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Incidence of Substandard Medicines in Khartoum, Sudan in 2009-2010: Results of Medicines Quality Monitoring Survey

Abstract:

Background: Medicines Quality Monitoring Survey has been conducted during the period 2009-2010 in Sudan. ***Method***: This was cross-sectional survey. ***Results***: Out of 30 samples of targeted trade products that have been analyzed 10 % of the samples has failed to comply with reference standards specifications in term of chemical analysis of APIs content. It wasn't significantly appeared that there is direct relation between the quality of medicines and its country of origin; nevertheless, substandard products from low income countries were more than local products. ***Conclusion***: It wasn't significantly appeared that there is direct relation between the quality of medicines and its country of origin, nevertheless, the larger percentage of detected substandard products were imported from low income countries comparing with the percentage of locally manufactured products among the collected medicines sample.

Introduction:

The harmful and ethical implication of allowing low quality medicines to be available in the market for human use is a non-debatable issue (TenHam, 1992). While in last decade there was great revolution in producing medicines; it is still valid that significant percentage of medicines circulated in the global markets was of low quality either substandard or counterfeit. According to WHO: "*Substandard drugs are genuine drug products which do not meet quality specifications set for them*" (WHO, 1997). The term substandard used to describe the quality status of genuine drugs produced by legitimate manufacturers. Normally, for each drug product the manufacturer produce it based on a set of quality standards or specifications. Such

specifications are also published in official pharmacopoeias such as the United States Pharmacopoeia, the European Pharmacopoeia, and the WHO International Pharmacopoeia. If any drug upon laboratory testing is with accordance to the specifications so it claimed to be complied and if fails to meet these specifications, then it is classified as a substandard drug (Layloff, 1997). According to WHO reports, low quality medicines represents about 10% of the global pharmaceutical market in which about 40% were substandard. When this fact is combined with the picture about the size of pharmaceuticals market it became obvious how this problem is triggering. Additional innovative techniques need to be developed to control the existence of substandard medicines in the market (WHO, Counterfeit Medicines," fact sheet, 2006). The statistics in developing countries showed even more critical situation regarding the existence of these medicines (Ravinetto, 2002). The degree to which these substandard medicines exist in Sudan is very difficult to be concluded in one figure or in simple report. This is due to the complicated detection mechanisms and not mentioning the concerns about the quality of the data. The available reports may provide indicative information if it becomes more systemized, arranged and gathered. It will help the decision-makers to obtain the true picture about cause-effect relationships that directly outline the situation in Sudan regarding the problem of substandard medicines. Establishing Post Marketing Surveillance (PMS) System in many countries in collaboration with WHO help these countries for better improvement of its regularity functions (WHO, 1997). PMS system considered as one of the important tools and methods to monitor the quality of medicines and as strategy of choice to improve the quality of medicines (FDA, 2007). In this system, the quality of any product could be surveyed by analyzing samples taken from manufacturers and from the distribution chain either randomly or on purpose (based on incidents reporting for suspected medicines). Quality tests in this system were performed to ensure conformance to pharmacopoeial requirements (e.g., British Pharmacopoeia, U.S. Pharmacopeia, International Pharmacopoeia, etc.) or to the manufacturer's specifications where necessary or applicable (WHO, 2007).

Chemical analysis is usually one of the main and essential quality control tests that should be conducted in order to assure the quality of different types of medicines (Layloff, 1997), (WHO, 1991). In many countries, the chemical analysis department in the medicines regulatory laboratories is essential part of the system and usually

countries consider its capacity development seriously as a part of the national priorities. The results of chemical analysis and other analysis data should be combined and interpreted carefully; so as to obtain authentic facts about the extent of any quality related problem (Harris, 2003). The chemical contents of each medicine usually play important role in medicines ineffectiveness problems. Because it indicates that the desired quantity of the medicine is available or not as patient need it; and any interruption in this relationship could lead to failure of therapeutic process (Watson, 2005). This is important because all treatment hypnosis's were based on producing certain and specific amount of the medication per unit dosage form; which will be used for certain patient with specific needs; so any disturbance in this balance could lead to failure of treatment. Chemical analysis by its own is usually not sufficient indicator about the quality of medicines. The data generated in this combined manner could point out some knowledge about what are the factors leads to suspected results from the analysis. By considering this, the results of the analysis will become supporting means to verify the quality suspected cases or could be used to support regular and routine checks of medicines.

