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Evidence-based Approach for Applying Risk Management Principles to Monitor the Quality of Pharmaceutical Products

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Full Research

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“The time is right now for a new framework on Post Marketing Surveillance System”

Amjad Idries

Statement of original authorship:

The work contained in this thesis wan not been previously submitted to meet requirements for an award at this or any other higher education institute. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

Signature:

Amjad Mohammed Idries

Date:

This work is dedicated to my father "my friend" for his nonstop support and to my compassionate mother "my teacher" for everything; for the soles of "Ayman & Assad" as you inspired me to compensate the emptiness you left in my life. This is for the joy of my life "Rend" and my wife for her patience and perseverance and to my friends my little brother and sister.

Contents

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Someone may think that the truth is always in the outside and we have to go there and find it. Although we adopt this approach in this study, it is very important to know that the truth is inside ourselves, are we believed in our self or not to find it, this is the most important truth.

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List of Abbreviations

ADRs	Adverse Drug Reactions
API	Active Pharmaceutical Ingredient
AUC	Area Under the Curve
BNF	British National Formulary
BP	British Pharmacopeia
Cap	Capsule
CMS	Central Medical Supplies
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
CV	Coefficient of variation
DQRS	Drug Quality Reporting System
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FMOH	Federal Ministry of Health
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
HPLC	High Performance Liquid Chromatography
ICH	International Conference of Harmonization
Inj	Injection
KAP	Knowledge – Attitude - Practice
K_E	Elimination rate constant
LC	Liquid Chromatography
LRTI	Lower Respiratory Tract Infection
MA	Marketing Authorization
MIC	Minimum Inhibitory Concentration

MRA	Medicines Regulatory Authority
NGOs	Non Governmental Organizations
NMPB	National Medicines and Poisons Board
NMRA	National Medicines Regulatory Authority
NQCL	National Quality Control Laboratory
NSAIDs	Non-Steroidal Anti Inflammatory Drugs
OTC	Over The Counter
PHC	Primary Health Care
PI	Principal Investigator
PMS	Post Marketing Surveillance
QA	Quality Assurance
QC	Quality Control
QRM	Quality Risk Management
QRS	Quality Re-evaluation System
SD	Standard Deviation
Syr	Syrup
Tab	Tablet
T_{max}	Time to achieve Maximum Plasma Concentration
UoK	University of Khartoum
URTI	Upper Respiratory Tract Infection
USP	United States Pharmacopeia
UV	Ultra Violet
WHO	World Health Organization

Abstract

Background: According to WHO reports, low quality medicines represent about 10% of the global pharmaceutical market of which about 40% were substandard medicines. Most of the studies of quality of medicines recommend development of additional innovative techniques to control the existence of substandard medicines in the market. In Sudan, the system applied to detect substandard and/or counterfeit medicines is not effective enough. A round 9% of pharmaceutical products are reported to be substandard medicines. A strong post marketing surveillance system would be a more powerful tool for detecting substandard and/or counterfeit medicines and showing a true picture of the situation in Sudan. Strengthening the system by applying risk-based model for supporting the decisions is proven to be useful and possible approach. **Setting**: This study was conducted in Khartoum city, Sudan. **Objectives**: this research aimed at developing risk-based quality monitoring scheme or model for pharmaceutical products. The model should help medicines regulatory authorities in resource limited settings to improve surveillance systems. The research will provide a practical model for the expanding the existing surveillance system for quality check of pharmaceuticals currently adopted in Sudan. **Methods**: different methods were used to build this model. These include health professionals' survey targeting the pharmacists and physicians and chemical analysis of 30 medicines. Based on the outcomes of these sub-studies, further experiments were conducted that include bioequivalence study of Glibenclamide products, microbiological sensitivity test on Amoxicillin; biological assay of three Ceftriaxone products and modeling process of data generated. **Results**: A model has

been successfully formulated and adopted to improve the surveillance system. This model is unique and it was the first time to develop such tool globally to help in indicating critical information about the quality of medicines and associated hazard factors to its quality. The model was designed as large and complex computerized system using Microsoft excel program. A sample from the outcomes of the model was printed and attached in annex number 9 for reference. The model was tested for its usefulness and effectiveness and the results obtained showed potential applications of the system in improving the system. This would include its use in the selection technique of products for inclusion in post-marketing quality monitoring. It can also be applied to increase the detection rate of low quality products. Using the developed model, the chance to detect substandard and/or counterfeit products will be increased by about 30%. **Conclusion**: the outcome of this proposed approach will enable the authorities to expand the input measures of its surveillance system beyond quality to consider also the efficacy of medicines.

الملخص العربي:

خلفية: رجوعاً لتقارير منظمة الصحة العالمية فإن الأدوية المتدنية الجودة تمثل 10% من إجمالي السوق العالمي للأدوية، وأن 40% من هذه الأدوية هي أدوية لا تطابق المواصفات. الدراسات التي تمت في مجال جودة الأدوية أوصت غالبيتها بضرورة تطوير تقنيات إضافية أكثر إبتكاراً للحد من تواجد الأدوية التي لا تطابق المواصفات في السوق. في السودان سنجد أن النظام المعمول به غير فعال بدرجة كافية للإستقصاء حول الأدوية غير المطابقة للمواصفات وتلك المغشوشة. تشير التقارير إلي أن 9% من الأدوية غير مطابقة للمواصفات. وبالتالي فإن وجود نظام قوي لمراقبة الجودة يمكن ان يعد بمثابة أداة فاعلة لإحتواء هذه الادوية ولعكس الصورة الحقيقية للوضع في السوادن. إن تقوية النظام عبر تطبيق نموزج قائمة علي إدارة المخاطر في دعم القرارات المتعلقة بالجودة أثبت فعاليته ونجاحه في هذا المجال. **موقع الدراسة:** أجريت هذه الدراسة في مدينة الخرطوم بالسودان. **الأهداف**: هذا البحث أجري بغرض تطوير نهج ونظام لمراقبة جودة المستحضرات الصيدلانية يعتمد في وضعه علي أساس مرتبط بإدارة المخاطر. النموذج الذي تم إقتراحه سيساعد السلطات المعنية بالرقابة علي الادوية في الدول ذات الموارد المحدودة في تطوير نظام رقابة الجودة عقب توزيع الأدوية في الأسواق. هذا البحث سيوفر نموزج تطبيقي لتوسيع نظام التأكد من جودة الأدوية وتحليلها بعد التسويق. **الوسائل**: عدة طرق أستخدمت لبناء هذا النموذج وقد تضمن ذلك مسح للكوادر الصحية في الخرطوم بالإضافة إلي تحليل كيمائي لبعض الادوية. بناء علي نتائج هذين المكونين تم إجراء دراسات اخرى تضمنت دراسة لمقارنة الإتاحة الحيوية لعقار الغليبنكلاميد، دراسة حول حساسية بعض الميكروبات لعقار الأموكسيسيللين، مقارنة لمنتجات من عقار السفترايكسون بطرق بايولوجية بالإضافة إلي ذلك تم إستخدام نظام حاسوبي لوضع النموذج المقترح بإستخدام المعلومات التي تم توفيرها. **النتائج**: تم تطوير نموذج فعال لتطوير أنظمة مراقبة الجودة بإستخدام كافة المعلومات المتاحة من مختلف المصادر سواء أن توفرت من مكونات هذه الدراسة أو البيانات والتقارير المتوفرة. النموذج يعد نظاماً متفرداً حيث أنه ولأول مرة يتم إستخدام أداة بهذا المفهوم علي المستوي العالمي للمساعدة في التعرف علي عوامل الإختطار التي تؤثر علي جودة الأدوية. تم تصميم النموذج علي شكل برنامج حاسوب كبير بإستخدام (Microsoft Excel program). عينة من مخرجات هذا البرنامج تمت طباعتها وإرفاقها في ملحق رقم 9 كمرجعية. تم اختبار مدى الإستفادة من النموذج وفعاليته مقارنة مع النتائج التي تم التحصل عليها من التجارب المشار إليها ومدى إمكانية إستخدامه في تطوير نظام لمراقبة الجودة والفعالية في المرحلة التي تلي تسويق الأدوية. هذا الإختبار تضمن مدى مساهمة النموذج في طريقة إختيار الادوية التي يتم تحليلها وكذلك مدى مساهمته في زيادة مقدرة النظام المعول به في التعرف علي الأدوية متدنية الجودة. بإستخدام هذا النموذج، فان الفرصة في التعرف علي المنتجات المتدنية الجودة ستزيد بما يقارب 30% مقارنة بكفاءة النظام الحالي. **الخلاصة**: مخرجات هذا النهج الذي تم تطويره ستساعد السلطات المعنية في توسيع مقدراتها و عملها في مجال مراقبة الادوية لتضم محور الفعالية بالاضافة لمحور الجودة.

Keywords:

Substandard medicines – generics – post marketing surveillance - pharmaceutical product – risk based model – low quality medicines – medicines regulatory authority – decision making – chemical analysis – bioequivalence – microbiological assay – bioassay

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Chapter 1: Introduction and Literature review

Background

The harmful and ethical implications of allowing low quality medicines to be available in the market for human use are a non-debatable issue (TenHam, 1992). While in last decade there was a 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. Nevertheless, these low quality medicines could be considered as not available for the effective and safe human use (WHO, 2007).

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 a 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).

Although WHO exert hard work and strategies to contain the problem of low quality medicines still there is obvious confusion between the nature of substandard and

counterfeit products (Pincock, 2003) (Yusufzai, 2002). Both types are critical and very important issue to pay focused attention on it; still the control of counterfeit medicines is a very complicated process. It includes multi-sectors collaboration and it entails direct criminal control interventions so usually it needs special and complex management plans (Kopp, 2003). On the other hand, the nature of substandard medicines is clear forward issue, its control involves fewer parties and it is usually under the direct responsibility of Medicines Regularity Authorities "MRAs" in each country. It is usually a controllable problem and this depends on the capacity and strength of MRAs in the country and how well prepared to carry out this function. In fact many interventions could contribute directly to resolve this problem, unlike the problem of counterfeiting which is illegal commerce that is very difficult to be compact (Arya, 1995). The control of substandard medicines is generally stressed by many factors; for example, these medicines are usually authorized products and are legal to be sold for the public within the retail facilities. This is important fact as patients and even pharmacy personnel can handle it as "safe and effective medicines" unless the authorities state other notification. This in fact adds more responsibility and pressure on MRAs to detect these medicines before it reaches the patients.

All of this raises many concerns about the strategies currently used on the ground to face this problem (Thomas & others, 2003). This may include, but not only limited to, the following:

- Development of more effective *quality monitoring system*;
- Improving the *detection rate* of substandard medicines;

- Increasing the availability and *sharing of information* about the existence of substandard medicines;

- The *advance analysis of the detected cases* (its nature, possibilities to be compact, crosscutting factors lead to the incident and other data).

- Application of *continuous improvement process* of the system (through research and development).

When we look into the current systems used to control substandard medicines in Sudan we can realize the problems associated with considering these factors to improve the system.

The availability of data from previous activities is essential part of any proposed actions for any problem solving scheme, as building any decision based on evidence become essential. It is important also to evaluate the cause-effect relationships in these kinds of problems. This could help the authorities to build effective strategies that are based on evidence of interrelationships and how each part contribute to the problem and how that could be managed and solved effectively.

The capacity of the regulatory authority in any country is the determinant factor that affects the ability of the government to control the problem. In fact, the capacity of the "Quality Control Laboratory, as one of the major components of the regularity authority, is determinant key (WHO, 2006). This issue has been raised several times in the previous period in Sudan. Many concerns were voiced out about the effectiveness and efficacy of the laboratories to meet the services expected from it and also in comparison to the nature of pharmaceuticals market in Sudan.

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). 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.

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. Once more the capacity of the system is major factor; because the information management in regulatory bodies in Sudan could be considered as a weak point of the system (WHO, 2010).

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). Usually two parts of the system, (Quality Assurance/Control "QA/QC" and Adverse Drug Reactions "ADRs" monitoring) are implemented together for better results (WHO, 2002). But this usually depends on the capacity of each country in terms of human resources and knowledge as well. In Sudan till this study there is no systemic widely established ADRs monitoring at national or at sub-national levels. When we consider PMS system, the main scope of the system is the observation and control of the authorized products "substandard" in the direct way and non authorized low quality products "counterfeit" indirectly (Fontanarosa PB, 2004).

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).

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 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.

The partnership models in detecting, analyzing and resolving the problem of substandard medicines become fundamental (WHO, 1997), (USP, 2004). The extent to which the key players; including communities, professionals and policy-makers from different sectors; are involved in implementation of PMS system, this make it easier to get support and collaboration in managing and compacting the existence of substandard medicines in the country (WHO, 2003). In country like Sudan this concept is required; as there are several contributing and limiting factors that affect the situation. For example; the vast area of Sudan, differences in climatic conditions, economic situation and the great differences and

diversities in cultures and believes among publics and even health workers; all of these limit the ability of the authorities to respond alone for this problem. With no doubt, health care professionals (pharmacists, doctors and others) are the major partners with potential importance and roles in improving the detection of substandard medicines. Since this category is well oriented and educated about this problem, they should be essential part of any solution. This will add additional value for appreciating the detection of these medicines before it reaches the patients. But at the same time any possible incorporation of these professionals should consider their knowledge, attitude and practice towards the issue of substandard medicines. This is important because how doctors and pharmacists act towards, and deal with, substandard medicines, is the corn-stone in any solution could help in improving the situation.

