Counterfeit Medicines and the GPHF-Minilab for Rapid Drug Quality Verification

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A mini-laboratory to help low-income countries detect counterfeit and substandard quality medicines has been developed by the German Pharma Health Fund (GPHF), a charity organisation established by research-based pharmaceutical companies in Germany. The GPHF-Minilab provides a reliable, simple and inexpensive method for rapid drug quality verification of antituberculosis, antimalarial and antiretroviral drugs as well as major antibiotics and some other essential medicines in particular for childhood diseases. The kit is of special interest to vertical disease programmes, hospitals and other healthcare providers, which are constantly at risk of having their supply chain infiltrated by pharmaceuticals of spurious quality.

Access to quality drugs: A constant concern

The concern about the access to quality drugs is as old as drugs themselves and, in the first century AD, the Greek physician Dioscorides identified substandard products and advised on their detection. At the beginning of last century, the unregulated proliferation of pharmaceutical industries in the western world lead to some spectacular cases of drug adulteration. One of the best cases known with a death toll of well above a hundred people is the blending of sulphanilamide elixirs with the toxic anti-freeze diethylene glycol in the USA in 1937 which consequently triggered off the establishment of the US Food and Drug Administration (FDA) [1, 2].

Much later, international norms on drug quality assurance systems have been established, for example the guidelines on Good Manufacturing Practices (GMP) issued by the World Health Organization (WHO) in 1967 and subsequent certification schemes for manufacturers, products and individual batches in the years thereafter. However, the global implementation of these schemes and guidelines has still to be achieved and due to this shortfall it is no wonder that new diethylene glycol scams with an overall death toll of 473 people, most of them children, showed up in Bangladesh, India, Haiti and Nigeria in the recent years [3–6]. Obviously, more lessons need to be learned before also the last country in the global world stops thinking the implementation of a decent drug quality assurance system as impracticable and beyond financial reach of authorities and local manufacturers.

Modern trade in counterfeit medicines

Modern trade in counterfeit drugs appears to be widespread internationally and affects both, developing and developed countries [7–17]. No country stays immune. New global trade arrangements, free trade agreements and deregulation measures, for example the extension of the European Union or lowering of the Chinese Bamboo Curtain, are dramatically changing the pharmaceutical market worldwide, resulting also in a proliferation of pharmaceutical products and secondary markets. This will set a scene which favours an increase in counterfeiting activities, and recent intelligence information indicates that counterfeiting of medicines is more and more moving from a small cottage industry filling spot shortages of drugs and devices towards sophisticated large-scale

global operations using highly professional equipment.

Counterfeiting of commercial pharmaceutical products is motivated mainly by the quick, easy and huge profits to be made when not obeying to the rules of Good Manufacturing Practices and dodging intellectual property rights. It is primarily flourishing in developing countries with the highest disease burden and the poorest economies with little or no drug regulatory authorities and quality control laboratories in place. And where legal distribution channels fail to deliver drugs to poor health settings outside urban areas, illegitimate distribution channels, for example market mamas, will take over and do the job and open the doors, unintentionally or fraudulently, for the infiltration of counterfeit and substandard quality pharmaceutical products.

The spread of counterfeit drugs is generally more pronounced in countries where the manufacture, importation, distribution, supply and sale of drugs is non-comprehensible, less regulated and enforcement of legislation may be weak. It is particularly prominent in societies where corruption and bribing subverts the entire system starting with recovering recruitment bribes at police sub-inspector level and ending with bad governance by a kleptomanic elite having completely lost control of the remotest reaches of their countries, the forbidden territories, the homes of the warlords, arms dealers, insurgent armies, latter-day slave traders and plain, old-fashioned bandits ruling the roost with semi-automatic rifles; the masters of the Medellin, the Horn of Africa and the Golden Triangle, certainly all drug traders "par excellence".

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Born in Germany's Rhein-Ruhr Valley, he studied pharmacy in nearby Bonn. Starting career in community pharmacy, he later moved on to gain its Ph.D. in the field of pharmaceutical formulation sciencies at Frankfurt University. After three years of R&D as principal scientist at GlaxoSmithKline UK, he went on as product manager for Laboratoires Sérolam Paris and Packaging Coordinator Incorporation (Allpack) Philadelphia. Adding a business management course to its pharmaceutical expertise, he then joined the German Pharma Health Fund (GPHF) as project manager delivering, since 1996, technical and organisational solutions for better health in developing nations.

