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Exposé

For PhD Dissertation

„QUALITY ASSURANCE AND DRUG SAFETY ISSUE ON
PHARMACEUTICAL PRODUCTS MARKETED
IN DEVELOPING COUNTRIES“

submitted by

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ABBREVIATIONS

DRA:	Drugs Regulatory Authority
ECOWAS:	Economic Community of West African Countries
EDQM:	European Directorate for the Quality of Medicines.
GMP:	Good Manufacturing Practice.
IMPACT:	International Medicine Products Anti Counterfeiting Task
ISA:	International Standard for Antibiotics
MJA:	Mutual Joint Audit
NAFDAC:	National Agency for Food and Drug Administration and Control
OMCL:	Official Medicines Control Laboratories
WCO:	World Customer Organization
WHO:	World Health Organization
WTO:	World Trade Organization

1 Introduction

The terms drug, medicine, pharmaceutical product and medical product in English generally are used interchangeably to refer to medicinal products intended for prophylactic, diagnostic or therapeutic use.

Pharmaceutical products – more commonly known as medicines or drugs – are a fundamental component of both modern and traditional medicine. It is essential that such products are safe, effective, and of good quality, and are prescribed and used rationally.

The development of norms, standards and guidelines to promote quality assurance is an integral part of WHO's Constitution and has been endorsed and supported through numerous World Health Assembly resolutions, and more recently in those on the Revised Drug Strategy.

Article 2 of the World Health Organization (WHO) Constitution establishes its obligation to set standards which have been implemented with regard to drugs by the Quality Assurance Program. It has the responsibility of setting norms, developing guidelines and advising WHO Member States on issues related to quality assurance of pharmaceutical preparations in national and international markets, with particular emphasis on generic products. Combating and preventing substandard medicines is an essential component of ensuring the quality of pharmaceutical products in national and international markets¹.

The aim of all the regulatory legislations (drug laws) and all Drug Regulatory Authorities (DRAs) are to provide patients with safe medicinal products based on the proof of quality, safety and efficacy.

Mutual Joint Audit (MJA), Tutorials and Training Visits are organized by EDQM with the aim of giving advice and helping the Official Medicines Control Laboratories (OMCLs) implementing and/or improving their quality management systems².

2 Key challenges

Quality assurance of pharmaceuticals is a major public health challenge, particularly in light of growing cross-border health issues and the international dimensions of trade. Substandard medicines result in prolonged treatment for patients, drug resistance and sometimes even death.

"The effect of either inadequate drug formulation or content leads to a sub-therapeutic dose and the development of drug resistance of infectious agents. The consequences of this are obvious;

(1) Relatively cheap drugs will become ineffective;

¹ Concept Paper for Effective International Cooperation WHO Health Technology and Pharmaceuticals January 2006

² Quality Assurance activities www.edqm.org

- (2) The loss of such drugs will require new drugs development, which will be more expensive and will further disadvantage for patients in the developing countries;
- (3) Selection of drug resistant pathogens will lead to increased morbidity, mortality and a significant economic burden in developing regions of the world³.

The laboratory resources, needed to support the regulation of any given market, will depend heavily on whether or not the products are manufactured within that market area or whether they are largely imported.

In many developing countries, however, an unfortunate combination of two factors exists. On the one hand, there is predominance of imported finished products and on the other, a lack of adequate analytical services and appropriate human resources.

Because of inadequate regulation and enforcement, the quality, safety and efficacy of both imported and locally manufactured medicines in many developing countries cannot be guaranteed. Smuggling and illegal importation of drugs are rife. Unsafe drugs are not only sold in countries with ineffective drug regulation but they are also exported or re-exported.

Distributors, brokers and their allies aggressively seek to avoid detection. They engage in elaborate conspiracies to disguise their activities. They establish fictitious businesses and front companies. They exploit weaknesses in border control whenever governments try to promote world commerce by reducing border inspections. They use false documents to obtain essential active pharmaceutical ingredients, as well as manufacturing equipment to replicate genuine products.

Some policy-makers have argued that drug regulation represents an unnecessary barrier to trade and should be reduced to a minimum.