This research aimed to examine the potential solutions and practical models to expand quality & efficacy monitoring of pharmaceutical products beyond chemical analysis. Through assessing the existence of substandard medicines and its detection tools, this could provide scientific approach for solving this problem (Taylor, Shakoor, & Behrens, 1997). The study focused mainly on selecting medicines that circulated in the market and there are major complaints about its quality and effectiveness. In this regard it is important to note that the number of reported occurrences from health professionals about particular medications may indicate not only the prevalence of the problem about it, but it may also reflects the reporters' perceptions of the its importance, law enforcement issues surrounding the medications, product's length of time in the market, and/or widespread use of the product. The study used this concept in identifying the possible problems behind reported cases of

suspected medicines. This approach was adopted as in many cases the results obtained from chemical analysis tests weren't somewhat enough to answer all of the complaints received from the health professionals about the quality issues. This emphasizes the fact that combining the interpretation of quality control results with other data about clinical or therapeutic outcomes for any medicines could be of potential importance. It helps to include or exclude any potential factors that contribute to treatment failure whether the product is anti-infective, chronic disorder treatment or over the counter product. The study team considered and adopts WHO definition of substandard as basic definition and the study concepts was built on that. The study concentrates mainly on medicines available legally as authorized products that obtained marketing authorization from the National Medicines and Poisons Board "NMPB" (national regularity authority). The study doesn't include the counterfeit medicines that are not authorized to be marketed in Sudan.

Currently used quality monitoring systems

Officials in areas related to pharmaceutical services are focusing most of their efforts on assuring the safety, efficacy and quality of pharmaceutical products. By reviewing the global policy directions in most of the initiatives established during the last 2 decades, whether by international agencies (like WHO) or by the relevant authorities within the countries, we noticed the obvious focus on safety and efficacy as dimensions of importance as safety always become first (Phanouvong, 2003), (WHO, 2006). The quality dimension gets the less attention among the three areas not because of its less significance but most likely this was related to its management system. This system relied greatly on the national authorities

from one side and more the manufacturers on the other side. As part of quality monitoring system, post-marketing surveillance (PMS) was not an exception of this observation. The system gets less consideration among drug monitoring information systems. Unlike the monitoring of Adverse Drug Reactions (ADRs) and other drugs associated harms which were improved noticeably during the last 10 years; PMS was not a subject of major changes towards more improvements in its process or outcomes during the same period. This is principally true in Sudan as case under study in this review. However, there are some individual and exceptional initiatives in some countries that aimed to improve the PMS and to develop new approaches in the system. The justification for establishing post-marketing quality surveillance in most countries was influenced by the fact that; the authorities have mild influence on premarketing quality management which relies on the compliance of the industry with quality assurance schemes. The need for strong post-marketing surveillance was the driven force for all of these projects.

Systematic review of these projects will be explored below to compare different approaches attempted in this area. The review mainly focused on what is currently implemented in key members in the International Conference of Harmonization (ICH). This help, to great extend, to inform the way in which this study was designed and the recommendations were formulated to expand the system in Sudan and globally as well.

European Union (EU)

It is known that EU Member States adopted the application of Mutual Recognition Procedure for the provision of Marketing Authorization (MA) of pharmaceutical products since 2005. This is usually coordinated by the European Medicines Agency "EMA" but the authorities in each member state should issue the MA separately. Besides that, the monitoring of the quality of any registered product is rests with the individual Member States (EMA, 2011). But since the products should be registered using the same dossier, this open important area for cooperation between the member states (OMCL, Co-operation in Post-Marketing Surveillance of MRP/DCP-Products, 2006). The authorities created voluntary surveillance scheme at the EU level in the field of independent official control of registered products (OMCL, 2007). The main principles of this scheme:

- Creation of optimal and cost-effective scheme through sharing the work i.e. by reducing the duplication of tests and by testing shared products (different batches from different states);
- The voluntary surveillance could help the member states to share the test results, which give the participants in this scheme broader and in-depth overview about the quality of targeted products and give them the opportunity to get more focused national surveillance activities

The design of the surveillance scheme under this initiative is risk based model (EMA, 2011). It uses risk evaluation approaches for targeting medicinal products for surveillance testing (EMA, 2008). The actual beginning of this scheme was in 2007 in a pilot phase. The most remarkable outcome of implementing this risk-based approach is its use in the

establishment of more “informed testing plans” (EMA, 2008). The new system enabled the member states moving from the focus on generics towards more focusing on certain trades with sufficient available evidences to justify these targeting decisions. By doing this, the member states could avoid unnecessary tests and decrease the load on the individual responsible laboratories. Moreover, the EU is now moving towards community based feedback system and started to focus more on the community concerns about quality aspects (EMA, 2011).

United States of America (USA) (FDA, 2006)**:**

Food and Drug Administration (FDA) used what is currently known as Drug Quality Reporting System (DQRS). In this system there are voluntary as well as mandatory reporting schemes that enrich the data to contribute in what is called Quality Risk Management (QRM). This basically used in premarketing phase of products’ lifecycle and then it was extended later to involve the post-marketing phase as well. Based on the experience of FDA; it was clear that in order to build a risk assessment model this may need many considerations to be included in the assumptions to support this model. The decisions taken based on this model are similar to other model known as “Problem Tree Model” in which different decision nodes could be identified based on the anticipated risk(s) at each stage.

The principles of quality risk management include:

- Evaluating the risk to quality that was based on scientific knowledge;
- Proportional responses from the authorities (effort, formality, and documentation of the quality risk management process) with the level of risk

FDA currently include the QRM as part of its regulatory operations especially inspection and assessment activities. This was considered for many reasons as this system assist in allocating the resources and in prioritization of the activities. In addition to that it becomes more uncomplicated to evaluate the significance of, for example, quality defects, potential recalls, and inspectional findings. Many methods could be used under QRM, FDA relaying more on Hazard Analysis and Critical Control Point (HACCP) methodology. The method increasingly used in food industry and other industries (car, chemicals and aviation), now extended to be applied in pharmaceutical industries. Specialists from different disciplines are part of the implementation of this method and training of staff from the authorities and the industry was considered before starting the system.

Japan (JPMA, 2011)**:**

Japan, as one of founding members of ICH, re-established its modified monitoring system in 1996, known as Quality Re-evaluation System (QRS), earlier than any other country in ICH. It was based on the idea that post-marketing surveillance should be able to gather and obtain data required for re-evaluation applications. These applications usually came out from different sources, including drug use-results surveys, specified drug-use surveys, and post-marketing clinical trials. The system, which is similar to great extent to EU system, responds to concerns about the quality from different sources. The system emphasizes more on the role of the marketer in assuring the quality of their products during all of its lifecycle. Focusing on formative case report formats, the system enables the authorities to build its re-evaluation decisions based on evidence. The “accumulated knowledge” about the products through this reporting mechanism becomes routine part of quality management system.

Based on this policy, the dissolution test was proposed as a routine verification method and since 1997 it improves to great extent the knowledge and decisions about the quality of products marketed in Japan. This step was done to assure the quality of generic drugs by confirming their equivalence to the original products (Adelman & Norris, 2002).

World Health Organization (WHO)

World Health Organization established many projects to strengthen the harmonization of medicines registration and quality control; e.g. in Southern African Development Community it established strong scheme in this area (WHO, 1999), (WHO, 2000) . Other similar project is the development of Good Manufacturing Practices (GMP) and the training programs on these guidelines. Strengthening the official medicines control laboratories in member states was additional major element of quality assurance projects in which the organization has clear inputs (WHO, 2002). In this regard it provided considerable amounts of international chemical reference materials to selected laboratories in order to enhance their capacity to carry the official tests (Kenyon, Kenyon, & Sibiya, 1994). In 2001 WHO with collaboration with USP introduced the use of “Mini-Labs” in analyzing certain antimalarials used in Africa (Ondari, 2003). The project respond to growing concerns about the quality of antimalarials circulated in the market (Phanouvong, 2004), (Odili & others, 2006). This initiative drew the attention back to the potential uses of basic tests of pharmaceutical products at different sites in improving the capacity of regularity bodies. There was significant argument behind the utilization of this approach to expand currently used quality surveillance and to the practical way to involve health facilities in this scheme. On the other hand there are many reservations about the drawbacks of using this technique in resource limited settings and in

countries with huge health system especially at the primary care level (Sudan is clear example).

Africa

In 2010 WHO published an overview of findings from 26 assessment reports of medicines regulatory systems in sub-Saharan African countries (including Sudan). One of the weaknesses identified by this review is the weak implementation of post-marketing surveillance which was very poor (WHO, 2010).

The report stated: "*Quality monitoring was not prioritized based on risk, but was generally performed in case of complaints if at all*"

In addition to that the report stated: "*Fourteen of 26 NMRAs (54%) lacked a quality monitoring programme altogether; 7 tested samples in case of complaints or in the framework of specific programmes, and only 5 (19%) had a systematic approach*". These findings are very important and remarkable.

The report recommends the following:

"A risk-based system of inspections and sampling should be in place to monitor the quality of pharmaceutical products on the market. Manufacturers should be obliged to report complaints and quality problems to the NMRA. An effective recall procedure should be in place to remove defective products from the market".

Studies done about the detection of substandard medicines

Adequate review of the available documents and searching through the internet was completed to find if any other similar studies were conducted within the same scope or fieldwork of this study (expansion of post-marketing surveillance system). No similar study found to be served as guidance for this study. Still there are other categories of studies that are connected to the area of medicines quality assessment which were summarized below:

Study Title	**Review of Drug Quality in Asia with Focus on Anti-Infectives 2004** (USP, 2004)
Objectives	• Reviews the drug quality based on the available information in 11 Asian countries with focus on anti-infective drugs in order to more fully understand the extent of the problem of poor drug quality • To identify gaps in quality assurance regionally and within countries and to point the way toward addressing the issues.
Results	• 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.

Study Title	**In vitro evaluation of the quality of essential drugs on the Tanzanian market 2002** (Peter & Others, 2002)
Objectives	• The study aims to evaluate the essential drug formulations in Tanzanian market that met potency requirements and yet had unsatisfactory in vitro availability as they were not robust enough to withstand storage under simulated tropical conditions.
Results	• All formulations passed the pharmacopoeia requirements for the drug content. • Seven formulations failed to meet the USP 24 tolerance limits for dissolution.

Study Title	**Pharmacopoeial quality of drugs supplied by Nigerian pharmacies** (Taylor & Others, 2001)
Objectives	• To investigate the quality of different drugs obtained from retail pharmacies in two urban areas of Nigeria, and, in instances of poor quality, to ascertain the reason why.
Results	• 279 (48%) samples did not comply with set Pharmacopoeial limits, and this proportion was uniform for the various types of drugs tested. • Some preparations contained no active ingredient, most had amounts just outside the Pharmacopoeial limits.

Study Title	**Assessment of the incidence of substandard drugs in developing countries** (Taylor & others, 1997)
Objectives	• Evaluation of drugs quality in Nigeria & Thailand in control and methodological manner
Results	• The results indicate that 36.5% of the samples were substandard with respect to Pharmacopoeial limits. • Decomposition was the cause of poor quality in a number of the samples but overall, poor manufacturing appeared to be prevalent. • The analyses generated little evidence to indicate fraudulent manufacturing. • Treatment failure and drug-resistance are possible consequences of the use of substandard drugs.

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. In conclusion after this review, building a post-marketing surveillance system for monitoring the quality of pharmaceutical products is not new. Developed countries succeed to establish different approaches and still they are in continuous research for more innovative models. The system formulation varies depends on the objectives behind its establishment, but they all share the same vision about the aim of the system. The review emphasizes the potential role of partnerships in expanding the system and how it is used as possible sources for information. Strengthening the system with analytical models (mainly risk-based model) for supporting the decisions is useful and possible approach.

Chapter 2: Research methodologies & materials

Study purpose & objectives

General:

- The main aim of this study is to develop risk-based quality monitoring scheme of pharmaceutical products. The scheme intended to be part of Post-marketing Surveillance System used by the Federal Board of Medicines & Poisons in Sudan.