Types and scale of counterfeit medicines

The incidence and proliferation of counterfeit and substandard quality medicines has been well identified internationally and grown to a disturbing proportion which leads to the devastation of diseases and constitutes serious health hazards [18–20]. The figures generally in use are coming from the US Food and Drug Administration (FDA) which estimates that as much as 10 % of all branded medicine is counterfeit with the level rising to 25 % in the developing world [21]. However, the true scale of the problem is hard to estimate because of poor reporting systems and the fact that death and worsening illness is frequently attributed to the disease itself rather than to ineffective counterfeit medicine.

The WHO defines a counterfeit medicine as one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both, branded and generic products, and counterfeit products may include medicines with the correct ingredients or with wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging [22]. This includes, for example ayuverdic medicine claiming to operate gently on natural products but which may be spiked with powerful drugs such as dexamethasone or sildenfanil to make things finally working. However, this definition does not include counterfeit branded line extensions which are not found in the portfolios of originator companies, for example medicinal soap extended to a non-existent brand of ointments.

A percentage breakdown of data on 325 of 771 cases reported from around the world to the WHO database between 1982 and 1999 shows that 60 % of counterfeits detected contained no active ingredient, 17 % had the wrong amount of the active ingredient and 16 % contained the wrong medicines [9]. Only 7 % were perfect copies with the right active ingredient in the right quantity matching the label's declaration. One third of all cases involved counterfeit antibiotics including also antimalarials and antituberculosis drugs. A recent breakdown of 42 cases collated by WHO between 2000 and 2001 came to similar results: 43 % contained no and 7 % the incorrect active ingredient. A further 21 % were of low drug content.

The WHO says that there are some 2800 illegal medicines sellers in Cambodia and 2100 in Laos [23]. And in 2002, Chinese authorities closed down 1300 illegally operating pharmaceutical manufacturing sites in their country [16]. Currently in India, 1800 court cases of drug counterfeiting are pending in the states of Andhra Pradesh and Maharashtra [24]. Individual country figures are worrisome. According to the WHO, substandard quality drugs are believed to make up 8.5 %

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of medicines in Thailand, 8 % in Vietnam and 16 % in Myanmar [23]. The rates for some products are even higher, for example 26 % of rifampicin and 24 % of cotrimoxazole batches failed quality assurance tests. And if it could get any worth, counterfeit rates of the antimalarial artesunate against multi-resistant malaria with no drug content at all are up to 38 % in this region [25]. As new combination therapy is needed to treat drug-resistant malaria, fears run high that more substandard quality and counterfeit medicines will enter the market in malaria-endemic countries.

Same fears exist for antiretroviral therapy as it is not available in sufficient quantities where it is most needed – Africa, Central and Eastern Europe, and throughout much of Asia and Latin America. At this end, the first counterfeit antiretroviral medicine with no active ingredient has been detected in Hongkong in 2000, and onset 2003, a fixed triple antiretroviral combination product with a label claim of 200 mg of zidovudine, 150 mg of lamivudine and 40 mg of indinavir (Ginovir 3D Cap) shipped from Singapore to Cameroon for final consumption was found to contain only one out of three active ingredients [26].

Impact on health and health systems

Counterfeiting of medicines takes all types of form, but the end result is, when administered to a patient, that the consequences range from treatment failure, increased toxicity, increased drug resistance to malaria, tuberculosis (TB) and AIDS, and even outright death as a result of any of the above [18–20, 27, 28]. For an insight into how fake drugs affect the lives of ordinary people, it is worthwhile to have a closer look to Nigeria where drug quality is highly questionable and pharmacy premises are often unsuitable, hot, humid, and cluttered with drugs, some of them expired. Even under the watchful eyes of doctors, counterfeit adrenalin has contributed to the death of two children undergoing heart surgery at the University Teaching Hospital in Enugu in eastern Nigeria towards the middle of 2003 [29]. Subsequent investigations revealed that the muscle relaxant was of substandard quality, the infusion solution non-sterile, and the counterfeit adrenalin with no drug content whatsoever been bought from unreliable sources at an open drug market around the corner. On all levels, from hospital down to the average household, the trust into the medicines supply channels is fading away.

