EDITORIAL

Drug Saf 2011; 34 (6): 445-448
0114-5916/11/0006-0445/$49.95/0



# Fraudulent and Substandard Medicines
## Getting Away with Murder?

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Several women have bled to death after childbirth because the oxytocin used was totally inactive and there was no emergency blood and other necessary facilities to hand. A nurse who complained to the authorities about this had threats to her life; no official record exists of this.

Now, the US FDA is worried about the less regulated area of so-called 'dietary supplements' or herbal remedies that could be contaminated by allopathic drugs or dangerous compounds, and they have recently issued a warning about such risks.[1] For the most part, developed countries do not see much of a problem with licensed medicines, although occasionally very clever fraudulent drugs do get into the supply chain for allopathic medicines, escaping notice even where the most sophisticated labelling is used and where quality assurance is good. The warning includes the following:

''Among the substances found in products that are marketed as dietary supplements and that contain hidden or deceptively labeled ingredients are:

- The active ingredients in FDA-approved drugs or their analogues (closely-related drugs).
- Other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients.

Where FDA investigations have discovered tainted products marketed as dietary supplements, the agency has issued warning letters and conducted seizures and criminal prosecutions.

FDA has also alerted consumers to hundreds of products with these often deceptively labeled and harmful ingredients, including more than 80 products marketed for sexual enhancement, more than 70 products marketed for weight loss, and more than 80 products marketed for bodybuilding.''[1]

Such products can be bought in shops and, overwhelmingly, via the Internet. A recent editorial in *Drug Safety* was about using the Internet for communication, particularly as a potential source for information about harm from medicines.[2] It was noted that free communication does not make it easy to find complete information; even though it may be available, it does not guarantee its quality. To sell a medicine on the Internet certainly does not guarantee its quality, nor does it ensure that it will be used properly.

On the whole, the involvement of health professionals has not always resulted in particularly good medicine use, but it does seem that it adds danger to sell products without direct health professional advice *and* that the drugs either do not work or are contaminated by potentially dangerous materials. This is even more significant when 'dietary supplements', etc., are regarded by many as 'safe'.

The European Alliance for Access to Safe Medicines gives advice about counterfeit medicines and buying on the Internet.[3] As an illustration of the dangers of buying on the Internet, there were reports about 5 years ago of very striking virilization of very young children, male and female, caused by topical application of bodybuilding steroids to the father's arms or chest that rubbed off onto their child when he or she was cuddled. The particular reason for this anecdote was that since these products were not licensed medicines and there was no control over Internet selling, nothing could be done about it. Have things changed significantly? Well just check on

''…Real No Bull Facts on Steroid Use, Explained in Layman's Terms by One of the World's Top Anabolic Steroid Experts''[4] and then see if you can get a testosterone patch or gel; it is still possible but not so easy. Whilst you are browsing you may be entertained by Sole Nazz House, a Malaysian bodybuilding supplement shop.[5] On this website you can buy a wonderful 'detox foot patch' that soothes headaches, beautifies skin and generally improves health. Although the ingredients are not stated, there is a detailed explanation of how to avoid fakes!

From about the turn of the century, both the WHO and the international pharmaceutical industry have taken an ever-increasing interest in the counterfeit drugs market. Although the WHO has held a database of counterfeiting since 1982 and dealt with cases of counterfeiting since the 1940s, the problem is burgeoning.[6-8]

This brings one to the real question: what can be done about it?

The major WHO meeting in Rome in 2006[6] came up with the idea of a framework convention: ''A framework convention offers the benefit of an incremental approach to law making, can establish a system of governance, and encourages both cognitive and political consensus. Most important, the process by which framework conventions are developed can include substantial input by industry, consumers, and other stakeholders, the views and expertise of which are particularly important for a comprehensive treatment of counterfeit drugs.''

The major points of the Convention are summarized in Annex 1 of the document entitled 'Combating Counterfeit Drugs: Building Effective International Collaboration', International Conference – Rome, Italy, 16–18 February 2006, i.e.

- To update national laws strengthening drug regulatory authority and adopt international minimum standards for drug regulation including locally manufactured and imported medicines and codes of good manufacturing, distribution, pharmacy practices.
- To establish a national counterfeit drug office.
- That there should be national measures to assure the quality of the whole drug supply chain with a chain of custody; licensing and documentation; tracking methodology and use of technology; quality control laboratories; education, training and public awareness campaigns and sanctions for offenders.

This lengthy and comprehensive document covered all the processes needed to control counterfeiting and all the stakeholders who should be involved, but once the important political and bureaucratic matters are agreed, what are the practical ways in which fraudulent drugs will be combated? The main ways envisaged in the document seem to be:

- global information exchange;
- prosecution of offenders;
- tightening of drug regulation over labelling and packaging;
- quality assurance and monitoring;
- increase public awareness.

Since all of the above are intended to apply to all points in the manufacture and distribution of a drug, as relevant, it is not a surprise to find at the foot of the document that managing the financial aspects and the resource implications will have to be resolved after the IMPACT (International Medical Products Anti-Counterfeiting Taskforce) is actually established. It is also no surprise that the problem of counterfeit and substandard products does not go away!