Specific objectives:

1. To understand the cause & effect relationships around substandard medicines in Khartoum city and to illustrate the influence of this problem on the practice of health professionals;
2. To analyze the knowledge, attitude and practice of pharmacists and doctors when they are facing quality related problems, and how they deal usually with that;
3. To serve as random check to detect the existence of substandard medicines in Khartoum city according to the feedback and surveillance of complaints emanated from health professionals; and
4. To investigate factors affecting the quality of clinical outcomes of three generics in Khartoum using different investigation methodologies

Study design and methodologies

In this chapter an overview about the studies and experiments done under this research will be described, this includes the materials used in each part. Since there are many parts of this research done in linked manner, the illustration of the materials and method under each part will be described separately. This includes:

1. Health professionals survey;
2. Collection of samples for chemical analysis;
3. Chemical analysis of selected medicines;
4. Bioequivalence study of 2 products of Glibenclamide tab 5 mg;
5. Microbiological sensitivity test of Amoxicillin;
6. Biological assay of 3 products of Ceftriaxone powder for injection 1 g; and
7. Qualitative evaluation of reconstitution practice of Ceftriaxone powder for injection in Khartoum 2010

Health professionals' survey

The study methodology of this survey was formulated in order to get benefit from the experience of health professionals who work in the field and have a good occurrence in dealing with medicines (prescribing, dispensing and evaluating its effectiveness). The study investigators decided to evaluate the quality of medicines which were circulated in the pharmaceutical market in Khartoum. Due to many reasons it was not easy, and complicated, to select the targeted medicines on which the study would focus. This methodology principally relied on the feedback from doctors and pharmacists. With special focus on their observations, their concerns and their comments on medicines they have concerned about its quality and/or effectiveness. Later, and based on the results obtained from the analysis of the feedback from health professionals, the investigators decided which medicines should be subjected to pharmaceutical analysis and testing for quality check.

1.1 Selection of information providers

1. ***Pharmacists:***

The list of private retail pharmacies located in Khartoum state has been requested from "Khartoum State Directorate of Pharmacy" and the sample determined according to this list (please refer to sampling technique in the sampling protocol below).

2. Doctors:

The list of doctors licensed to practice into private clinics in Khartoum state that issued by "Khartoum State Ministry of Health" has been used to determine the sample of doctors clinics in Khartoum city (please refer to sampling technique in the sampling protocol below).

1.2 Questionnaires design

The opinions of doctors and pharmacists were collected using two different types of questionnaires in the study:

1. *Non-self administrative questionnaire* designed for pharmacists. It was consisted of 23 questions that aimed to evaluate the knowledge, attitude and practice of pharmacists towards low quality medicines. Beside that it was designed to collect their opinions about the quality of certain medicines (please see annex 1).

2. *Self administrative questionnaire* designed for doctors. It was consisted of 20 questions that aimed to evaluate the knowledge, attitude and practice of pharmacists towards low quality medicines. Beside that it was designed to collect their opinions about the quality of certain medicines (please see annex 2).

These two questionnaires have been discussed in organized group discussion to evaluate its structure and to critically assess the questions included. According to the comments and feedback from the participants some changes have been made and adopted by the study supervisors. Then the questionnaires were tested in the field using random sample of the target groups (10 pharmacists and 10 doctors). The data obtained from this pilot

was analyzed and some amendments made in the questionnaires based the recommendations of another group discussion conducted for this purpose.

NB: The results of the pilot study see annex 3.

1.3 Medicines selection criteria

The information providers were asked to provide their comments on certain medicines. These were 20 generics selected based on certain criteria. The idea was to illustrate more about how the health professionals evaluate the quality of medicines they use.

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);

1. **Consumption:**

According to the statistical reports; top 5 most consumed generics in 2007 were:

1. Amoxicillin;
2. Metronidazole;
3. Paracetamol;
4. Ampicillin + Cloxacillin;
5. Glibenclamide;

2. **Experience in other countries:**

Studies from other countries were reviewed and the following generics were reported in many studies as involving quality problems:

1. Chloramphenicol inj;
2. Chloramphenicol cap/tab;
3. Gentamycin inj;
4. Cefuroxime sodium 750mg Vial;
5. Ciprofloxacin;
6. Methylergometrin;
7. Streptokinase;

3. **Pharmacological Diversity:**

By the end of the selection process 20 items has been selected from different 7 pharmacological groups in order to be surveyed using the questionnaire. This includes: Anti-infectives, NSAIDs, Cardiovascular system, Endocrine system, Antihistamines and Steroids.

Final selection of medicines to be surveyed

Based on all of these factors, the following medicines were included in the questionnaires:

Generics			
1.	Amoxicillin susp/cap	2.	Co- trimoxazole
3.	Ampiclox	4.	Digoxin inj/tab
5.	Artesunate	6.	Ethinylestradiol/levonorgestrel
7.	Aspirin	8.	Furosemide
9.	Atenolol tab	10.	Glibenclamide tab
11.	Carbimazole tab	12.	Hydrocortisone
13.	Cefuroxime sodium inj	14.	Mefenamic Acid
15.	Chloramphenicol cap/tab	16.	Metronidazole susp/tab
17.	Chlorphenarmine	18.	Nifedipine
19.	Ciprofloxacin tab	20.	Paracetamol

1.4 Study geographical area

Sudan is one of the largest countries in the region and this vast area usually represents enormous challenge for medicines regularity authority. The authority is mandated to ensure that all populations in the country receive/use safe and effective pharmaceutical products and of good quality. This is not in Sudan only but also in all over the world. Khartoum is the capital and the main city in the country. It comprises about 13.5% of the total populations in Sudan. Khartoum, Omdurman, Khartoum Bahri are the main cities within the state; among which Khartoum include more than 35% of the population in the state (CBS-Sudan, 2007). Studies indicated that the major health services for citizens in Khartoum state and other country sites actually provided in Khartoum city (large number of public and private health facilities). The patients' frequency in Khartoum cities is the highest among all cities in the country (FMOH, 2008). Khartoum city also host the core

pharmaceutical activities in Sudan, as the headquarters of main organizations in pharmacy sector are based in Khartoum city. This includes the National Medicines and Poisons Board "medicines regularity authority", Central Medical Supplies Corporation, National Medicines Quality Control Laboratory, Federal Ministry of Health, some of local pharmaceutical plants, 95% of medicines wholesalers. Due to all these facts, Khartoum was selected as study site for this research.

Indicator	Khartoum city	Rest of Sudan
Total number of the population	3.4 million	36.7 million
% of the total population	08.6%	91.4%
Total patients frequency	19.3%	80.7%
Number of hospitals	09.1%	90.9%
Number of retail pharmacies	23.9%	76.1%
Number of private doctors clinics	25.4%	74.6%

Table 11: Essential health indicators - Sudan

Source: FMOH Annual Health Statistics Report 2007

1.5 Study population

There are many players in Sudan Health System and they represent the main health services/care providers in the system. They include:

1. The public sector:
    - Primary health care facilities
    - Health centers
    - Hospitals
2. The private sector:
    - Private clinics
    - Private retail pharmacies
    - Private hospitals
3. Non Governmental Organizations Sector.

Statistically the private sector represents the major targeted sector for the provision of health services (in Sudan as general and in Khartoum state in specific). As studies showed this is due to inefficiency of the health services in the public sector as well as NGOs sector (Shariff, 2004).

For that reason the study focused on the private sector in Khartoum city and it consider the representation of the following categories:

1. ***Private clinics:***

   These clinics are usually under the authority of Khartoum State Ministry of Health *(Department of Private Curative Establishments)*. Each clinic should be licensed for certain medical practitioner to be allowed for practicing.

   This includes:

   - Specialists;
   - Registrars; and
   - General practitioners

2. ***Private retail pharmacies:***

   These pharmacies are also under the regulation of Pharmacy Directorate in Khartoum State (Department of Pharmaceuticals Establishments). Similarly, each pharmacy should be licensed for certain pharmacist to be allowed for practice. This includes all registered pharmacists except those practicing less than 1 year after graduation.

1.6 Sampling protocol

1. **Information provider:-**

A. The purpose of sampling the information providers:

To get representative data regarding the opinions of health care professionals about the problem of low quality medicines in Khartoum, how they evaluate the situation and how they deal with it.

Sampling of the targeted groups:

First: Pharmacies

The list of private retail pharmacies located in Khartoum state (as per end of January 2007) has been requested from Pharmacy Directorate in Khartoum State and the sample was determined and located according to this list. This list consisted of 789 retail pharmacies in Khartoum state in which 328 were based in Khartoum city. According to statistical sampling tables the sample size was estimated to include 75 sampling unit (pharmacy). The sampling interval was calculated according to these figures to determine the details of the sample. Then the first item in the list was selected as starting point and the remaining units were determined based on the interval until the details of the sample were completed.

Second: Clinics

The list of doctors licensed to practice in private clinics in Khartoum state (as per end of January 2007) that issued by Khartoum State Ministry of Health was used to determine the sample of clinics. This list consisted of 1015 private clinics in Khartoum state in which

420 were based in Khartoum city and according to statistical sampling tables in this range of population the sample size was estimated to include 95 sampling unit (clinic). The sampling interval was calculated according to these figures to determine the details of the sample. Then the first item in the list was selected as starting point and the remaining units were determined based on the interval until the details of the sample were completed.

1.7 Data Management and Analysis Plan

Data analysis process was done using mixed analysis methods according to the type of data and the tool of data collection, but in general it was done using the following:

- Manual analysis;
- Computer programs e.g. SPSS and MS Excel

Collection of samples for chemical analysis

A. The purpose of samples:

The selection of medicines for this study was based on the feedback from the field (pharmacists and doctors) as described above. The collection technique of medicines sample considered the sampling methodology adopted to survey the health professionals. The samples have been collected and then it was subjected to pharmacopoeias quality control tests including physical and chemical tests.

B. 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. The sampling sites should be only within Khartoum city as study area;
2. The samples collected only from the retail private pharmacies within the determined area;
3. The sampling technique took into consideration the differences between the geographical areas within Khartoum;

- The 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

4. The sampling method was based on collection process using the trade products available in the market

C. Determination of sampling sites:

The availability of selected medicines was essential factor in this sampling methodology. Accordingly, it was important to found the targeted trade product itself rather than to focus on certain batch(s) of that trade product. Still whenever it was possible, the collection concentrated on maximum of 2 batches of each trade product targeted. The selection of the sites wasn't based on the fixed number of pharmacies but the target was to collect the required quantities with special consideration to the geographical areas and

pharmacies classification as illustrated above (With conditional aspect regarding the total number of collection sites which should not exceeded five sites in worst scenario).

D. 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:

- For each solid dosage form products (tablets and capsules) minimum of 100 units were collected from different sites;
- For each injectable products minimum of 10 units were collected from different sites; and
- For each liquid dosage form products (suspension and syrups) minimum of 10 units were collected from different sites

E. Storage of the samples:

After the collection process was completed, the samples were treated considering the following points:

1. Each sample was stored with its prefilled “Sampling form-A”; (annex No 4);
2. The sample was labeled using small stickers containing the sample code;
3. Each sample was kept in storage conditions specified by the manufacturers;
4. The samples were stored in their original containers until the start of the next procedure

F. 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. This system based on the following:

1. *Pharmacies & private clinics:*

   The codes consisted of serial numbering that used for each pharmacy or clinic included in the sample. Any facility in the list has identity number that pre-recorded in the questionnaire and the information provider wasn't asked to write or provide his/her name or his/her premises name or any other identification data.

2. *Generic name:*

   All generic names were ordered alphabetically and the coded according to its order; for example:

   (G06)

   G for Generic as fixed letter and 06 for its order

3. *Companies' Code:*

   All companies (that own any product under testing) were ordered alphabetically and coded according to its order; as example:

   (C33)

   C for Company as fixed letter and 33 for its order

4. *Trade Products Code:*

The code of each trade name contains its company code, generic name code and in addition to that trades was ordered alphabetically and coded according to its order; as example:

(G06/C33/T14)

T for Trade name and 14 for its order within all trade names

5. *Sample Code:*

Each sample code contains all of the above codes in addition to its unique number based on its order in collection process; as example:

(G06/C33/T14/S05)

S for Sample and 05 for its order in the collection process

Chemical analysis of selected medicines

2.1 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. This collaboration remarkably has driven this study in effective way to address the important issues and to concentrate on vital policy issues. Also this study benefit from such collaboration, because there is different capacities in each laboratory (the University & National labs) and this gave the opportunity to conduct different quality control tests in both laboratories. This was reflected on the quality of the data obtained and the coverage of all selected medicines included in the study.

2.2 Level 1 - Visual/physical inspection

The following indicate how this inspection process was done for the samples:

- Physical quality check was completed for each batch/sample collected from the field using standardized check list (for details see annex 8);
- The integrity of packs, appearance of tablets, or other physical characteristics of the dosage forms were visually being inspected and reported for each sample;

- Determination of remaining shelf-life, compliance with approved labeling, packaging, and shipping instructions were all checked and verified by data obtained from “NMPB”;

- 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;

- Visual inspection was done to ensure that no breakdown, fragmentation, or cracks in the collected dosage forms for all products collected;

- 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;

- 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.

2.3 Level 2 – Chemical Analysis

- This level usually combined many types of testing methods to be under taken. But due to the limited scope of this part of the research; only chemical assay of each product under testing was conducted;

- All of the collected samples were subjected to this level of assessment;

- Analytical tests were performed according to the quality specifications in the monographs of reference pharmacopeia with respect to each sample examined;

- The results of each sample were compared with the limits of contents in the reference pharmacopeia to determine whether or not it complies with the standard specifications;

- Samples that failed to comply with the reference limits of content were subjected to further assay tests up to 3 times to ensure the validity of the results;

- Accordingly the study team decided to develop the analysis plan based on the capacity of each laboratory and this result in the following:

Generics	Dosage Form	Assay	Laboratory
Ciprofloxacin	Tablet	LC	National Lab
Glibenclamide	Tablet	LC	National Lab
Amoxicillin	Capsule	LC	National Lab
Diclofenac	Tablet	LC	National Lab
Ceftriaxone	Injection	UV	University Lab
Paracetamol	Tablet	UV	University Lab
Chlorphenarmine	Tablet	UV	University Lab
Mefenamic Acid	Tablet	Titration	University Lab
Aspirin	Tablet	Titration	University Lab
Metronidazole	Tablet	Titration	University Lab

Table 2: generic medicines selected for chemical analysis

2.4 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.

