The plague of counterfeit medicines

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The traffic in counterfeit medicines is booming. It misleads, and it kills. A University of Liège team is making Rwandan and Congolese health care workers aware of the problem, whilst informing and training them, so that they may detect and monitor these products, thanks to made to measure appropriate technical systems.

Nigeria, 2008: 100 babies die after having received counterfeit syrup, presented as containing paracetamol. Panama, 2006: counterfeit excipients slipped into medicines cause 300 deaths. According to the **Food and Drug Administration** (United States), counterfeit medicines have infected and polluted 10% of the global market. In Central Africa, these false products or products of lower quality exceed 25%. To the great profit of certain actors: the traffic in fake medicines is said to be 25 times more profitable than the traffic in drugs. For sales made over the internet or face to face, they offer impressive profits, ranging from 6,000 to 20,000%.

In a report published in December 2008, the **World Health Organisation** declared that in 2007 it had registered over 4 counterfeit medicines per day. Thus, in Africa, from 30 to 70% of antimalarial drugs in circulation are fake, entirely or partially. Medicines based on artesunate, aimed at fighting against chemio-resistant malaria, have been faked by up to 40%. 80% of the stocks of the Congo's dispensaries contain counterfeit substances. In 37% of cases counterfeiting targets products in the genito-urinary domain, 12% of cases concern anti-infection ingredients, and the same proportion is true of products aimed at the central nervous system (1). To ensure the quality of medicines and to counter - at their level - the development of counterfeits in poor or developing countries, **Philippe Hubert**, **Roland Marini Djang'eing'a** and **Eric Ziemons**, three University of Liège pharmacists, are co-ordinating two long term projects.

The first of these two projects is being carried out in Rwanda and the Congo: **Edulink Europ**, the training programme they have developed, aims to, amongst other things, make the healthcare workers involved aware of the problem of counterfeiting medicines. Their second project has just become the subject of a publication (1): its goal is to promote low-cost equipment to make available apparatus with reduced costs-in-use destined for medicine analysis laboratories, and to test their effectiveness in monitoring these products. The effective performance of these different systems has been demonstrated. This equipment will thus be used to fit out two African laboratories. The training given within the framework of the Edulink will also be put into practice there, by carrying out on site medicine analysis and monitoring, and at a cost accessible for developing countries and local producers with limited means.

(1) *'Reliable low-cost capillary electrophoresis device for drug quality control and counterfeit medicines.'*
R.D.Marini, E.Rozet, M.L.A. Montes, C.Rohrbasser, S.Roht, D.Rheme, P.Bonnabry, J.Schappler, J.L. Veuthey, Ph. Hubert, S.Rudaz
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All or nothing

A medicine is a system composed of both a responsible active principle (and principles) with pharmacological properties and excipients. It brings about a biological action. The counterfeit medicine can come in various forms. Sometimes it contains the active principle or the right excipients, but in too low or incorrect quantities. It can also contain a bad active principle or a bad excipient. It can also be the case that it contains no active principle. Finally the products are sometimes presented in counterfeit packaging. In every case, and in a deliberate and fraudulent manner, these fakes are presented as respecting the legislation and as being in compliance with the imitated products. When Roland Marini shows you two boxes of antimalarial drugs recently bought in the Congo, go and figure out which of the two is a fake!

On a medical level the consequences of these counterfeits can prove tragic, with deaths, treatment failures or with resistance to medicines developing. On a socio-economic level fake medicines can impoverish the people duped into buying them. *'In the Congo and elsewhere, the buying of medicines can represent an important proportion taken out of an income which is nonetheless very low,'* adds Philippe Hubert. *'Yet it is currently impossible to know if the sums being spent are done so advisedly, in other words to really obtain the proper medicine.'* As Roland Marini reminds us, *'in the Congo the average salary is 100 dollars. Antimalaria treatment costs between 10 and 20 dollars. But today nobody is capable of saying if the packet bought - even if it consists of the most expensive product - effectively contains a quality medicine.'* For the pharmaceutical companies these counterfeits can also bring about, amongst others, job losses, the loss of revenue and a loss of credibility.

An 'easy' fraud

As Roland Marini reminds us (2), numerous factors 'stimulate' and encourage the development of counterfeit medicines. Thus lifestyle 'blockbuster' drugs (such as the notorious erection pills) have created a demand for an unlawful use, and what is more in a context in which a culture of self-prescription is growing. Furthermore the globalisation of the markets has made the distribution of these products easier, whilst access to the technological possibilities of production often does not pose a barrier. If we add to this non-exhaustive list of points sanctions under civil and penal law which are generally far from acting as a deterrent, it can be understood why people involved in organised crime are more and more choosing to invest in this booming and very profitable market, which is in the end not very risky for its organisers: even in the case of arrests it is generally small-time traffickers at the bottom of the chain who take the rap.