In Nigeria's neighbouring country Benin, drug poisoning is on the increase and at least one patient per day dies at the National Hospital in Cotonou on kidney failure usually as a direct result of taking medicines bought from outlets operating outside the legally authorised distribution channel [30]. Nowadays, the magnitude of side effects related to counterfeit and substandard quality medicines can easily outdo the rates of side effects related to the active ingredient itself. Hence, medical staff working in the developing world should be aware that the probability of product related adverse side effects is somewhat between 1:10 000 and 1:100 000 only, whereas the probability of side effects and failure rates attributed, to fake and substandard quality medicines can well be within in the range of 1:10. In case a patient showing toxic side effects and/or is not responding to a drug treatment, practitioners should consequently also think of a possible non-effective, dangerous counterfeit drug been taken. This can be diagnosed only when the product in question is subjected to physical and chemical testing in order to see whether drug identity and content are within the limits of the product's claims. For tourists travelling to tropical beaches, it is highly recommended to supply themselves with drugs from home before leaving, or alternatively, getting the names of reputable local hospitals in order to buy from them, if required.

As evidence proofs, counterfeiters are going through a great deal of trouble to mimic genuine products, for example adding small amounts of chloroquine to antimalarial pills to give a bitter taste and/or adding a fake hologram to the packaging to give a realistic picture of the bogus product [25]. Production of fakes is on large scale. In South East Asia, one non-governmental organisation (NGO) was delighted to buy 100 000 units for about 50 % of the original price, only to find out that the product they were buying was fake. In May 2000, dozens of people died in Cambodia after taking counterfeit antimalarials [31]. The victims included the head of Cambodia's wildlife protection office in the town of Siem Reap, who fell into a coma and died six days after unknowingly taking counterfeit medicine that was marketed as the powerful antimalarial drug mefloquine, however, actually containing nothing but compressed flowers. The price was ridiculously low, US-$ 7 for 100 tablets. Unless well informed tourists, the officer ignored this early warning indicator that the product was spurious and died. Worldwide over recent years, there have in all probably been thousands of unrecorded deaths caused by counterfeit pharmaceuticals. Fighting this global problem puts an additional burden on public health systems that are often already over-stretched in low-income countries.

GPHF-Minilab for drug quality testing on the spot

Owing to the widespread danger of counterfeit medicines, drug quality control in the distribution system of developing countries has acquired new dimensions today. If adherence to good pharmaceutical working practice, trading and distribution cannot be assumed, a greater number of samples have to be tested in

order to maintain an appropriate assurance of drug quality. At the same time, however, pharmacopoeial analyses have become more and more expensive and only a few centres of excellence in some countries are currently available to perform them. The development and use of simple tests should therefore facilitate a balance between the need to increase the amount of drug testing on the one hand, and the need to contain costs on the other.

The German Pharma Health Fund (GPHF), a charity organisation established by research-based pharmaceutical companies in Germany, set out to develop and supply a portable, tropics-compatible and easy-to-use mini-laboratory which could verify the drug's content and thus detect counterfeit and substandard quality medicines by employing inexpensive analytical techniques [32–34]. The intention was also to close the capacity gap on drug quality testing by providing simple and affordable analytical techniques for countries where the means for an effective drug quality-control system are not yet fully in place. The first pilot lab was launched in the Philippines on the island of Mindanao in October 1997, and now over a 140 Minilabs are covering more than 35 countries in three continents, 80 of them being based in sub-Saharan Africa.

Testing the quality of drugs by means of the GPHF-Minilab involves a four-stage test plan that employs very simple physical and chemical analytical techniques. The first step in identifying potential counterfeit drugs is the careful visual inspection of the product, and its packaging and labelling for an early rejection of the more crudely presented counterfeits. The first step is followed by a simple tablet and capsule disintegration test performed in water for a preliminary assessment of deficiencies related to drug solubility and availability. For example, products wrongly stored during transit may fail this test on the basis that they are getting hard as concrete when attracting moisture in the night and drying up again during the day. The third step employs simplified colour reactions for a quick check of any drug present, thus ensuring that the drug is actually there before tackling the final step, a thin-layer chromatographic run for a quick check whether the quantities of drug claimed on the label are actually in the product. The results obtained by a simple visual inspection of the chromatoplates produced can be as accurate as 10 % if great care is taken and skill executed. In order to achieve this accuracy training of staff might be required before using the Minilab's procedures first time.

GPHF-Minilab test methods have initially been developed for 30 active ingredients taking into account the WHO Essential Drug List and prevailing prescription practice. The early list covered the following range of products: acetylsalicylic acid, aminophylline, amoxicillin, ampicillin, artesunate, cefalexin, chloramphenicol, chloroquine, ciprofloxacin, cloxacillin, cotrimoxazole, erythromycin, ethambutol, furosemide, glibenclamide, griseofulvin, isoniazid, mebendazole, mefloquine, metamizole, metronidazole, paracetamol, phenoxymethylpenicillin, prednisolone, pyrazinamide, quinine, rifampicin, salbutamol, sulfadoxine combined with pyrimethamine and tetracycline. Recently, six more drugs have been added to this list covering now also the antiretrovirals didanosine, indinavir, lamivudine, nevirapine, stavudine and zidovudine. The new procedures on thin-layer chromatography allow also the simultaneous verification of identity and quantity for fixed combination products, for example lamivudine combined with zidovudine or lamivudine combined with nevirapine and stavudine, respectively. Some more test methods on the antimalarials primaquine, amodiaquine and the fixed-dose combination of artemether and lumefantrine have recently been added.