The forms used to collect these data (physical and chemical) were filled using the coding system described before and it will be kept confidential as stated before

2.5 The materials used in chemical analysis

Absolute ethanol , acetone, acetonitrile HPLC, anhydrous acetic acid, ether, methanol HPLC, potassium dihydrogen orthophosphate, orthophosphoric acid, sodium dihydrogen orthophosphate, triethylamine.

2.6 Methods of analysis

Serial Number	1
Generic Name	**Acetylsalicylic Acid**
Dosage Form	Tablet
Concentration	300 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. **Procedures:**

   - 20 tablets were weighed and powdered. To a quantity of the powder containing 0.5 g of Acetylsalicylic Acid 30 ml of 0.5M sodium hydroxide was added. The solution was boiled gently for 10 minutes and the excess of alkali was titrated with 0.5M hydrochloric acid using phenol red solution as indicator. The operation was Repeat without the substance under analysis. The calculation was made and the quantity identified as 95.8 % of the stated concentration.

2. **Modifications of the method:**

   - None.

Serial Number	2
Generic Name	Amoxicillin Trihydrate
Dosage Form	Capsule
Concentration	500 mg
Reference Pharmacopeia	BP
Limits for Contents	92.5 to 110.0% of the stated amount

Chemical Analysis:

1. **Procedures:**

- The analysis was conducted using liquid chromatography method. Mobile phase A was prepared as follows: 1 ml of acetonitrile and 99 ml of a 25% v/v solution of 0.2M potassium dihydrogen orthophosphate was mixed and adjusted to pH 5.0 with 2M sodium hydroxide. Mobile phase B was prepared as follows: 20 ml of acetonitrile and 80 ml of a 25% v/v solution of 0.2M potassium dihydrogen orthophosphate was mixed and adjusted to pH 5.0 with 2M sodium hydroxide. 80 ml of mobile phase A was added to a quantity of the mixed contents of 20 capsules containing the equivalent of 60 mg of amoxicillin that shacked for 15 minutes. The resulted solution was mixed with the aid of ultrasound for 1 minute, and sufficient mobile phase A was added to produce 100 ml, the resultant solution was mixed and filtered. 50 µl of this solution were injected. 0.070% w/v of amoxicillin trihydrate working standard (potency 100%) was mixed in mobile phase A and 20 µl of this solution were injected. The calculation was made and the quantity identified as 103.1 % of the stated concentration.

2. **Modifications of the method:**

- None.

Serial Number	3
Generic Name	Ceftriaxone sodium
Dosage Form	Powder for injection
Concentration	1 gm
Reference Pharmacopeia	USP
Limits for Contents	92.0 to 108.0% of the stated amount

Chemical Analysis:

1. Procedures:

- A quantity of powder containing 100 mg of Ceftriaxone sodium working standard with potency 99.7% has been taken and dissolved in sufficient quantity of water to produce a solution equivalent to 1% w/v of the working standard. Series of dilution process has been done to produce other 6 different solutions in concentrations 0.1%, 0.05%, 0.01%, 0.005%, 0.0025 and 0.001% (w/v) of the working standard. The absorbance of the produced solutions was measured at the maximum at 270. The absorption of each solution was plotted versus the relevant concentration and the calibration cure then was drown. This process has been repeated for 3 times to ensure the validation of the method, and the results obtained were reproducible and relevant in linearity. A quantity of powder containing 100 mg of the sampled powder containing Ceftriaxone sodium has been taken and dissolved in sufficient quantity of water to produce a solution equivalent to 1% w/v of Ceftriaxone sodium. The resulting solution was diluted to produce solution equivalent to 0.01% w/v of Ceftriaxone sodium. The absorbance of the produced solution was measured at the maximum at 270. The calculation was made and the quantity identified as 103.8% % of the stated concentration.

2. Modifications of the method:

- The official method in the pharmacopeia for chemical assay of Ceftriaxone chloride using HPLC analysis has been replaced by this especial method due to difficulty to obtain all chemicals and reagents needed for Pharmacopoeial test.

Serial Number	4
Generic Name	Chlorphenarmine Maleate
Dosage Form	Tablet
Concentration	4 mg
Reference Pharmacopeia	BP
Limits for Contents	92.5 to 107.5% of the stated amount

Chemical Analysis:

1. Procedures:

- A quantity of the powder containing 3 mg of Chlorphenarmine Maleate was weighted and shaken with 20 ml of 0.05M sulphuric acid for 5 minutes. 20 ml of ether was added and shake carefully. The acid layer was filtered into a second separating funnel, the ether layer was extracted with two 10-ml quantities of 0.05M sulphuric acid, each acid layer filtered into the second separating funnel and the filter was washed with 0.05M sulphuric acid. The combined acid extracts were washed to be made just alkaline to litmus paper with 1M sodium hydroxide, and 2 ml in excess was added and the mixture was extracted with two 50 ml quantities of ether. Each ether extract was washed with the same 20 ml of water and then extracted with successive quantities of 20, 20 and 5 ml of 0.25M sulphuric acid. The combined acid extracts diluted to 50 ml with 0.25M sulphuric

acid, 10 ml of this solution was diluted to 25 ml with 0.25M sulphuric acid and the absorbance of the resulting solution was measured at maximum at 265 nm. The calculation was made and the quantity identified as 95.6 % of the stated concentration.

2. Modifications of the method:

- None.

Serial Number	5
Generic Name	Ciprofloxacin Hydrochloride
Dosage Form	Tablet
Concentration	500 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. Procedures:

- The mobile phase was prepared by adding a mixture of 13 volumes of acetonitrile and 87 volumes of a 0.245% w/v solution of orthophosphoric acid and then the pH has been adjusted to 3.0 with triethylamine. To a quantity of the powdered tablets containing the equivalent of 2 g of ciprofloxacin 750 of the mobile phase was added and the mixture then subjected to ultrasound for 20 minutes the completed to 1000 ml using the mobile phase. The resulting solution was filtered and the filtrate was diluted using sufficient quantity of the mobile phase to produce solution with final concentration of 0.05% w/v of ciprofloxacin and 20 µl

of this solution was injected. 20 µl of a solution containing 0.058% w/v of ciprofloxacin hydrochloride working standard with a potency of 99.8% was injected with the mobile phase. The calculation was made and the quantity identified as 99.3 % of the stated concentration.

2. Modifications of the method:

- None

Serial Number	6
Generic Name	Diclofenac Sodium
Dosage Form	Tablet
Concentration	25 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. Procedures:

- The analysis was conducted using liquid chromatography method. The mobile phase was prepared as follows: a mixture of 34 ml of a mixture of 34 ml of a 0.1% w/v solution of orthophosphoric acid and a 0.16% w/v solution of sodium dihydrogen orthophosphate were mixed and pH adjusted to 2.5, and added to 66 ml of methanol. 10 tablets of the product have been shaken with 700 ml of methanol (50%) for 30 minutes with the aid of ultrasound. Sufficient mobile phase was added to produce 1000 ml and then mixed, an aliquot centrifuged and the supernatant liquid was filtered through a 0.45-µm filter. The filtrate was diluted with the mobile phase to produce a solution containing 0.005% w/v of Diclofenac

Sodium. 20 µl of this solution were injected. 0.005% w/v of Diclofenac sodium working standard (potency 99.8%) in the mobile phase. 20 µl of this solution was injected. The calculation was made and the quantity identified as 104.7 % of the stated concentration.

2. Modifications of the method:

- None

Serial Number	7
Generic Name	Glibenclamide
Dosage Form	Tablet
Concentration	500 mg
Reference Pharmacopeia	BP
Limits for Contents	Glibenclamide

Chemical Analysis:

1. Procedures:

- The analysis was conducted using liquid chromatography method. The mobile phase was prepared as follows: a mixture of 47 ml of acetonitrile and 53 ml of a 1.36% w/v solution of potassium dihydrogen orthophosphate previously adjusted to pH 3.0 with orthophosphoric acid. Quantity of the powdered tablets containing 5 mg of Glibenclamide was mixed, with the aid of ultrasound, with a mixture of 2 ml of water and 20 ml of methanol until fully dispersed then filtered through a 0.2-µm membrane filter (Anatop LC is suitable). 20 µl of the resulting solution was injected with mobile phase. 50 mg of Glibenclamide BPCRS dissolved in 10 ml of methanol with the aid of ultrasound for 20 minutes, sufficient methanol was added to produce 50 ml. 10 ml of this solution was diluted to 40 ml with methanol

and 2 ml of water was added to 20 ml of this solution and then mixed. 20 µl of the resulting solution was injected with mobile phase. The calculation was made and the quantity identified as 95.3 % of the stated concentration.

2. Modifications of the method:

- None

Serial Number	8
Generic Name	Mefenamic Acid
Dosage Form	Tablet
Concentration	500 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. Procedures:

- Quantity of the powdered tablets containing 0.5 g of Mefenamic Acid was dissolved in about 80 ml of warm absolute ethanol previously neutralized to phenol red solution. The solution resulted was subjected to alternation between heating and ultrasound to aid dissolution the cooled. Sufficient quantity of the neutralized absolute ethanol was added to produce 100 ml; then mixed and titrated with 0.1M sodium hydroxide VS using phenol red solution as indicator. The calculation was made and the quantity identified as 99.4 % of the stated concentration.

2. Modifications of the method:

- None

Serial Number	9
Generic Name	Metronidazole
Dosage Form	Tablet
Concentration	250 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. **Procedures:**

- Quantity of the powder containing 0.2 g of Metronidazole was transferred to a sintered-glass crucible and extracted with six 10 ml quantities of hot acetone and the cooled. 50 ml of acetic anhydride and 0.1 ml of a 1% w/v solution of brilliant green in anhydrous acetic acid was added to the combined extracts. The resulting solution was titrated with 0.1M perchloric acid VS to a yellowish-green end point. The operation was repeated without the powdered tablets and the difference was calculated. The calculation was made and the quantity identified as 95.1% of the stated concentration.

2. **Modifications of the method:**

- None.

Serial Number	10
Generic Name	Paracetamol
Dosage Form	Tablet
Concentration	500 mg
Reference Pharmacopeia	BP
Limits for Contents	95.0 to 105.0% of the stated amount

Chemical Analysis:

1. **Procedures:**

   - Quantity of the powder containing 0.15 g of Paracetamol was added to 50 ml of 0.1M sodium hydroxide and diluted with 100 ml of water. The resulting solution has been shaken for about 15 minutes and sufficient amount of water was added to produce 200 ml then the solution was mixed and filtered. 10 ml of the filtrate was diluted to 10 ml with water. 10 ml of the resulting solution was added to 10 ml of 0.1M sodium hydroxide and diluted with water up to 100 ml. The absorbance of the resulting solution was measured at the maximum at 257 nm. The calculation was made and the quantity identified as 98.4 % of the stated concentration.

2. **Modifications of the method:**

   - None.

Bioequivalence study of 2 products of Glibenclamide tab 5 mg

4.1 Equipments and materials

5% dextrose IV solution in water, 0.9% sodium chloride IV solution in water, 10% dextrose IV injection, heparinised blood containers, plane serum containers, QBC Horizon Model 755VES Centrifuge, non-volumetric pipettes, 5 ml Syringes, Accu-chek® Glucometer, methanol, acetonitrile, dihydrogen, ortho-phosphate and ortho-phosphoric acid in addition to water for analytical purpose.

4.2 Study rationale

This study designed to provide necessary information in order to evaluate the quality of two Glibenclamide products available in the market to inform the decision makers about the registration of this drug in Sudan.

4.3 Study objectives

- To investigate factors affecting the quality of clinical outcomes of Glibenclamide in Khartoum using different investigation methods; and
- To estimate the bioavailability and to evaluate bioequivalence of a single dose of the test formulation (containing Glibenclamide 5 mg tablet, manufactured by company C06 - Sudan) and to compare it with a single dose of reference formulation (containing Glibenclamide 5 mg tablet, manufactured by company C09 - Germany) under fasting conditions.

4.4 Study design & methods

WHO guidance on bioavailability and bioequivalence stated the following *"Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives AND if their bioavailability after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same"* (WHO, 2003).

This study intended to provide evidence for action; accordingly its design provided comprehensive data and evidence. Comparative in-vivo bioavailability (bioequivalence) study, in which Glibenclamide concentration in plasma was measured according to WHO guidelines for bioavailability and bioequivalence studies as described below (WHO, 2003). The study design benefited from the experience and guidance of other bodies as well (FDA, 2000). In this study there are two formulations under investigation. The study was designed basically as a comparative framework, so, single dose study was applied with a two-period, two-sequence crossover design (as recommended for this kind of studies). This was applied as two phases of treatment separated by 14 days as washing period.