'Our project turns around the quality of the medicine - our primary concern - and not on suppression,' stresses Philippe Hubert. *'Currently, in a large number of poor or developing countries people don't know how to interpret the documents which accompany medicine supplies. And people have no means, or as good as no means, to check these products in tailor-made laboratories.'* It was on the basis of these facts that the Edulink Europ project (run by Roland Marini) in 2007 led the Liège team pharmacists to establish preliminary contacts in Rwanda and the Congo. Their educational programme is aimed at making healthcare workers aware of the problems of counterfeit medicines, but also at training personnel so that they can monitor these medicines. The training officially began on December 31, 2008, and will come to a conclusion at the end of 2011. Most of the courses are given on site in the respective countries, but certain people selected by exams benefit from training programmes of 3 to 6 months at Liège. One of the course modules has also been designed in the form of e-learning, in order to avoid unnecessary travelling and journeying.

(2) These data, which originate notably from the WHO and the FDA, were cited in a lecture given at Kisangani (Democratic Republic of Congo) on July 31 2010, entitled *'Counterfeiting medicines: tools to fight against this plague'.*

A chain of monitors

'With Edulink we are aiming at several sections of the population,' specifies Philippe Hubert. *'On the one hand, scientists and academics, such as university assistants at Butare and Kinshasa. On the other hand people responsible for inspections are also involved, whether they work at the Medicine Agency in the Congo, the Pharmacy Task Force in Rwanda, or whether they belong to trading groups.'* In addition, in order to encourage the development of local production, which is still pretty modest, above all in the Congo, the training also concerns people who are likely to work in this type of industry. *'Finally,'* adds Roland Marini, *'tradi-practitioners,' who practice 'improved traditional medicine, recognised by the WHO, using products from natural origins, generally plant based, are included in this training. They have available knowledge passed down from parent to child. But for them the challenge is being able to standardise their preparations as much as possible. That isn't so easy, as the composition of their products risks varying depending on the season, the rains, or the quantities of plants or stems removed, or even the parts of the plants used.'*

Nevertheless, having available personnel who are aware of counterfeiting and/or trained to analyse medicines cannot in itself suffice. It was also necessary to design and develop tools which enable analysis laboratories to be installed in the areas concerned. Their objective: meeting the security agencies rapid reaction needs, and with an unquestionable scientific reliability. *'We have to be realistic: poor or developing countries cannot purchase complex equipment and technologies which allow such analyses to be carried out,'* explains Philippe Hubert. *'Even the cost of solvents or the various products required for the functioning of these machines, their regular use and their maintenance, presents a problem.'*

To overcome this obstacle another project thus came into being, with the help of Eric Ziemons. It was carried out in parallel with that of the Edulink project. Supported in Belgium by the University Cooperation for Development, it took the form of a Targeted Inter-university Project (PIC) in which several Belgian and Swiss universities took part, as well as the Geneva University Hospital. The study which has just been published maps out its path and its astonishing results (2).

Against the fakes, genuine solutions

In the fight against counterfeit medicines it is impossible to settle for what the senses indicate: smell (to check, for example, the smell of an aspirin tablet), taste, touch, hearing (to test, for example, a pressurised container) have their uses, but remain limited. At the same time, simple analytical tools, such as precision weighing scales, can for example be used to check the uniformity of the contents of injected containers, but they are again insufficient. Clearly more complex equipment is necessary. In Western countries they range from liquid chromatography to capillary **electrophoresis**, and from near-infrared **spectroscopy** to mass spectrometry. In poor or developing countries laboratories with such equipment available are either lacking or they don't function: installing them, using them regularly and systematically and maintaining them often involve unattainable costs.

To get round this problem, the researchers decided to develop specific reduced cost techniques. Out of the various 'adaptable' techniques their choice came down to near-infrared spectroscopy and capillary electrophoresis, which are capable of giving results which supplement each other and can, if necessary, confirm their reciprocal results. *'The technique of near-infrared spectroscopy really offers an interesting model,'* points out Eric Ziemons. '*It allows a sample to be irradiated with a source which emits a light in the near infrared (a system a bit comparable to the waves emitted by a lamp). Depending on the structure of the sample, a proportion of the light will be absorbed. In being placed in a sensor it will produce a spectrum showing the bonds of its molecules, with their chemical and physical signposts. And this allows the product's compliance to be checked.'*

Near-infrared spectroscopy has great advantages: it doesn't destroy the sample, which can subsequently be subjected to other tests, the sample requires no preparation, the equipment needs virtually no maintenance, and it is a not very costly analysis. Moreover no solvent is necessary, which, besides the savings in costs, also means the environment is respected. *'With this system we are in the realm of green chemistry,'* points out Eric Ziemons.

For its part capillary electrophoresis equipment consists of two electrodes. Applying a current will create an electrical field which will make the substances or the compounds move around depending on their electrical charges and their size. Subsequently obtaining a so-called electropherogram profile, which consists of peaks corresponding to the substances present in the samples, will enable the product's compliance to be checked. *'This type of equipment, which allows you to work with small samples, is potentially of value for monitoring conventional medicines, but also improved traditional medicines. In addition it also functions with very few solvents,'* notes Roland Marini.