All 40 compounds are found at the top of drug supply lists for hospitals and other health facilities based in Africa, Asia and Latin America. People working there are now able to perform basic quality tests on these compounds on site in a very short time. Designed for rapid drug quality screening, GPHF-Minilab tests are pointing with good effect to substandard quality and counterfeit medicines infiltrating the markets and will assist protecting health facilities against pharmaceuticals of inferior quality otherwise administered to the patients. However, all samples considered to be potentially counterfeit or of substandard quality would need to be referred for testing according to legally accepted reference methods to validate the findings of the initial screenings before enforcing legal actions. Until the final confirmation has been obtained, batches under scrutiny should be freezed and put under quarantine or, preferentially, not be accepted from a pending offer.

The German Pharma Health Fund and its Minilab project are not walking alone. Domestic project partners are the German Medical Mission Institute Würzburg, the German Medical Aid Organisation *action medeor*, the German Technical Cooperation (GTZ), Technology Transfer Marburg (TTM) and the universities of Bonn and Saarbrücken. Appreciation and support on international level comes from more than 20 institutions, for example from the Roll Back Malaria Programme of the WHO, from Management Sciences for Health (MSH) from Arlington in the USA which runs a project with 15 Minilabs within the SEAM-project in Tanzania and from the Global Assistance Initiative of the United States Pharmacopoeia (USP) currently running a major drug quality control programme on antimalarials with more than 20 Minilabs in the Mekong region including China's most southern province of Yunnan. Ten training workshops have been performed in seven countries (Ghana,

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Tanzania, Kenya, Nepal, India, Thailand and the Philippines) and 120 individuals been trained out of which 40 are now trainers themselves. Furthermore, 450 training manuals have been disseminated to health facilities in more than 30 countries.

Response from vertical disease programmes and individual case reports

Frequently, feedback is difficult to obtain as the real stakeholders in the inhumane business of drug counterfeiting are not known and unearthing the existence of counterfeit medicines might be detrimental to other programme objectives of local project champions. Telling the truth in public might also be detrimental to career and health, best shown by the example that the head of Colombia's central drug quality control lab required several times the employment of bodyguards for protection [35].

Bearing this in mind, it explains why the GPHF obtained only oral reports from the Catholic Drug Centre, its local project champion in Ghana. Let it call *the African solution* and the story goes like this: Having employed four Minilabs throughout the country, one supplier was finally identified to continuously deliver counterfeit and substandard quality medicines to the diocesan pharmacies. On the drug centre's annual reception many suppliers of medicines have been invited and one major subject on the table was the drug quality status in the country. After a long public discussion, there was no doubt about that nobody wanted to see counterfeiters being among them, the ones doing a bad job destroying the reputation of the others. Calls for punishment for the smart persons behind the crime went from long-term imprisonment up to death penalty. Days after the reception, the company doing the bad job was approached by the church people submitting the general manager the findings made with the Minilabs throughout the years 1998 and 1999. He was then asked to stop the supply of counterfeit medicines instantly or else his name would be made public by word of mouth starting in the church community and finishing with the general public. After this confrontation, no further counterfeit medicines have been obtained anymore.

Some more cases detected with the GPHF-Minilab: In India, the Kurji Holy Family Hospital in Patna checked 167 batches. Five batches containing salbutamol, acetylsalicylic acid and paracetamol had been classified as counterfeit medicines. Two more cases on metronidazole have been added after a drug quality survey has been performed by the Institute of Clinical Pharmacy of Basle University in Calcutta. The central governmental lab in Mali used the Minilab 250 times and detected 14 counterfeit and 12 substandard products. The national Laboratoire de Contrôle de Qualité of Guinea-Conakry reported two counterfeit and three substandard pharmaceuticals out of 24 batches checked with the Minilab. And finally, the Food and Drug Board of Ghana identified two counterfeits and nine products of inferior quality after having screened 63 samples with the Minilab's standard operation procedures.