The volunteers received a dose of 5 mg of Glibenclamide (from test and standard products) under fasting conditions in two separate sessions using a randomized crossover design. Plasma samples were obtained at selected times over 24 hours and stored frozen until analyzed using basic HPLC technique. Pharmacokinetic parameters were compared using the analysis of variance for a cross-over design and ratios of AUC24h and Cmax, 90% confidence intervals were obtained for summery of the results. Results were

considered positively if the confidence intervals did not exceed the limits of acceptance (80--120%) for AUC24h and Cmax.

4.5 Subjects

Most of the published studies in this area adopt sample size between 12 – 26 subjects (depends on the variability of drug under study) and this number showed sufficient statistical significant evidence (Buice, 2005). Accordingly, 12 Sudanese male/female healthy volunteers were recruited in this study. The detailed process of selecting these subjects followed the recommendations of Helsinki Declaration regarding the ethical principles for medical research involving human subjects (WMA, 2008).

The following issues were considered while selecting the subjects:

- All subjects were residents of Khartoum State;
- 6 males and 6 females were selected;
- Females were not pregnant nor lactating;
- The range of age was (≤18 to 55 ≥ years); and
- The health status of the subjects was evaluated based on information obtained from each volunteer regarding the following:
    - Free from history of DM (both types)
    - No smoking history
    - No recent history of hospitalizations in the last 12 months

Other health considerations which were verified for each volunteer and only those with normal parameters for the following investigations were selected:

- ECGs
- Clinical blood chemistry
- Measuring Blood Pressure
- Subject has no evidence of burns
- No evidences for impaired renal or hepatic functions

As part of inclusion criteria, the volunteers during the study period (or within 1 month) were not taking any of the following medicines: Allopurinol, Captopril, Enalapril, Anticoagulants, coumarin or indandione derivative, Miconazole, Fluconazole, Appetite suppressants, Corticosteroids thiazide Diuretics, Barbiturates, Beta-adrenergic blocking agents, Cimetidine, Ranitidine, Fluoroquinolones, Quinine, Rifampin, Chloramphenicol, NSAIDs, Sulfonamides or Hyperglycemia-causing agents (Katzung, 2001).

A check list was used to record the above information for each participant (for further details of this check see annex XXX)

4.6 Sampling

4.6.1 Selection of the volunteers:

The selection process of the volunteers was aimed to minimize the variations between the individuals participated in this study. Age, weight, gender and health status of the participants all were taken into considerations. The recruitment of the subjects in this study was on voluntary basis and all the ethical considerations were taken into account. This process designed to avoid the selection bias of the subject as much as possible.

Volunteers received a welcoming package to orient them about the study (its objectives, methods, instructions for preparations, sample collection and other relevant information). Besides that, they received basic information sheet about them to fill (for more details see annex XXX).

4.6.2 Medicines selection criteria:

The process of selecting medicines for this part of the study was based principally on the findings generated from part 1 and part 2 of medicines quality assessment. Selected product under testing represented the main trade product which health professionals in Khartoum were concerned about its quality in term of clinical outcomes. This was linked to the results obtained from the laboratory analysis regarding the chemical contents. The standard product was the originator's product, as it has been normally associated with good therapeutic outcomes (based on the feedback form part 1 of the study).

4.6.3 Study site:

The study was taken place in University of Khartoum Hospital after getting the permission from the hospital administration. The hospital staffs were very cooperative and support the provision of quality care for the participants and the collection and storage of the samples.

4.7 Other considerations

The factors that expected to affect the study were considered and monitored carefully during the study course. This includes environment, diet, fluids intake, physical conditions and blood sampling scheme during the day (day or night). Standardized information

sheet, annexXXX, was developed and distributed to all of the participants prior to the starting date. This aimed to ensure the consistency of all affecting factors to minimize the variations between subjects included and hence the results obtained.

4.8 Ethical considerations

- This study was conducted by independent professionals from the academic sector and was designed for scientific and academic purposes only. The investigators express no conflict of interest in selecting the products or suppliers under testing.
- The principal investigator was committed prior to start the study for his responsibility to ensure the protection of the rights, safety and well-being of subjects involved in this study. This was planned to be attained, among other things, by reviewing, approving, and providing continuing review of this study protocol and the methods and material used in obtaining and documenting informed consent of the study subjects. The ethical approval has been obtained from the National Board for Ethical Review of Health Research. In addition to that, the study team included certified medical doctor in order to monitor the subjects closely during their admission in the hospital.
- All study subjects after receiving the information sheet and upon agreement to taken part of the study; were asked to sign a consent form before considering him/her as study subject. This was kept well with other confidential documents under this study.

4.9 Blood sampling scheme

The purpose of this proposed sampling scheme is to get representative samples of blood concentration from selected subjects based on known pharmacokinetic properties of Glibenclamide. This includes mainly the half-life that play critical role in determining the elimination profile of Glibenclamide. Accordingly its dose response curve in addition to the elapsed time to reach the maximum concentration (absorption and elimination period) were the determinant factors for this sampling scheme (Meyer, Muller, Luus, & Eckert, 1989).

The sampling period and schedule were determined to cover 24 hours following drug administration. Blood samples (13 samples) were collected at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 4.5, 6 and 24 hours after administration of the dose.

Using 5 ml syringes, the samples were transferred to heparinised tubes after labeling. Each sample was then centrifuged for 5 minutes using regular centrifuge at 3000 rpm. Serum was separated from the residual part and then transferred into 3 ml plain containers. The samples were re-labeled using the final codes, carefully transported and frozen up to the time of analysis based on the proposed schedule.

Parallel with the collection of blood sample, sample collectors used small amount of blood (0.1 ml) to measure the glucose level in the sample using Accu-chek® Glucometer. This provided additional useful data for the comparisons between the two products.

4.10 Samples preparation and analysis

In order to analyze the collected samples, basic HPLC techniques were used to measure targeted parameters. The analysis was done in collaboration with the Central Laboratory in Faculty of Science – University of Khartoum.

4.10.1 Chromatographic conditions:

The method adopted for this process was developed by SD Rajendran and others with some minor modifications as needed (Rajendran & others, 2005). The HPLC system consisted of a Shimadzu LC-10AT liquid chromatographic pump, SIL-10a manual injector and SPD-10A UV/Vis UV absorbance detector (Shimadzu, Kyoto, Japan). Data collection, integration and calibration were accomplished using Class VP Chromatography Data System Version 6.14 computer software (Shimadzu, Kyoto, Japan). The chromatographic separations of Glibenclamide and internal standard (glimepride) were accomplished using a 150 mm×4.6 mm ID Shim-Pack VP-ODS analytical column (SHIMADZU). A Guard-Pak precolumn module (Phenomenex, USA) containing an ODS cartridge insert was placed serially just before the analytical column. The mobile phase consisted of acetonitrile: 25 mM phosphate buffer (pH: 3.5) in a combination of 80:20 v/v. Before use the mobile phase was degassed by passing it through a 0.22 µm filter. The mobile phase was pumped at an isocratic flow rate of 1 ml/min at room temperature. The UV detection wave length was set at 253 nm. The wave-length of 236 nm represented the UV maximum of Glibenclamide in acetonitrile: water in 1:1 ratio.

4.10.2 Assay procedure:

A stock solution representing 100 µg/ml of Glibenclamide was prepared in acetonitrile: water in 1:1 ratio. These solutions were stored at -20 o until use. The working standard solutions were prepared prior to use from the stock solution by sequential dilution with a combination of acetonitrile: water in 90:10 ratio to yield final concentrations of 50, 100, 200, 400, and 500 ng/ml of Glibenclamide. The internal standard stock solution was prepared by dissolving 1 mg of glimepride in 100 ml of acetonitrile: water in 1:1 ratio. This solution was stored at -20 o until use. In a 2 ml microcentrifuge tube, 500 µl of serum was added along with 500 µl of internal standard solution. The serum was precipitated by the addition of 500 µl of methanol, and then the tubes were vortexed for 30 s and centrifuged at 5000 g for 8 min. The supernatant was transferred to a clean, similarly labeled tube and was subsequently re-centrifuged for 2 min. The resulted solution was injected in to the HPLC.

4.10.3 Assay parameters:

The extraction efficiency was determined by comparing the peak area of known amounts Glibenclamide (unextracted) in mobile phase directly injected to peak area of samples containing the same amounts of Glibenclamide in plasma after extraction. Quantification was based on calibration curves constructed using peak area ratios of drug to internal standard vs. nominal concentration. The procedure was repeated on three separate days to allow determination of inter-day precision and accuracy. Intra-day accuracy was estimated based on the mean percentage error, and the inter-day accuracy was calculated as the mean of the intra-day accuracy determinations. The precision,

expressed as a percentage, was evaluated by calculating the intra- and inter-day relative standard deviations. The standard drug solutions in varying concentrations ranging from 50 ng/ml to 500 ng/ml were examined by the assay procedure. The peak area was calculated. The calibration curve was plotted using peak area vs. concentration of the standard solutions.

4.11 Data Management and Analysis Plan

The data analysis process was done using mixed analysis methods according to the type of data and the tool of data collection, but in general it was done using the following:

- Manual analysis;
- Computer programs e.g. SPSS and MS Excel

Microbiological sensitivity test of Amoxicillin

Materials: Sterile throat swabs, Microscope slides, Bunsen burner, Inoculating loop, Blood agar,

6.1 Study rationale

This study was designed to provide necessary information to evaluate the outcomes of Amoxicillin available in the market to inform the decision-making about the registration of this drug. This was especially planned to provide evidence to inform a comprehensive policy directions to review Amoxicillin registration, uses and monitoring in the country. The focus of this study is to investigate factors affecting the quality of clinical outcomes of Amoxicillin in Khartoum using antimicrobial sensitivity approach.

6.2 Specific objectives

To investigate the incidence of microbial resistance for Amoxicillin using the microbiological assay experiment on throat clinical isolates.

6.3 Study design

Study area: Khartoum city was divided into four geographical areas and the samples divided between these areas.

Study population: Targeted populations were selected and included based on the following criteria:

- Only patients living in Khartoum locality were considered in this study;
- Patients approaching the private pharmacies in the study area were the only targeted study population; and
- Patients complaining from symptoms of upper respiratory tract infection asking for treatment with or without a prescription.

Patients with the following criteria were excluded:

- Recent administration of sub-optimal dose of antibiotics or incomplete treatment duration within 2 weeks;
- Recent use of antimicrobial treatment during the last 3 months (especially cephalosporin derivatives);
- Under 14 years and over 60 years of age;
- Underlying diabetes;
- History of recent hospitalization

6.4 Sample size

The purpose of sampling, in this part of the study, was to get rapid description of the current situation regarding the incidence of resistance to Amoxicillin among targeted population. In Sudan there is no drug utilization review completed recently to show any data about the quantitative use of medicines in the country (uses, quantities, sources ...ect). Accordingly, for this study the sample size was determined using a technique of

total coverage of eligible patients during 10 working days. Accordingly 102 samples were collected from the study sites.

6.5 Sampling technique

Samples were obtained from patients approaching the retail pharmacies in Khartoum city. Pharmacists working in the selected pharmacies were asked to collaborate with the study team to identify the patients receiving Amoxicillin product (based on the inclusion criteria as above). The pharmacists were trained on collecting the samples. Patients selected as part of the study received verbal information about the study and its purpose. They were informed about the reasons behind the request for biological samples from their throat using a piece of swab. Upon acquiring the verbal consent from the patients, disposable swaps were used to collect the throat sample from the patients and then inculcated into 15-20 ml of Cary-Blair transport media. The samples stored at room temperature at the collection site and then it was transported on daily basis to the Central Laboratory in Faculty of Pharmacy or Faculty Science – University of Khartoum.

6.6 Preparation of blood agar media

The method adopted for this process was developed by Bendict L. and others with some minor modifications as needed. Blood was drawn from sheep's neck area which was shaved and swabbed with iodine (Benedict & others, 1974). A venipuncture was performed in the jugular vein using a 36-inch blood collection set. The blood was collected in a Becton Dickinson Vacutainer bottle containing 1 ml of 5% SPS (Imada, India) for each 100 ml of blood to be drawn. The bottle was inverted occasionally to facilitate

mixing. The blood was stored at 4 C prior to use. Sterility testing was performed by inoculating 5 ml of blood into two evacuated bottles. The bottles were then incubated at 37 C for 2 days and checked daily for visible evidence of microbial growth, prior to use. 15-ml sample of blood was used in performing a hematocrit and for sterility testing as described previously. The blood was aseptically added to the cooled agar to give a final concentration of 5%. Approximately 18 ml of blood agar was dispensed into sterile 100-mm Petri dishes and allowed to harden. All prepared plates were stored at 4 C.

6.7 Preparation of bacterial isolates for sensitivity tests

Subcultures of collected Cary-Blair transport media was prepared by inoculating a sterile loop. Each isolate was inoculated into 2 ml of Trypticase soy broth (BBL), and the turbidity was adjusted to the barium sulphate standard used in the Kirby-Bauer method of antibiotic susceptibility testing. A loopful from this broth was streaked onto the blood agar plate for all samples. All plates were incubated at 37 C. Readings and monitoring of the growth was done in a continuous process.