In order to support the efforts of medicines regulatory authority in Sudan to detect the existence of substandard medicines, a team of experts conducted Medicines Quality Monitoring survey (MQM) during the period 2009-2010 in Sudan. The survey was conducted to serve as random check to detect the existence and availability of substandard medicines in Khartoum. The quality check was conducted based on the feedback received form health professionals about from observations, experiences and concerns about the quality. There are other similar studies conducted to evaluate the existence of substandard medicines in other countries. A Review of drug quality in Asia was conducted in 2004 with Focus on Anti-Infectives 2004 (USP, 2004). The review showed that the reported percentage of substandard/counterfeit drugs ranges from 2% to greater than 60%. On average the availability of substandard medicines ranged from 8% in Vietnam up to 27% in Bangladesh.

Another assessment was conducted to evaluate the incidence of substandard drugs in developing countries (Taylor & others, 1997) The results indicated 36.5% of the samples were substandard with respect to Pharmacopoeial limits. No similar study has been conducted in Sudan and no available documents or data found states that similar study done in the previous period in Sudan.

Methods:

Medicines selection criteria

In MQM survey the information providers were asked to provide their comments on certain medicines. These were 20 generics selected based on certain criteria. The selection criteria for choosing the surveyed medicines include: (1) highly consumed medicines –was based on statistical report 2007 (FMOH, 2008); (2) quality problems experienced in other countries; based on the literature review including studies and reports from the authorities (Kopp, Counterfeiting: An overview Counterfeiting: An overview of problems and of problems and dangers, 2003) ; (3) all medicines selected were classified as essential medicines in Sudan based on the Essential Medicines List 2005 (FMOH, 2006); (4) therapeutically different medicines were selected among different pharmacological groups and dosage forms; and (5) Considerations regarding health system indicators in Sudan; priority diseases based on the statistical report 2007 from MOH (FMOH, 2008); Based on all of these factors, the following medicines were included in the questionnaires: Amoxicillin susp/cap; Ampiclox; Artesunate; Aspirin; Atenolol tab; Carbimazole tab; Cefuroxime sodium inj; Chloramphenicol cap/tab; Chlorphenarmine; Ciprofloxacin tab; Co- trimoxazole; Digoxin inj/tab; Ethinylestradiol/levonorgestrel; Furosemide; Glibenclamide tab; Hydrocortisone; Mefenamic Acid; Metronidazole susp/tab; Nifedipine and Paracetamol.

Based on the results obtained from the survey; certain criteria have been set to select particular medicines which will be the subject of Quality Control laboratory analysis. The criteria set were as follows: (1) Top 10 generics (in %) that professionals concerns about it; (2) Feedback obtained from the professionals about specific medicines related problems (Top 5 generics); (3) Distribution of selected medicines (the 15 generics from 1&2 above) in terms of pharmacological groups, number of registered items per each generic, quantitative assay methodology and type of dosage form; (4) Availability and possibility to access suitable analytical settings. The screening process was made to select the final list of generic medicines. Based on that 10 generics were finally selected according to the above mentioned criteria as follows: Ciprofloxacin; Aspirin; Metronidazole; Glibenclamide; Mefenamic Acid; Chlorphenarmine; Paracetamol; Diclofenac; Amoxicillin;

Ceftriaxone. These 10 generics represented the core list for quality control analysis. The next step was the selection of representative trade products registered in Sudan. The way the trades were selected in this part developed to avoid any sort of bias so as to ensure the selection of representative samples correspond to the situation as much as possible. Based on the questionnaire analysis and upon the response of the targeted groups, it was noted that the respondents sometimes relate and link the products quality by its countries of origin. This observation was considered in order to select the sample of trade products and also this could help in verifying the validity of this assumption. In Sudan there are large number or registered source origins of pharmaceuticals that shaped the market in Sudan. Based on that, the study team decided to categorize the countries of origin based on the country income according to the World Bank reports (WB, 2007). This assisted the investigators to systematize the sampling process. There are major classifications for countries income level according to World Bank reports and this include: (1) High income countries; (2) Upper-middle income countries; (3) Lower-middle income countries; (4) Low income countries.

The final selection of medicines included 30 products for quality control assessment.

Collection of samples for chemical analysis

Sampling considerations:

This sampling methodology was used in order to verify the quality of medicines reported in the feedback from the health professionals with concerns about its quality. Accordingly, the sampling technique took into the considerations the following factors: (1) sampling sites should be only within Khartoum city as study area; (2) samples collected only from the retail private pharmacies within the determined area; (3) sampling technique took into consideration the differences between the geographical areas within Khartoum; (4) sampling method considered also the classification of pharmacies located in household areas and that located near clinics and hospitals in the central areas of Khartoum; and (5) sampling method was based on collection process using the trade products available in the market.