The Roll Back Malaria Drug Quality Study on Antimalarials performed by the WHO in seven countries of sub-Saharan Africa (Gabon, Ghana, Kenya, Mali, Mozambique, Sudan and Zimbabwe) in the years 2000 and 2001 identified several significant problems of substandard quality medicines within the drug distributions chains [36]. Percentage failures in ingredient content ranging from 20 to 67 % for chloroquine tablets and 5 to 38 % for sulfadoxine/pyrimethamine tablets and in dissolution failures ranging from 5 to 29 % for chloroquine and from 75 to 100 % for sulfadoxine/pyrimethamine tablets cannot be ignored. Results obtained with the GPHF-Minilab matched well the results generated additionally in a fully-fledged laboratory. In view of the potential danger that the substandard quality antimalarials could already be posing in the fight against malaria, the WHO suggests that an intervention plan should be considered immediately such as setting up quality surveillance systems within drug regulatory authorities in this and other regions.

A second study performed by the Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale (OCEAC) in Cameroon was focusing on the quality of antimalarials to be found in the self-medication market [37]. Samples of chloroquine, quinine and antifolates were collected from various sites throughout the country over a one-year period in the years 2001 and 2002. Drug quality was assessed by simple colour reactions and semi-quantitative thin-layer chromatography using the Minilab's standard operation procedures. Fifty of 133 (38 %) chloroquine, 52 of 70 quinine (74 %), and 10 of 81 (12 %) antifolates had either no active ingredient, insufficient active ingredient, wrong ingredient, or unknown ingredient(s).

The Global Assistance Initiative of the United States Pharmacopoeia (USP) is currently running jointly with WHO Mekong Roll Back Malaria a third drug quality control study with 25 Minilabs in six countries of the Mekong region (Cambodia, Laos, Myanmar, Thailand, Vietnam and China's Yunnan province). The study's objective is to obtain and document field evidence-based data on the quality of selected antimalarial medicines in this region. Drugs screened with the Minilab are quinine, chloroquine, mefloquine, artesunate and tetracycline. A total of 355 batches have been tested already. More data on further 700 batches will be added by the end of 2005. Preliminary results revealed that the incidence of substandard quality and counterfeit antimalarial medicines is very high in Laos (23.1 %) and Cambodia (10.4 %) and low in Vietnam

(4.2 %) and Thailand (2.2 %). Counterfeit and substandard quality levels for artesunate are extremely high in Laos (66.7 %) and Cambodia (23.6 %) whereby the level of 25 % in China's Yunnan province is put down to poor manufacturing practice. Even for the cheapest antimalarials available, substandard drug quality levels are high for quinine in Cambodia (42.0 %) and for chloroquine and tetracycline in Laos (50.0 % and 62.6 % respectively) [38, 39].

All three studies are proving that it is still commercially viable to counterfeit even the cheapest antimalarial drugs available in the market if only the volumes of consumption are high enough. Even where antimalarials are given away completely free of charge through public health programmes as in the case of arteminisin-based combination therapy in Vietnam, counterfeiting still clings to private sector and other distribution channels. It must also be concluded that self-medication with antimalarial drugs purchased from unofficial vendors is not a reliable strategy to diminish malaria morbidity and mortality. Counterfeit malaria pills contribute to the spread of drug-resistant malaria parasites and may lead to increasing therapeutic failure and medical expense [28, 40]. As new combination therapy is needed to treat drug-resistant malaria, fears run high that more substandard quality and counterfeit medicines will enter the market in malaria-endemic countries.

Summary

The Minilab project of the German Pharma Health Fund (GPHF), an initiative of research-based pharmaceutical companies in Germany, met the current needs for drug quality verification of stock material of public, private and religious health facilities based in low-income countries. Furthermore, the Minilab accommodates the infrastructure needs of vertical disease projects and programmes for easy and rapid drug quality verification of antituberculosis, antimalarial and antiretroviral drugs being used in huge quantities, for example by the Global Fund to Fight TB, Malaria and AIDS. In the past five years, over 140 Minilabs have been shipped to more than 35 countries of three continents and they have become a global concept used by governments and other healthcare providers worldwide.

It has been shown that the employment of GPHF-Minilabs, an AntiCounterfeit Kit based on colour reactions and thin layer chromatographic assays, protects patients from taking counterfeit and substandard quality medicines detrimental to health and life. They reduce the workload of central drug control laboratories and can play a key role in keeping the costs of drug analyses in the developing world as low as possible. Establishing them as an early alert system out in the field will enable health authorities and other healthcare providers to tackle the widespread danger of trade in counterfeit medicines in a more efficient manner.

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