6.8 Data Management and Analysis Plan

The data analysis process was done using mixed analysis methods according to the type of data and the tool of data collection, but in general it was done using the following:

- Manual analysis;
- Computer programs e.g. SPSS and MS Excel

6.9 Ethical Considerations

- This study was conducted by independent professionals from the academic sector and was designed for scientific and academic purposes only. The investigators express no conflict of interest doing this research.
- The principal investigator was committed prior to start the study for his responsibility to ensure the protection of the rights, safety and well-being of subjects involved in this study. This was planned to be attained, among other things, by reviewing, approving, and providing continuing review of this study protocol and the methods and material used in obtaining and documenting informed consent of the study subjects. The ethical approval has been obtained from the National Board for Ethical Review of Health Research.
- All study subjects after receiving the information verbally and upon agreement to taken part of the study; were asked to sign a consent form before considering him/her as study subject. This was kept well with other confidential documents under this study.

Biological assay of 3 products of Ceftriaxone powder for injection 1 g

Materials: Ceftriaxone powder for solution, nutrient agar, nutrient broth, standardized suspensions of; Escherichia coli, Staphylococcus aureus and Klebsiella pneumoniae, normal saline, cork-borer (no. 7), pipette and distilled non ionized water.

The experiment was conducted in Faculty of Science – University of Khartoum.

5.1 Procedure for microbial methods

Solutions of different concentrations from the powdered form of three products were subjected to antimicrobial activity tests. The organisms used were of American Type Culture Collection (ATCC). They were obtained from stock culture of National Sanitary Laboratory and maintained on slang agar in a refrigerator. The organisms subject for the tests were; Streptococcus pneumoniae ATCC25922 (S.p), Staphylococcus aureus ATCC25923 (S.a) and Klebsiella pneumoniae ATCC35657 (K.p).

5.2 Preparation of culture media

The media used for antibacterial screening tests were nutrient agar and nutrient broth. Twenty six grams of nutrient agar (from Scharlau Chemie, Spain) were suspended in one liter of distilled water and heated on a boiling water bath to dissolve the media completely and then divided into 20 ml portions in small vials. Thirteen grams of nutrient broth (from Fine-Chem. LTD. India) were dissolved in one liter distilled water, heated on a water bath to dissolve the media and divided into 10 ml portions in small vials. The

prepared nutrient agar and nutrient broth media were sterilized by autoclaving at 121 degree (at atmospheric of 15 pounds) for 15 minutes.

5.3 Preparation of standard bacterial suspensions

Each 10 ml portions of sterilized nutrient broth were inculcated with loopful of each bacterial slant agar culture and were incubated for 18-24 hours at room temperature. 10% dilution from each liquid culture was prepared in sterilized normal saline and kept in a refrigerator.

5.4 Preparation of serial dilutions of extracts

Serial dilutions having the corresponding concentrations for the 1, 4 and 8 folds of Minimum Inhibitory Concentration (MIC) of Ceftriaxone against the bacteria under testing. In the table below the MIC for different bacteria was shown, this was used for the serial dilution purposes (Palmer & others, 1995).

Organism	MIC_{90} mg/ml
Streptococcus pneumoniae	0.060
Klebsiella pneumoniae	0.125
Staphylococcus aureus	4.000

Table 3: Corresponding MIC for targeted microorganisms

The equivalent amount of powder from different products was dissolved in distilled water to obtain the required dilutions.

5.5 Antibacterial assay

The cup-plate agar diffusion method adopted in this study was that of Murray and others with some minor modifications to assess the antibacterial activity of the products [Ref31]. From each of the standard stock suspension 0.1 ml was thoroughly mixed with 20 ml of sterile Petri dishes and left to solidify on a plain surface. Then, four cup-shape wells (10 mm diameter/each) were made in each plate using sterile cork-borer (no.7). The agar discs were removed and the alternate cups were filled with 0.08 ml sample of each concentration from the solution of one product at time. The forth alternate cup was filled with the solvent used (water) for control purposes using sterile adjusted pipette. The plates were then incubated in the upright position for 18-24 hours at room temperature. Three replicates were carried out for each solution against each tested organisms. After incubation periods, the inhibition zones diameters were measure and the mean value were tabulated.

5.6 Data Management and Analysis Plan

The data analysis process was done using mixed analysis methods according to the type of data and the tool of data collection, but in general it was done using the following:

- Manual analysis;
- Computer programs e.g. SPSS and MS Excel

Qualitative evaluation of reconstitution practices of Ceftriaxone powder for injection in Khartoum teaching hospital 2010

Materials: PowerPoint presentation, checklist

6.1 Study rationale

Some of available literature related to Ceftriaxone effectiveness considered the reconstitution practices as essential factor that could play determinant effect on its quality. Ceftriaxone has the tendency to formulate precipitation product if mixed with any solutions containing salts of Calcium or Magnesium or any other trivalent cations (Murney, 2008), (Hayward & others, 1996). Accordingly the reconstitution practices of Ceftriaxone powder for injection in Khartoum hospitals need to be evaluated to figure out whether or not it could contribute to poor quality and outcomes of Ceftriaxone injections.

6.2 Specific objectives

To evaluate the reconstitution practices of Ceftriaxone powder for injection by nurses in Khartoum hospitals in 2010.

6.3 Study design

The study was designed as cross sectional study using qualitative approaches.

Study area: The study focus on Khartoum locality and hospitals for this locality were included in this evaluation.

Study population:

Selection of hospitals: As the study include qualitative component, only one hospital was included in this study. In this case Khartoum Teaching Hospital was selected because it is the largest hospital in the city.

6.4 Sample size

Based on the criteria above 22 nurses from both sexes attended the group discussion.

6.5 Sampling technique

Selection of nurses:

The selection of nurses was random; the announcement for the group discussion was sent to Matron in each hospital ward. The Matron was asked to pick the first two nurses complied with the criteria below and presented their interest to join the group. Targeted nurses were selected and included based on the following criteria:

- All nurses worked as fulltime in Khartoum Teaching Hospital;
- The nurse should have at least two years working experience in the field;
- One of the nurses from each ward should work for at least one year in the private sector;
- Both female and male nurses could be selected;

6.8 Data management

The data analysis process was done using manual analysis techniques for qualitative data.

Chapter 3: Results

Health professionals' survey

For all of the following results, and in the processing of statistical analysis, the results were considered statistically significant for a P value of less than 0.05. The 90% confidence intervals of all parameters under testing were also estimated.

1. Sample size

	Retail pharmacies	Doctors Clinics
Total Number in the area	328	420
Sample Size	82	95

2. Classifications - pharmacies:

- **Response:**

The response rate among pharmacists is relatively higher than doctors. 100% of the targeted pharmacists responded to the questionnaire while 78% of the doctors agreed to respond in the questionnaires sent to them.

- **Area in Khartoum:**

Area	Pharmacies % (n=82)	Doctors % (n=95)
Centre – hospital street	10.1	47.3
Centre - other	17.7	8.8
East	17.7	8.8
South	45.6	25.3
Peripherals	8.9	9.9

- **Information providers - pharmacies:**

In the targeted pharmacies, the respondents whom were pharmacists represent about 92% of the sample while other categories (including pharmacy assistants) represent the rest of the sample.

- **Pharmacy type:**

The distribution of the pharmacies was relatively equal between the pharmacies in household areas (50.6%) and that located near clinics and hospitals (49.4%).

- **Experience of information providers - pharmacies:**

Experience	% (n=82)
1 year – 2 years	31.6
3 years – 5 years	30.4
More than 5 year	38.0

- **Information providers - doctors:**

Category	% (n=95)
Specialists	56.0
Registrars	25.3
General physicians	18.7

- **Information providers specialty (n=95):**

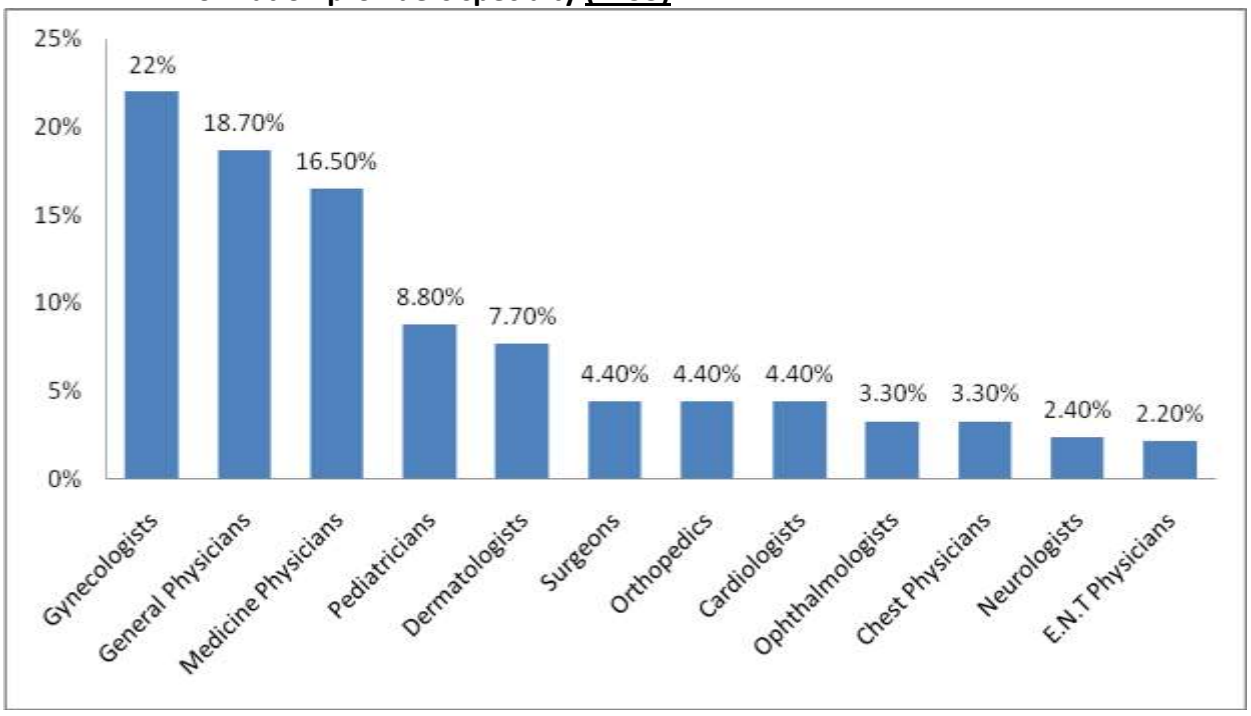

Figure 1: Distribution of doctors by specialties in the sample

The existence of substandard medicines problem

About 80% of pharmacists believed there are substandard medicines available in the market versus 70% of doctors. Pharmacists usually deal directly with medicines and gets direct feedback from the patients about it unlike the doctors.

Response	% of pharmacists N=82	% of doctors N=95
Yes	82.3	70.3
No	17.7	3.3
No Comment	0	4.4

1. Level of the problem

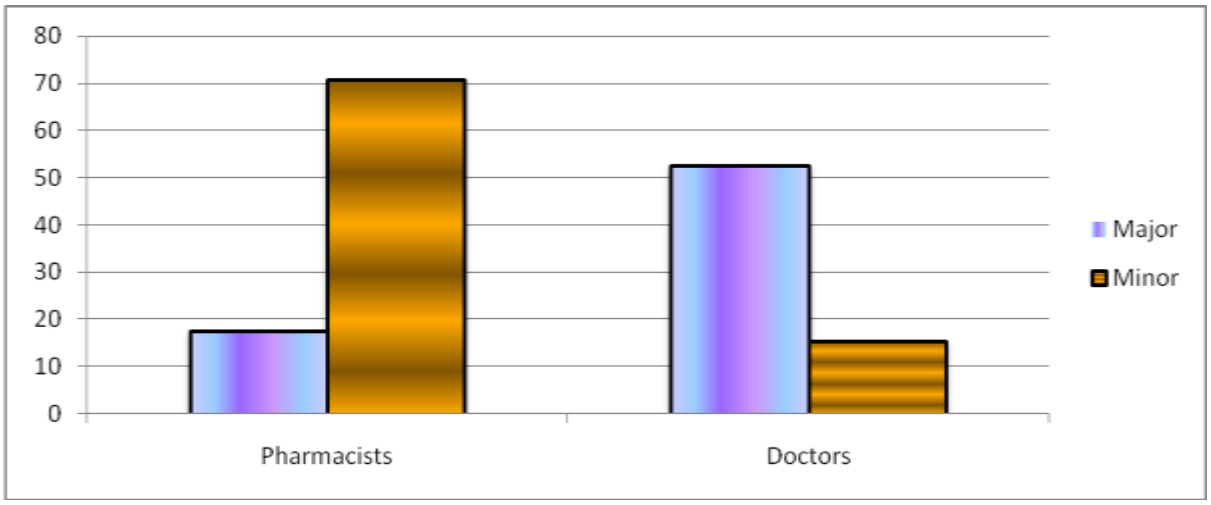

Figure 2: Professionals' evaluation - Level of the problem

The great difference and variety in the results between pharmacists & doctors seems to be due to differences in definition of (major/minor). The way the data was actually collected may play obvious effect on how each profession define that. This one of known observations about self versus non-self administrated questionnaires. For doctors the determination of the meaning depends solely on the perception of the information provider rather than the

standard definition in the study. This justification is clear when we consider the proportion of doctors who don't respond to this question.