The heart of the matter is that there is much money to be made in the counterfeit medicines 'industry', particularly outside the regulated medicines area, via over-the-counter sales in non-pharmacy outlets and via the Internet. Catching those who sell and manufacture them is not easy; constant vigilance and testing is required, both of which cost money and add to the burdens of already resource-poor countries. Moreover, resources are needed not only from the medical community, but also from customs and other law enforcement agencies.

It is also important to note that the global problem of antibiotic resistance is adversely affected by the use of products with less than the required antibiotic activity.

## A Role for Pharmacovigilance?

It was a considerable surprise to me to find some years ago that 'medicine ineffective' was the

tenth most frequent adverse reaction in the WHO Adverse Drug Reactions database. It is now ninth most common. Nearly all countries contribute such reports. The trouble is that we do not often know the reason for such a report, which might result from a drug interaction; adherence failures; prescription, dispensing and other medication errors. It must be significant that we have such reports since they are not strictly reports of adverse reactions – by older definitions anyway – but someone is clearly concerned enough to report to an authority with the power to help them. We know that medicines do not work for every patient, but there must be some suspicion of an unusual problem for reporters to bother to send in a report. It seems likely that the only place in many countries where anyone can report such a concern about a product is to the pharmacovigilance centre.

There seems to be an important public health reason to do something with these reports, other than file them – but what? I have learned a couple of things from underresourced countries, both first hand and also confirmed by others. Patients notice things and want to report them, but they are frequently put off by narrow-minded professionals. It is clear that when someone reports that their tablets have turned to powder in the bottle in which they were bought that there is a problem; if soluble tablets fail to dissolve there is a problem; if a different looking frusemide tablet fails to produce diuresis, there is *probably* a quality problem. These are actual examples of reports to pharmacovigilance centres; they affect the safety of patients and it is our responsibility to follow them up or refer them to those who can do it more easily. But the last example, of the most common single term related to drug inefficacy in Vigibase (medicine ineffective), is challenging in pharmacovigilance circles for two reasons:

- Sudden failure of effect, for example, in a patient receiving frusemide is fairly unusual, and a knowledgeable health professional seeing such a report should hear some warning bells in the background. However, in some places the reports are entered into a database without being seen by a broadly trained health professional, so that professional background knowledge cannot be applied and, furthermore, *relevant* information for this situation (e.g. change of brand of medicine) is not obtained.
- The second issue is that, in some therapeutic areas at least, unless the numbers of the reports are very large, an investigation on 'medicine ineffective' would not cause much reason for special attention. For example, I ranged the reports of 'medicines ineffective' in descending order and 14 of the top 50 reports related to antivirals, most used in the treatment of HIV/AIDS. We know that these antivirals have been subjects of counterfeiting but unless there is a report-by-report analysis it is unlikely that substandard products would stand out in a disease area where treatment failures of individual medicines are relatively high.

So, is there more that we can do? Firstly, I think our colleagues in resource-poor settings are more likely to find substandard and fraudulent medicines, and we should be very aware of their experiences. With overall proportionally less reports coming in, and less focus on new drugs, they view more broadly and deeply the implications of each case report than colleagues in developed settings. They will also see more instances of problems that pass by the resource-limited drug registration facilities and control in those countries. Sharing their knowledge with the rest of the world is indeed a good way to go.

At the Uppsala Monitoring Centre, in considering how we might be able to help using Vigibase, we have come up with the following proposal, which has just been examined in a pilot study, funded by the EU FP7 project. The primary defining criteria around substandard products (and for antibiotic resistance) are for clusters of reports of ineffectiveness to occur in time and/or place. This can be examined in a variety of ways, but one way is to use disproportionality. Simple in concept, the challenges are to be able to group appropriate Medical Dictionary for Regulatory Activities (MedDRA®) terms and to optimally circumscribe a 'cluster'. From this pilot study, several subgroups were examined, and the ability to find substandard products was confirmed. Examples are levothyroxine, where there

were reports of inefficacy in a cluster found over a 3-year period; malfunction of an adrenaline (epinephrine) pre-filled auto-injector; and counterfeit Lipitor® (atorvastatin). In the pilot study, special attention has been given to all antibacterials, selected because of the combined problems of counterfeit product and drug resistance. In spite of the methodological challenges, when reports were arranged according to maximum disproportionality, the top candidates quickly yielded two case clusters where there was some information in case narratives that the antibiotic was not of poor quality, and in one an index case of resistance was mentioned. No such reassurance was available for three other clusters, which then raises the suspicion of substandard medicines; two of these instances have subsequently been confirmed.

Apart from help from the case narrative, it seems likely that clusters based on brand names rather than generic names would be more likely to be counterfeit. Those with patterns of appearance in Vigibase linked geographically, both together in time and by the brand marketing territories, might also be more suspect.

As always, the more and better the information on the report, the more effective the analysis.

Given the extent, persistence and seriousness of fraudulent and substandard products, there seems to be no excuse for any group that thinks it may have access to useful data to fail to make good use of this data. Dr Dora Akunyili, ex-General Director of Nigeria's National Agency for Drug and Food Administration has said "Counterfeit drugs are murder …"[9] If not murderous in intent, to knowingly manufacture counterfeit drugs could well be regarded as manslaughter, given the virtual certainty that someone will die because a necessary drug does not work. Who wants to be an accessory to that?

## Acknowledgements

The author has no conflicts of interest to declare that are directly relevant to the content of this editorial.

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