Sample size:

The size of sample collected was determined according to the requirements of reference pharmacopeia for the official tests. This done under the following guidelines: (1) For each solid dosage form products (tablets and capsules) minimum of 100 units were collected from different sites; (2) For each injectable products minimum of 10 units were collected from different sites; and (3) For each liquid dosage form products (suspension and syrups) minimum of 10 units were collected from different sites

Coding system:

Due to the confidential nature of this part of the study, it was necessary to develop well structured coding system that ensured the confidential identity of all entities under the study. This coding system enabled only the study investigators to identify the trade names or the manufacturers and even the analysts were not able to expose the identity of any drug.

Quality control tests:

After the completion of medicines selection process and samples collection, the samples were subjected to general physiochemical analysis regarding its compliance with quality requirements and specifications in the reference pharmacopeia. The process done in collaborative approach between the study team, Faculty of Pharmacy – University of Khartoum and National Quality Control Laboratory - Federal Board of Medicines and Poisons.

Visual/physical inspection:

The following indicates how inspection process was made for the samples. (1) Physical quality check was completed for each batch/sample collected from the field using standardized check list; (2) The integrity of packs, appearance of tablets, or other physical characteristics of the dosage forms were visually being inspected and reported for each sample; (3) Determination of remaining shelf-life, compliance with approved labeling, packaging, and shipping instructions were all checked and verified by data obtained from “National Medicines Poisons Board”; (4) The physical

appearance of the dosage form (including its shape, size and color) were all compared based on random selection process to ensure similarity of the samples collected for each product; (5) Visual inspection was done to ensure that no breakdown, fragmentation, or cracks in the collected dosage forms for all products collected; (6) The conditions of the primary and secondary packages for each sample were also examined to ensure that there are no defects exist, beside that to make sure if there are incomplete, damaged, or missed labels; (7) Random selection of samples among each trade product has been selected to compare the outer package identity in terms of color, size and other physical factors.

Chemical Analysis

The analysis plan of this study was developed for all of products under testing.

Generics	Dosage Form	Conc	Assay	Pharmacopeia
Ciprofloxacin	Tablet	500 mg	LC	BP
Glibenclamide	Tablet	5 mg	LC	BP
Amoxicillin	Capsule	500 mg	LC	BP
Diclofenac	Tablet	25 mg	LC	BP
Ceftriaxone	Injection	1 gr	UV	USP
Paracetamol	Tablet	500 mg	UV	BP
Chlorphenarmine	Tablet	4 mg	UV	BP
Mefenamic Acid	Tablet	500 mg	Titration	BP
Acetylsalicylic Acid	Tablet	300 mg	Titration	BP
Metronidazole	Tablet	250 mg	Titration	BP

Table 1: generic medicines selected for chemical analysis

Samples retesting:

This has been regarded as specific considerations for medicines that didn't comply with the requirements during the first round of analysis. Its purpose was to verify the failure results for further assurance. After the determination of the medicines that fail the tests the plan was developed, then additional samples (the same batch) were collected from the retail pharmacies using the same method used before and this sample tested in the same way. The results from each round of analysis compared with each other. The comparisons were made to determine the type of problems that are possibly affecting the results.

Results:

Shelf Life:

It is true that the quality of any product in the market could be affected directly or indirectly by its remaining shelf life in addition to conditions under which the product was stored (York, 1977), (Barmania, 1990).

Origin	Median	Minimum	Maximum
Products from high income countries	34 Months	19 Months	53 Months
Products from low income countries	23 Months	2 Months	51 Months
Products locally produced in Sudan	18 Months	8 Months	33 months

According to the results obtained during the sample collection process from the field it was noted that: (1) The maximum remaining shelf life was 53 months for a product produced in Switzerland, and the minimum remaining period was 2 months for Indian and Jordanian products; (2) The overall median remaining shelf life of the products in the market at the time of sample collection was 21 months; (3) 75% of the products collected have remaining shelf live more than 33 months; (4) In 3 batches the expiry date wasn't imprinted on the internal packages 2 batches were locally produced; (5) Imported products generally have longer remaining shelf life than that local products; (6) The tablet dosage forms characterized by remaining shelf life longer than other dosage forms.

Manufacturers' storage conditions:

Each sample collected from the field was evaluated in terms of storage conditions specified in its outer package collected using the following evaluation criteria: (1) Reach of children precautions; (2) Temperature requirements; (3) Humidity considerations (dry... etc) (4) Light protection. Although in some cases these criteria were not applied for some products, still the indication of each specification for this issue is important. The results showed that the manufacturers consider these criteria as follows: (61%) for Reach of children precautions; (67%) for Temperature requirements; (37%) for Humidity considerations and (33%) for light protection.