Effectiveness problems

The aim of this part of the questionnaires is to assess, (based on professionals' opinion), if the problem of substandard medicines usually implies on ineffectiveness and/or therapeutic failure problems that facing them. This may be direct observation from them and/or based on patients' monitoring and/or patients' complaints.

A. Patients complaints to pharmacist about ineffective medicines:

Pharmacies type	Yes	No
All Pharmacies (collective) n=82	97.5	2.5
Households Area n=42	100	0
Near Clinics or Hospitals n=40	94.9	5.1

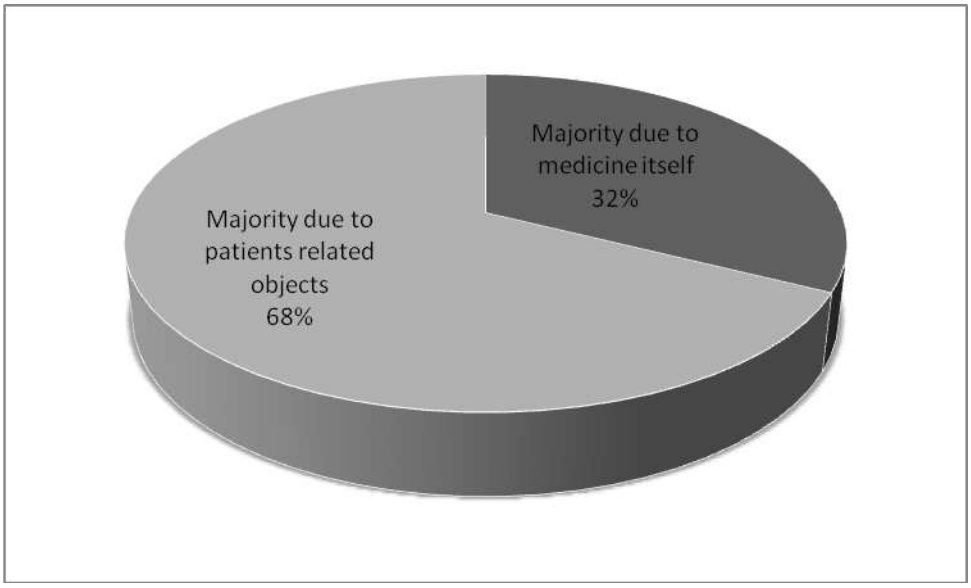

Figure 3: Classification of complaints reported by pharmacists

Pharmacies type	Medicine itself	Patients related	No comment
All pharmacies (collective) n=82	31.6	65.8	0
Households area n=42	32.5	67.5	0
Near clinics or hospitals n=40	30.8	64.1	5.1

One of the pharmacists in the hospital street; who don't receive any recent complaints from the patients; refer to the fact that: "*patients usually take their medicines as the doctor prescribed it without any complaints, even if they complain at all they refer that most likely to pharmacies near their residency*". This in fact was supported by the results obtained from pharmacies located in household areas, as all of it without exception received complaints from the patients.

On the other hand most of pharmacies, 66% of the total, refer the problems in these complaints to factors related to the patients rather than to factors related to medicines itself. The following summaries these mentioned factors:

1. Factors related to the administration method and its impact on effectiveness;
2. Factors related to the selection of right medicine for specific case (rational prescribing or rational dispensing);
3. Factors related to subject-to-subject variability and different response for same drug.

B. Classifications of complaints:

Complaints	% n=79
Symptoms not relieved	78.5
Alternative trade was not effective	38.0
Side effects	35.4
Physical appearance	8.9
Other	20.3

The above table indicates the frequency of receiving each category of complaints from the patients. For example, 38% of pharmacies received complaints from the patients about certain alternative trade they used instead of another trade they custom themselves to use regularly. On the other hand, 35% of pharmacies receive complaints about side effects of medicines. These results when combined with the other data and findings this will support of considering the feedback from the patients, of special interest the feedback received by pharmacies. They will be important source of information and one of the channels to detect substandard medicines.

C. Therapeutic failures - doctors :

The table below showed the response for the question about the regularity of receiving cases with treatment failure.

Category	Yes always	Not always	No
All doctors (collective) n=95	14.3	60.4	3.3
Specialists n=53	15.7	60.8	2.0
Registrars n=24	17.4	56.5	4.3
General physicians n=18	5.9	64.7	5.9

Unlike the pharmacists, 45 % of the doctors believed that the quality of medicines itself is the major factor in cases in which there is therapeutic failure. This figure is critical as these doctors assume that they prescribe the right medicines for right cases and the administration of medicines was also perfect. If this is the case then the quality of medicines will be the determinant factor for such failure reports.

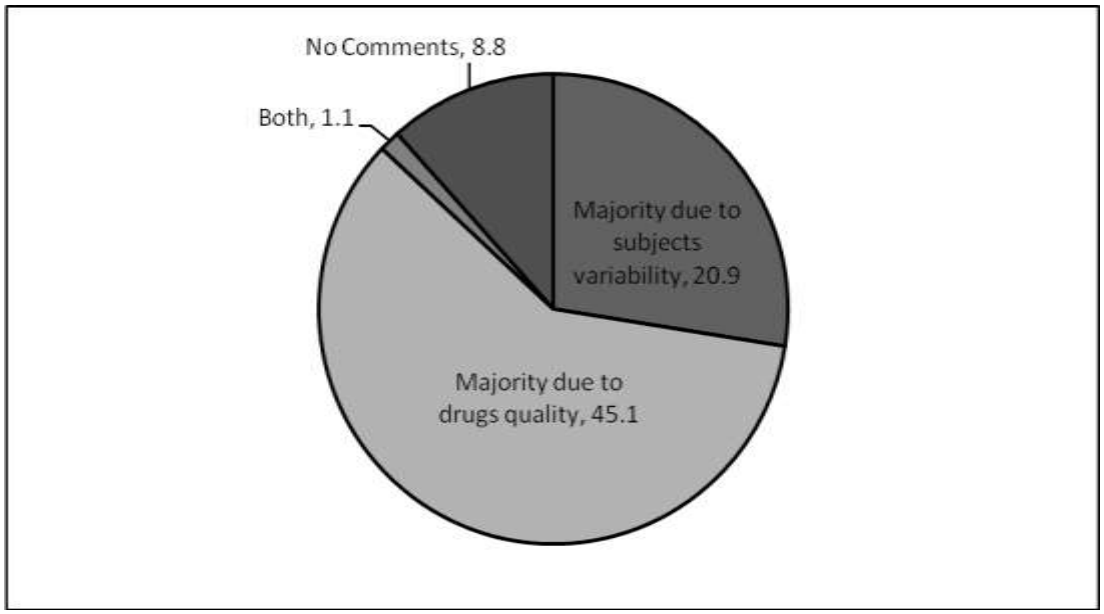

Figure 4: Classification of therapeutic failure reports

Category	Subjects variability	Drugs quality
All Doctors (collective) n=95	20.9	45.1
Specialists n=53	21.6	41.2
Registrars n=24	21.7	52.2
General physicians n=18	20.9	45.1

Looking to the trend in the above table, registrars were more extreme than other categories regarding the primary justification for cases with treatment failure.

Medicines which pharmacists and doctors complain about

The following data represents the generics which health professionals complained about it (either in terms of its quality, efficacy problems or complaints from the patients).

A. Pharmacists:

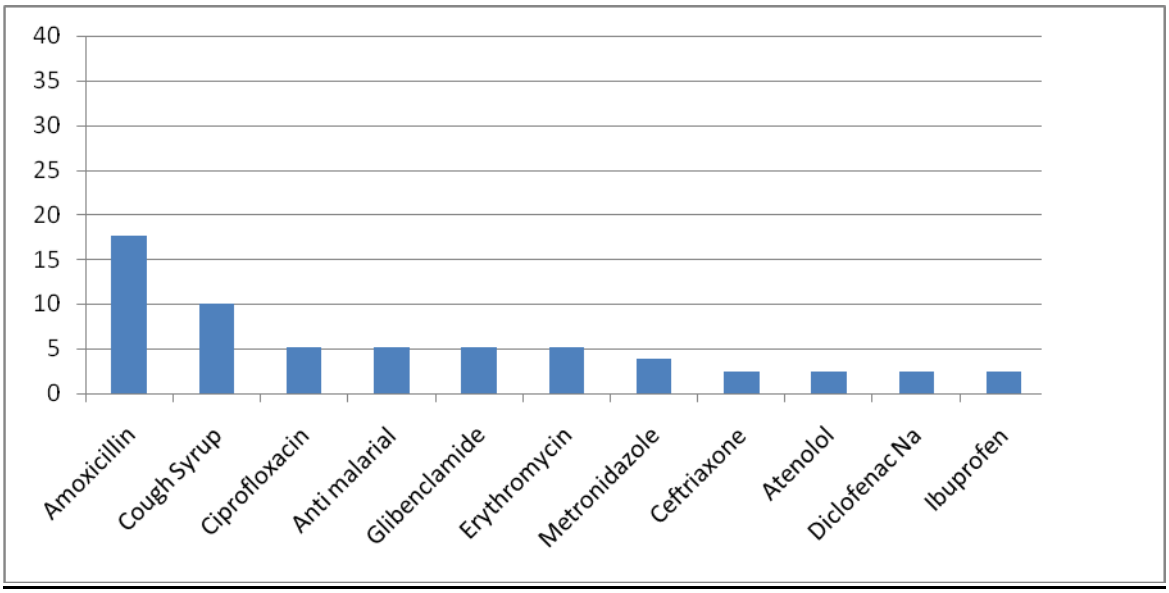

Figure 5: Medicines with top complaints from pharmacists

Other medicines:

- Salbutamol, Nifedipine, Mefenamic Acid, Cephalexin, Multivitamins, Ampiclox, Omeprazole, Amox-clav and Clarithromycin

Pharmacological groups:

Groups	% n=81
Anti-infectives	44.3
Respiratory tract	15.2
NSAIDs	7.6
Cardiovascular system	5.1
Endocrine	5.1
Anti-Malarial	3.8
Gastrointestinal tract	3.8
Blood preparations	2.5
Vitamins	1.3
Other	1.3

Origin	% n=81
Sudan	53.2
India	10.1
Some countries in Europe	10.1
Other Asian countries	6.3
Other Arab countries	5.1
Jordan	2.5
Syria	1.3

B. Doctors:

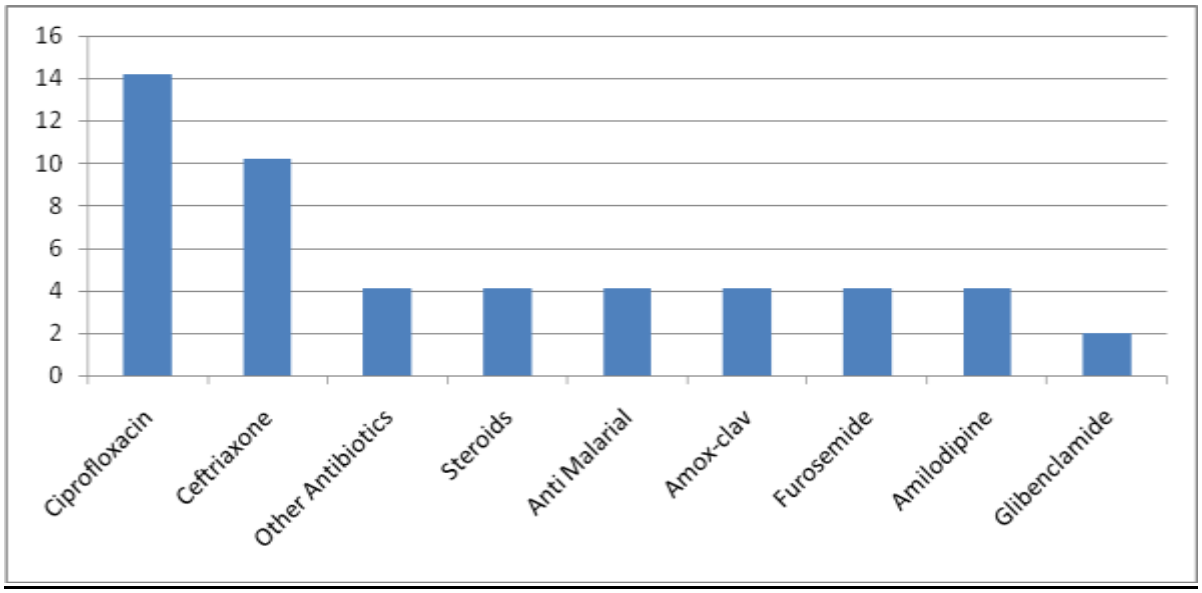

Figure 66: Medicines with top complaints from doctors

Other Medicines:

Carbamazepine, Cefuroxime, Diclofenac Na, Omeprazole, Prednisolone and Salbutamol

Pharmacological Groups	% n=74
Anti-infectives	25.3
Cardiovascular system	5.5
Endocrine	5.5
Central Nervous system	2.2
Anti-Malarial	2.2
Gastrointestinal tract	1.1
NSAIDs	1.1
Other	.1

Shifting practices patients from **"Product A"** to **"Product B"**

This part of the results represents the major indicators that describe the practice and attitude of health professionals when they take decisions to shift their patients from one product to another and the criteria around their decision. The generics reported in shifting process generally similar to those mentioned by the pharmacists' response including (Ciprofloxacin, Amoxicillin and other antibiotics).

