, even after eliminating potential counterfeit and obviously degraded products from the dataset. ACTs produced by manufacturers in the US and EU have by far the fewest products with too little API. Other manufacturers have worse quality records, especially manufacturers based in China, and to a lesser extent India.

Market availability of poor quality drugs from non-approved manufacturers, many local to the country in which they are procured, is a difficult problem to overcome. Increased funding for projects such as the US Agency for International Development (USAID)/US Pharmacopeial Convention (USP) Promoting the Quality of Medicines (PQM) is desperately needed. The PQM project helps local authorities identify substandard and counterfeit drugs and also helps them identify good and bad manufactures in advance, thereby improving the quality of available drugs [15]. It is important that attention be focused on the quality of products made by non-approved manufacturers, since inferior products not only increase development of drug resistance but also put patients at risk of death.

One of the AMFm's public health goals is to minimise the selective pressures promoting resistance to ACTs. The AMFm procures only SRA and/or WHO PQP approved ACTs, and the results of this study find that WHO-approved manufacturers perform demonstrably better than non-approved manufacturers (2.6% versus 12.5%), hence other things being equal, the AMFm should help slow the development of drug resistance.

But since this study, and previous research, showed that not all WHO-approved ACTs are universally of good quality, and this is not likely due to counterfeiting or degradation, there is reason to ponder whether improvements in procurement systems could lower to zero the number of donor-supplied products that fail quality control. Such a system has already been implemented by the PMI. According to the PMI, it "subjects every batch of every drug...procured with malaria funds to various analytical quality testing [4]," and has occasionally returned products with quality issues to the manufacturer [7].

Meanwhile, the largest donor of ACTs, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), has tasked Principal Recipients (PR) with quality control testing along the supply chain of approved ACTs procured with Global Fund resources [16]. Should a quality issue be identified which is the fault of the manufacturer, it is up the

PR to determine what action(s) will be taken. While this may be a step in the right direction, it does not do enough to ensure only good quality ACTs are being procured and distributed with Global Fund resources. It is unclear how often quality control testing is actually being performed, on how many batches it is being performed, and how often it is being performed after the drugs reach pharmacy shelves.

If our aim is to significantly reduce the risk of resistance to ACTs developing or spreading then no donor-procured drugs should be under dosed and hence contribute to drug resistance. Modern techniques, such as handheld Raman or near-infrared spectrometers, simplify quality control testing enormously and are non-invasive. They are close to fool proof when it comes to authenticating known products - as would be the case if samples of every batch of donor-procured ACTs were tested prior to distribution in endemic countries.

If the PMI has the capacity to conduct such testing surely the time has come for other donors to follow its lead. After all, if a small percentage of the drugs are failing, and the PMI is returning such products, surely other donors are indeed sending substandard ACTs into endemic country markets. If the US Government's flagship malaria programme insists on such quality control measures, should not all donor agencies receiving taxpayer dollars do likewise? We suggest implementing the following policy: Any manufacturer found with failing batches of ACTs on more than three occasions in a year, will not be eligible for tendering in the following year. The exact policy will require consultation but whatever the decision it should have teeth. The foreign aid budget will come under financial pressure in the next Congress, so it is time that all US-funded donors ensure that the drugs they ship to endemic countries are of the highest quality to save lives.

5 Conclusions

Most donors ensure they procure medicines from WHO-approved manufacturers. This is just as well since we find in this study that non-approved manufacturers' products fail basic quality control nearly five times as often. Unfortunately, given the evidence presented in this study, even some approved manufacturers' products occasionally fail basic quality control.

The largest bilateral donor is the US PMI. PMI tests all batches of the medicines it sends to recipient countries. Other major donors, such as the Global Fund, do not claim to do so, yet PMI has occasionally found problems with approved drugs, reinforcing our findings. If PMI finds problems and returns or destroys failing products, we suggest other donors should also systematically test every batch of drugs they buy.

6 Authors' contributions

This paper draws on numerous other research studies where others did some of the scientific testing, they are acknowledged below. In this study, RB did new drug testing and edited the manuscript. KH drafted the manuscript and edited the data.

7 Acknowledgements

The authors would like to thank the Legatum Institute for funding most of the drug collections and testing, and the Social Sciences and Humanities Research Council of Canada for funding more recent assessments. The authors also thank Amir Attaran, Lorraine Mooney, Richard Tren, Julissa Milligan, Thompson Ayodele, Franklin Cudjoe, Barun Mitra and numerous covert shoppers for their assistance with drug collections and results reporting in previously published research. Harparkash Kaur, Albert van Wyk and Naiela Malik of the London School of Hygiene and Tropical Medicine are thanked for conducting HPLC analyses.

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