A recent survey by the WHO of seven African countries found that between 20 and 90 per cent of all anti-malarial failed quality testing⁴.

One study found that 31% of anti-tuberculosis drugs in Botswana are substandard⁵, contain a toxic ingredient or do not contain any active ingredient.

In 2001 it was reported that China had 500 illegal medicines factories⁶ and while no newer data is available, it is safe to assume that number has since increased.

According to the WHO, in South East Asia region, Cambodia had 2800 illegal medicine sellers and 1000 unregistered drugs on the market in 2003. The same report showed

³ Behrens RH, Awad AI, Taylor RB. *Substandard and counterfeit drugs in developing countries*. Trop. Doct. 2002 Jan; 32(1): 15-7.

⁴ The quality of antimalarials: a study in seven African countries," Geneva: WHO
<http://whqlibdoc.who.int/hq/2003/WHO>

⁵ Kenyon TA, Kenyon AS, Kgarebe BV, et al. Int J. Tuberc Lung Dis 1999; 3(11): S347-S350.

⁶ <http://bmj.bmjournals.com/cgi/content/full/327/7424/1126-a>

that Laos had about 2100 illegal medicines sellers, while in Thailand, substandard medicines account for approximately 8.5 per cent of the total market⁷.

One 2002 study by government officials showed that 9 per cent of all drugs tested in India were substandard. Some 15,000 generics manufacturers operate in India⁸; although the majorities are legitimate, a small minority is likely to be 'fly by night' operations that do not comply with proper standards. Unfortunately it is well known that most of the medicines in Africa sub Sahara originate in China and India, a fact that leads the NAFDAC (National Agency for Food and Drug Administration and Control) to threaten to ban the import of all drugs from India in 2003. However, it should be noted that 70 per cent of the Indian domestic market is supplied by around 20 companies that regularly pass inspections from visiting officials from Western countries⁹.

This Framework called for a multiple approach to address the problem and included the following measures

- Secure the movement of drugs
- Secure business transactions
- Heighten Vigilance and awareness
- International cooperation.

3 Purpose of the Dissertation

The aim is to expose the global quality safety and efficacy issue of pharmaceutical products in developing countries in general and particularly in African sub Sahara countries. I would like to expose the current and concrete issues on quality and safety of pharmaceutical distributed in developing countries especially in Africa sub Sahara.

The range of substandard medicines on national and regional markets will be illustrated in my dissertation.

I will analyze the efficiency of international collaboration and programs for safe drugs on markets of those countries, also analyze the impacts of programs such as EDQM efforts, Prequalification programs from WHO to support regional efforts for access to good quality, efficient and safe medicines in developing countries.

In this context, local competent Authorities action plan in concerned countries and regions will be outlined in the dissertation. The stand of efforts accomplished will be presented in details.

⁷ <http://www.who.int/entity/bulletin/volumes/81/12/WHONews.pdf>

⁸ http://pharmalicensing.com/articles/disp/1120475327_42c918bf09048

⁹ Selling cheap generic drugs, India's copycats irk industry,
<http://chakra.org/articles/2000/12/03/indian/drugs>

Inland and regional position and their capacity to follow international standards in order to ensure that the pharmaceuticals marketed in developing countries are of good standard, efficient and safe will be outlined.

With my dissertation, I would like to provide recommendation for the implementation of global regulatory system and regulations in these countries.

4 Time lines and steps

The first two years will be used to gather useful information on Quality Assurance issues from the concerned organizations such as World Health Organization in Switzerland, EDQM in France and some regions in Africa. There is a necessity to visit first the WHO quarters in Geneva, the EDQM's office in Strasbourg and some countries in West Africa; if possible other concerned regions. The third year for review and redaction.

4.1 The World Health Organization's quarters in Geneva (Switzerland)

The WHO quarters in Geneva (four to six weeks for data research and discussion with experts).

The quality of pharmaceuticals has been a concern of the World Health Organization WHO since its inception in 1946.

With my visit in WHO headquarters, I will seek to launch discussions on a mechanism of effective international collaboration. The Geneva trip will enable me to have access and discuss many reports on quality assurance issues of pharmaceuticals in all WHO regions; I will emphasize my dissertation on WHO views on Quality Assurance issues concerning African countries and the rest of the world where for any reason I may not personally reach. Preliminary contact has been launched with the WHO's Unit for Quality Assurance in Geneva.