Equipment which is ten times cheaper

And the gamble paid off! The Swiss university professors who worked on the project (including personnel at the Freiburg College of Engineering and Architecture), and who, along with the Liège team, are members of the Pharmelp association, got down to the task of designing and developing capillary electrophoresis prototypes and succeeded in fabricating low cost equipment. In an interview carried out for a programme broadcast on a Swiss television channel, professor Serge Rudaz, a Senior Research Associate at the **University of Geneva**, was confident that the capillary electrophoresis equipment designed by the Swiss teams costs up to ten times less than those currently used.

For its part the Liège team paid particular attention to the system's robustness, in order to anticipate the problems which might arise in Africa, as well as all the aspects of quality control.

'In both cases we are talking about equipment which is 'easy' to export; in other words we avoid having to rely on spare parts, as might be the case for other techniques, and we avoid the need for costly use products,' underlines Philippe Hubert. 'In the end the idea consists of setting in place, in the laboratories, equipment which is perfectly ready to be used for monitoring medicine quality.' To achieve this, beforehand one needs to equip the near-infrared spectrometer with programmes - in other words mathematical models or libraries of spectrums - and to have tested their performances by comparing them to a generic method analysing the same products.

Finding the right models

'The 'feasibility' of monitoring medicines by near-infrared spectroscopy has been demonstrated on low dosage paracetamol syrups, in other words on a product which is very widespread but which, due to counterfeits, has already caused deaths in Africa. A similar 'feasibility' study has been applied to capillary electrophoresis, using anti-AIDS products,' points out Eric Ziemons. *'The reliability of the system has also been demonstrated: our equipment is effective. It succeeds in testing and analysing in a trustworthy manner anti-inflammatory and antiinfection drugs, including antimalaria medicines.'*

As a priority the team developed methods enabling the equipment to check medicines capable of fighting the diseases responsible for the most deaths in the targeted regions, as well as standard very common medicines, such as painkillers. *'Eventually, we might add methods allowing us to screen substances used in cardiac pathology treatments,'* anticipates Philippe Hubert. *'But, in the meantime - and this is the important thing – we already know that we have available two techniques which have been validated in terms of feasibility and are perfectly adequate and adapted to the targeted goals'* (3).

Whilst the personnel continued to be trained in the regions concerned or in Belgium, the Belgian team moved on to the last stage of its projects: installing two laboratories in the Congo (Rwanda already has two laboratories available, there again thanks to assistance from another project involving Liège university academics, in particular Professor L. Angenot and M. Frederich). A site still needs to be found to house the general laboratory. The University of Kinshasa will host the second laboratory, and it will also enable counter-evaluations to be carried out. '*The coming year will be used to renovate the premises and to contact suppliers who will, for example, provide the air conditioning. During this period the technical training of these laboratories' future personnel will carry on, as will the development of new models allowing the two systems to increase the number of products they are capable of checking,'* points out Roland Marini. In effect it is a question of continuing to enrich the model, to 'feed' it information, in order to make it more 'canny' and better able to check a yet higher number of products.

The researchers estimate that it will doubtless require three to four more years before the Congolese laboratories can function autonomously. *'The objective is to enable local producers and monitoring agencies to make use of these laboratories, and at moderate prices as the equipment's running costs are low. Thus a monitoring system aiming at the improved quality of medicines could become widespread,'* forecasts Philippe Hubert.

The reality principle

In Belgium at the beginning of October 2010, an international operation against the online selling of counterfeit and illegal medicines allowed the seizure, at Zaventem airport, of 76 parcels sent to Belgian buyers. Inside were found, in the following proportions, 26% counterfeit erection stimulants, 25% illegal slimming products, 6% antihypertensive products, 5% diuretics, 13% hormone substances and 8% sports stimulant supplements. At Bierset, 18 other parcels were blocked by customs officers, in which were products which mainly came from China, including counterfeit antibiotics. In a great number of 'poor' countries, a lot more threatened than we are by the traffic in counterfeit medicines, such suppression measures are still a long way off. *'At the present time, medicine inspection in the Congo involves 69 inspectors (for 70 million inhabitants), of which 40 are in Kinshasa. In Nigeria a female inspector was subject to attempted murder and now only moves around with bodyguards,'* underlines Roland Marini. At their own level, the Liège pharmacists' projects contribute to responding to this traffic and to supplying the population with quality medicines. One figure, a single one, to measure what is at stake: according to the WHO every year 200,000 people die because of counterfeit products.

(3) *'Analytical tools to fight against counterfeit medicines'.*
R.D. Marini, J. Mbinze Kindenge, M. De Lourdes Aja Montes, B. Debrus, P. Lebrun, J. Mantanus, E. Ziemons, C. Rohrbasser, S. Rudaz, Ph. Hubert.
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