Brief physical description:

This part of the evaluation was based on the general comments regarding the physical status of the products collected before it was stored in the laboratory to be subjected for official analysis (physical and chemical). In general (4%) of the samples collected have clear physical problems, this was varied from one product to another and all of the problems were identified in the solid forms.

Overall results:

Generic/Source	Detection limits	Local	Low income country	High income country
Amoxicillin	92.5 to 110.0% of the stated amount	103.1%	100.1%	100.2%
		Comply	Comply	Comply
Aspirin	95.0 to 105.0% of the stated amount	95.8% & 90.4%	92.7%	NA
		Comply & not comply	Not comply	NA
Ceftriaxone	92.0 to 108.0% of the stated amount	NA	99.1% & 103.8%	99.8%
		NA	Comply & comply	Comply
Chlorphenarmine	92.5 to 107.5% of the stated amount	95.6%	97.7%	98.9%
		Comply	Comply	Comply
Ciprofloxacin	95.0 to 105.0% of the stated amount	99.3%	93.8%	99.1%
		Comply	Not comply	Comply
Diclofenac	95.0 to 105.0% of the stated amount	98.5%	102.0%	104.7%
		Comply	Comply	Comply
Glibenclamide	95.0 to 105.0% of the stated amount	95.3%	97.8%	98.2%
		Comply	Comply	Comply
Mefenamic Acid	95.0 to 105.0% of the stated amount	99.4%	96.1%	104.7%
		Comply	Comply	Comply
Metronidazole	95.0 to 105.0% of the stated amount	95.1%	98.5%	98.2%
		Comply	Comply	Comply
Paracetamol	95.0 to 105.0% of the stated amount	98.4%	98.1%	99.1%
		Comply	Comply	Comply

General comments on specific generics:

Generic	Aspirin 300/100 mg tab
- Doctors and pharmacists comparably have fewer concerns about its efficacy and quality comparing to other generics; - Other studies indicated no significance instability problems if the storage conditions were adequate, however, upon poor conditions possible loss of chemical nature could be occurred (Nazerali & Hogerzeil, 1998); - Considerable difference between manufacturers in terms of manufacturing specifications; - Few trade options available in the market, diminutive shifting decisions	
Generic	**Amoxicillin 250 mg cap**
- The second generic that health professionals widely complain its effectiveness; - Top generic that health professionals shift the patient from it to another antibiotic; - Questions regarding possibility of developing microbial resistance to this generic in Sudan due to wide misuse; - Other studies indicate no significance instability problems (Nazerali & Hogerzeil, 1998); - Among highly consumed products in the market; - Expiry remaining period are satisfactory in general; - Significant physical appearance problems for most of the trade products	
Generic	**Ceftriaxone sodium 1g inj**
- Doctors in particular were more complaining about its quality and efficacy; - The mostly likely generics that doctors take decisions to shift the patients' treatment either shift in trade products or to another different generic; - This generic wasn't subjected to post marketing analysis in Sudan; - No local pharmaceutical manufacturers; - Most of the products available in the market have comparably less remaining shelf life than other generics;	
Generic	**Chlorphenarmine Maleate 4 mg tab**
- No direct health professionals' complaints from this generic regarding the efficacy, nevertheless considerable physical problem cases have been recorded; - Significant number of products has been recalled from the field in the last few years; - Most of the products characterized by long remaining shelf life	

Generic	Ciprofloxacin 500 mg tab
- The leading generic that health professionals have comments and complaints about its quality and efficacy; - The second generic on which most of the shifting process were taken place among the decisions of doctors and pharmacists; - Recent studies indicated the possibility of developing microbial resistance for some strains of susceptible bacteria (Seyoum & Blum, 2004), (Palmer & others, 1995); - No physical problems usually associated with the products available in the market; - Some products have been withdrawn from the market based on post marketing analysis.	
Generic	**Diclofenac Sodium 25 mg tab**
- No serious concerns have been verified during this study regarding the quality of the available products in the market; - Considerable number of pharmacists shifted their patients from one product to another; - In products available in the market there is no clear physical problems documented	
Generic	**Glibenclamide 5 mg tab**
- Among highly argued chronically used products regarding the effectiveness of some products available in the market; - Significant cases have been shifted from one product to another as a recommendation from pharmacists and doctors as well; - No physical problems were defined in the market regarding the registered products	
Generic	**Mefenamic Acid 500 mg tab**
- Moderate sort of problems have been associated with the efficacy of registered products in Sudan; - In some of the available products in the market, physical changes have been experienced by some pharmacists; - 2 batches from different manufacturers, available in the market, were detected that lack the identification of the expiry date	
Generic	**Metronidazole 250 mg tab**
- There were no major complaints about the efficacy of most available products in the market, however, there were significant patients complaints regarding the side effects of specific product comparing with other products; - The packaging material used for some trade products available in the market hinder the possibility of observing physical appearance problems	