4.2 The European Directorate for Quality of Medicines (EDQM) in Strasbourg

As part of the partnership activities carried out with the European Commission, a European network of national medicines control laboratories was set up in 1994 and developed by the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe, particularly with a view to carrying out collaborative studies on the quality control of marketed medicines¹⁰.

European Directorate for the Quality of Medicines (EDQM) support whose IMPACT initiatives and strategy on crimes involving Health Care products. In the different WHO regional areas, EDQM has made a great effort in medicines quality management and has been designated a WHO collaborative centre for International Standards for antibiotics (ISA).

¹⁰ EDQM Related document 675/ 11.2 ; 675 Meeting of the Ministers' Deputies 15 June 1999

In Strasbourg, the council of Europe has launched many programs to support developing countries in Drug Regulatory management; the Quality Assurance training/education program organized by the Council of Europe to assist developing countries includes many African countries. There is a necessity for my dissertation that I personally explore and discuss the issue with the concerned branch of the EDQM, focusing my work on Reference standards, compliance testing, Standard 'Aide Memoire' for the Mutual Joint Audit of OMCLs as well as for Environmental Conditions of Pharmaceutical.

A preliminary contact has been done with the EDQM's branch for approximately two months journey in Strasbourg.

4.3 Economic Community of West Africa States (ECOWAS) research journey

ECOWAS is a regional economic community which assembles 16 West Africa countries. As a native of the region, a study on the way medicine products are distributed to the ambulant pharmaceuticals sellers, street market and pharmacies is in my dissertation's program. I will find out how effective are the pharmaceutical legislation (if any), their implementation and follow up measures within countries and on regional level. In each country my research and documentation will be done in the Ministry of health, National Pharmacies board, associations for Public protection, Traditional Medicines board and customer services. I will analyze the efficiency of international collaboration and programs for Quality Assurance and safe drugs. Then I will compare with the official data base in WHO quarters in Geneva and whatever I get from EDQM centre in Strasbourg. Due to the standard of the facilities over there, the research may last up to eight months.

5 Conclusion

A system based on strict, rational pharmaceutical purchasing and distribution policies with quality assurance at every level of the supply chain is needed to guarantee that patients receive safe, effective and high quality healthcare product.

In most of developing countries there is no drug regulatory authority at all and in those where one exists, it is either inadequate to regulate drugs generally and/or does not have the power to apply measures to suppress the factors that lead to parallel distribution of unsafe pharmaceuticals.

The European Commission, donor countries and International organizations invest heavily in programs to make reliable medicines available in many developing countries. They are extremely important institutions that have ability to influence policy makers in developing countries worldwide.

Product quality can be better assured if an inspection force is available to periodically visit manufacturing sites and review production records. It is necessary to address those dynamics which encourage the manufacture and supply of substandard medicines.

Since the majority of these drugs originate in Less Developed Countries, it should be a matter of priority to address those lacunae of governance which allow counterfeiters to ply their trade with relative impunity. Most importantly, it is essential that contracts, property rights and the rule of law be upheld in the countries in which the majority of these drugs are produced or marketed.

A framework convention can be a key element of an overall global strategy to stem the unacceptable risks of harm and death and burden of disease associated with exposure to unsafe medicines. Also a simpler mechanism such as an international taskforce could suffice for achieving improved cooperation and effective intervention. The establishment of an international framework convention on substandard medicines requires political will and consensus of most WHO member states.

Intergovernmental initiatives have included the establishment of a comprehensive multilateral legal framework within the World Trade Organization (WTO), as well as co-operation in a number of specific fields.

The World Customer Organization (WCO) provides training and technical support for governments to combat trade in counterfeit and pirated products. Working together with governments and industry to address enforcement issues through information exchanges, and guidelines for effective enforcement¹¹.

Good Manufacturing Practice (GMP) standards that represent a global consensus on how drugs should be apply all over to ensure safety, efficacy and quality of medicines.

¹¹ www.wcoipr.org