Generic	Paracetamol 500mg tab
- Being OTC product made it difficult to the doctors to judge its efficacy and the feedback was mainly obtained from pharmacists; - Over the available products in the market, specific products were identified by the patients as the “best quality” and the other were “lower in its quality”; - Some physical appearance problems have been recorded many times for certain locally manufactured product - Other similar study in Bangladesh showed comparable results (Saha, 1992)	

Summery discussion:

The availability of data regarding the quantities of detected substandard medicines in the market is essential information (Frempong, 2003). This is particularly important to assess the situation in the country regarding the availability as one dimension of medicines access model that supported by quality and accessibility for essential medicines (MSH, 2001). Despite that the private sector provides 70% of medicines in the market with availability of more than 90% for medicines in retail pharmacies in Sudan (FMOH, 2007). The outcomes from quality control tests could be considered as important tool to take evidence-based decisions regarding the quality at any level of the supply chain (Seiter, 2005). This is especially true when we consider the great revolution in medicines production capacity, QC management and the expanded needs for medicines. The QC results, including chemical analysis results, should be used only as a tool to improve the quality of circulated medicines through the implementation and enforcement of laws and regulations (Jayasuriya, 1985). Usually the resulting data from QC alone were inadequate for establishing direct linkage between the findings of QC analysis and the imposition of regulatory sanctions to be applied (Editorial, 1997). This should be combined with other different factors that lead to better understand the cause-effect relationships and to take the right decisions based on that (Nicholson, 2005).

It is noted that many factors usually could affect the quality of available medicines in the market (WHO, 2007). The possible relationships that should be considered factors related to pre-marketing surveillance test results; acceptability of the remaining shelf-life at time of receipt; the history of the drug and its agent at NQCL

before distribution (satisfaction or failure); the quality status at time of collection in accordance to Pharmacopeia; the quality at the end of the shelf-life; drugs most frequently failed the tests; the lost of potency among the time. In addition to all of these factors; another study indicated that there are possible effects of the quality of starting materials and raw materials used in manufacturing medicines and this issue should be considered when evaluating the quality of medicines especially when proved to be substandard (WHO, 2003). Most of the studies that has been conducted in this area affirmed that the problem of substandard medicines usually existed due to one of the major causes or all of them. In most of the cases the problem was due to inadequate quality control/assurance measures during the production and/or stability problem due to instable nature of the API and/or inconvenient storage conditions of the final product (Nicholson, 2005), (USP, 2005).

The quality of commercially available drugs varies greatly among countries and the focus was on the more expensive brands. Substandard drugs found even among cheaper products, because some manufacturers wish to avoid costly quality control and good manufacturing practices (Ondari, 2003). Even in one study in India that comparing two products within the same generics it has been found that the cheaper product was better in its quality than that of the highest price which was almost doubled (USP, 2004). But we should also note that when the prices of medicines are high and price differentials between identical products exist there is a greater incentive for the consumer to seek medicines outside the normal supply system. Poverty, then, is one of the major factors in the production and consumption of substandard products (Dukes & other, 2003).

Despite that the statistics showed the facts that, even some of large multinational firms could produce substandard medicines still there is continuous linkage between generic products or products manufactured by small businesses and low quality medicines. In fact well-manufactured generics are of as high quality as well-manufactured branded medicines (HAI, 2003). Recent different two studies in India and Bangladesh, regarding the linkage between sources of origin and manufacturing sites capacity, indicated that most of the substandard medicines were produced from small sized firms in both countries. From the observations in both studies it seems that these manufacturers failed frequently to meet the MRA standards in some areas (USP, 2004).

Conclusion:

Out of 30 samples of targeted trade products that have been analyzed 10 % of the samples were failed to comply with reference standards specifications in term of chemical analysis of APIs content. It wasn't significantly appeared that there is direct relation between the quality of medicines and its country of origin, nevertheless, the larger percentage of detected substandard products were imported from low income countries comparing with the percentage of locally manufactured products among the collected medicines sample.

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