A. Pharmacists:

- ***Shifting attitudes:***

Pharmacologically	% n=71
Shifting within the same generics	54.4
Shifting not within the same generic but same group	13.9
Shifting not within the same generic and not same group	17.7

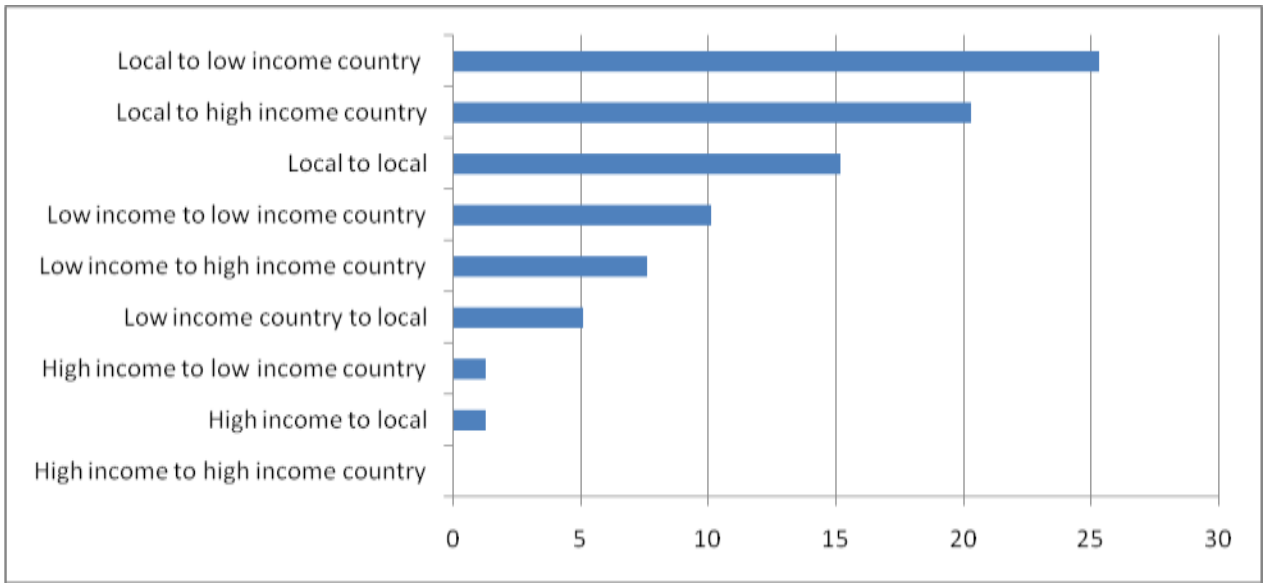

Figure 7: Pharmacists shifting attitude

Most of the pharmacists (85%) experienced at least one shifting decision for one patient from one product to another different product. Most of these decisions (54%) have been taken to shift the treatment within the same generics using different trade product. In other aspect, most of the shifting decisions (46%) include substitution of locally produced products by other imported products. This is important findings as pharmacists stated different attitude about their trust in the local products in comparison to low income countries products (46% prefer the local products over products manufactured in low income countries). Still in 40% of the decisions the shifts occur among products that manufactured in low income countries. The issue of generics substitution is currently burning issue on the agenda of global pharmaceutical sector as it has very critical impact on the shape of the global markets (Meredith P. , 2003).

- ***Generic names "Product A":***

Generic Name	% n=71
Amoxicillin	27.8
Ciprofloxacin	12.7
Glibenclamide	11.4
Diclofenac	5.1
Amox-clav	3.8
Erythromycin	2.5
Cephalexin	2.5
Omeprazole	2.5
Ibuprofen	1.3
Other medicines	17.8

Other medicines:

- Amilodipine, Aspirin, Atenolol, Hydrocortisone, Mefenamic Acid, Ranitidine, Tetracycline, Lisinopril, Prednisolone and Laxative

- ***Generic names "Product B":***

Generic Name	% n=71
Ciprofloxacin	15.2
Glibenclamide	11.4
Amox-clav	8.9
Azithromycin	8.9
Erythromycin	7.6
Amoxicillin	5.1
Diclofenac Na	3.8
Omeprazole	2.5

Other medicines:

- Ampiclox, Ibuprofen, Amilodipine, Aspirin, Atenolol, Anti Flu, Ranitidine, Lisinopril and Laxative

- ***Origins of "Product A":***

Origin	% n=71
Sudan	59.5
India	12.7
Other Arab countries	3.8
Europe	3.8
Jordan	2.5
Egypt	1.3
Other Asian countries	1.3
Syria	1.3

- ***Origins of "Product B":***

Origin	% n=71
Europe	27.8
Jordan	22.8
Sudan	20.3
Egypt	3.8
India	3.8
Other Arab countries	3.8
Other Asian countries	2.5
Syria	1.3

B. Doctors:

- ***Shifting attitudes:***

Pharmacologically	% n=36
Shifting within the same generics	85.7
Shifting not within the same generic but same group	9.5
Shifting not within the same generic and not same group	4.8

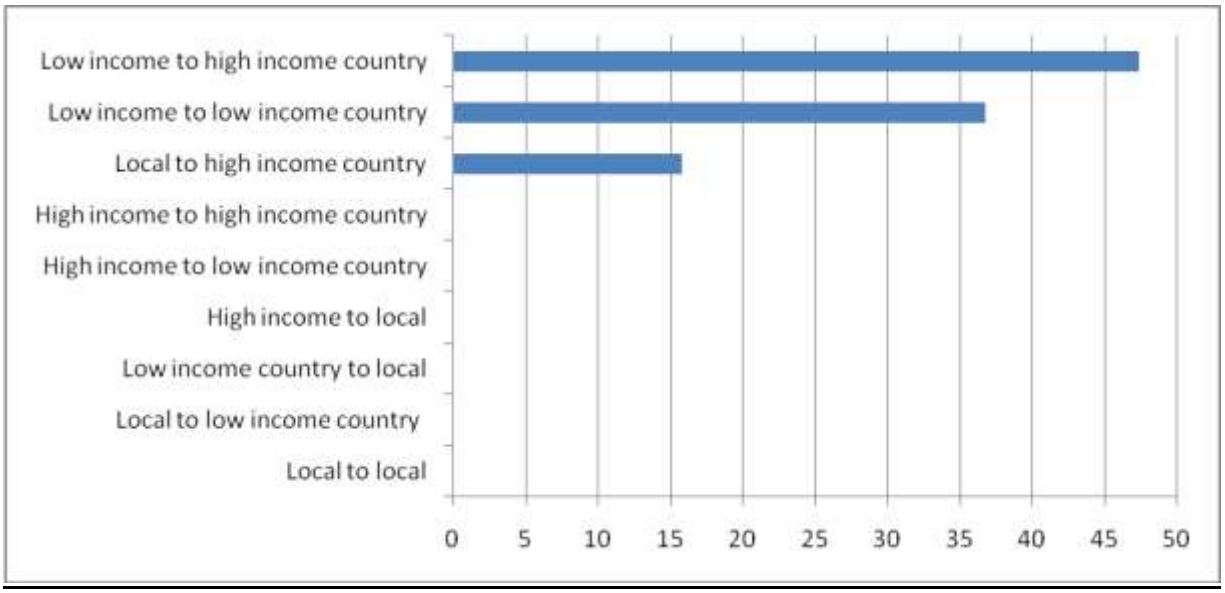

Figure 8: Doctors shifting attitude

Unlike the feedback obtained from the pharmacists, 86% of doctors took decisions to shift their patients from one product to another product but within the same generic. It is also clear that 84% of the decisions taken by the doctors to direct their patients from products manufactured in low income countries to other manufactured in high income countries.

- ***Generic names "Product A":***

Generic name	% n=36
Ceftriaxone	5.5
Ciprofloxacin	3.3
Amox-clav	2.2
Azithromycin	2.2
Other Antibiotics	3.3
Other medicines	3.3
No comments	19.8
Not applicable	75.1

- ***Generic names "Product B":***

Generic Name	% n=36
Ceftriaxone	6.6
Amox-clav	3.3
Ciprofloxacin	2.2
Other Antibiotics	2.2
Other medicines	2.2
No comments	24.2
Not applicable	53.8

- ***Origins of "Product A":***

Origin	% n=36
India	7.7
Sudan	5.5
Other Arab countries	3.3
Other Asian countries	2.2
Syria	1.1
No comments	19.8
Not applicable	57.3

- ***Origins of "Product B":***

Origin	% n=36
Europe	13.2
Other Arab countries	6.6
India	1.1
No comments	19.8
Not applicable	59.3

Trust of the professionals in local products as alternatives

This component of the questionnaire addressing the concerns usually rose about the quality of locally manufactured products, especially when compared with the imported products. In few questions the information providers were asked to evaluate their trust and opinion regarding the local production and whether or not they will use it as alternative if it is available in the market. The results showed that 80% of the pharmacists trust the local products versus only 55% of the surveyed doctors trust the local products and they used as alternative.

In more depth analysis, it seems that the degree of trust is related to the experience of information provider. Experienced professionals trust the local production more than the younger professionals (whether pharmacists or doctors).

A. Pharmacists:

Category	Yes	No
All pharmacists (collective) n=82	79.7	16.5
1 year – 2 years (n=26)	72.0	24.0
3 years – 5 years (n=25)	79.2	16.7
More than 5 years (n=31)	86.7	10.0

B. Doctors:

Category	Yes	No	No comments
All Doctors (collective) n=95	53.8	15.4	8.8
Specialists n=53	60.8	7.8	9.8
Registrars n=24	34.8	34.8	8.7
General physicians n=18	58.8	18.8	5.9

Price as indicator of quality

"Product of high price usually has good quality than that of low price product"

This aphorism is not uncommon among health professionals; and it is associates usually with the fevering one product over other products just according to this rule. The feedback from pharmacists and doctors regarding this subject indicate that, pharmacists were divided in their approaches as some were objectors, some agree totally while other agreed with some reservations. On other hand 44% of the doctors believed the saying generally true "but not always".

A. Pharmacists:

Category	Yes always	Not always	No
All pharmacists (collective) n=82	29.1	39.2	31.6
1 year – 2 years (n=26)	24.0	52.0	24.0
3 years – 5 years (n=25)	20.8	50.0	29.2
More than 5 years (n=31)	40.0	20.0	40.0

B. Doctors:

Category	Yes always	Not always	No	No comments
All Doctors (collective) n=95	17.6	44.0	1.0	5.5
Specialists n=53	17.6	41.2	13.7	5.9
Registrars n=24	8.7	54.2	8.7	8.7
General physicians n=18	29.4	41.2	5.9	0

Relations with the regularity bodies

The role of pharmacy or health regularity bodies is very important and vital in the linkage between the professional practitioners and the products they use during their work. The feedback of the practitioners about the products efficacy, safety and quality should be communicated with the authority. Still the final assessment of these products should be referred to these bodies. Few proportion of health professionals (only 15% of pharmacists and 10% of doctors) have been ever notified any complaints or reports to any regularity body regarding medicines related problems. Upon surveying those who communicate with the authorities regarding the response to their reports; the majority of the reporters received no response to their reports.

Many of the information providers refer this probably due to:

- Inefficient complaints receiving and management system;
- Poor documentation system within the authorities;
- Weak decision making procedures

A. Notification of complains to any Regulatory Body regarding medicines related problem:

Ever notify	Pharmacists n=82	Doctors n=95
Yes	15.2	9.9
No	79.7	50.5
No comment	5.1	12.1

B. If yes; what was the response:

Response	Pharmacists	Doctors
Prompt & good response	16.7	-
Delayed response	-	-
Weak response	-	-
No response	75.0	44.4
No comment	8.3	55.6

Comments of providers on the quality of medicines from particular origins

This part of the questionnaires discussed the possible relation between the country of origin and the quality of medicines. The information providers were asked to evaluate and comment on products originated in different sources. This included Sudan, other low income countries, high income countries and products manufactured by multinational industries; this classification of countries was based on World Bank classifications (WB, 2007). They were asked to classify products generally either of "good quality" or of "low quality" for specified origins. This question reflected their impression about the relation between the origin and the quality in their perception. 67% and 48% of pharmacists and doctors respectively believed that products manufactured in low income countries were general worse than that from high income countries and products from multinational companies. In general 64% and 35% of pharmacists and doctors respectively believe that the locally produced products are of good quality. With in-depth analysis, 46% of pharmacists and 30% of doctors consider locally manufactured products are better in its quality than that produced in low income countries. This again reflects the trust of health professionals in the local production of pharmaceuticals.

A. General:

Product Type	Pharmacists		
	Good quality	Low quality	No comment
Original brand name (international Companies)	97.5	2.5	0
Generic product from high income countries	97.5	2.5	0
Generic product from low income countries	32.9	67.1	0
Generic product locally produced in Sudan	64.6	35.4	0

Product type	Doctors		
	Good quality	Low quality	No comment
Original brand name (international companies)	56.0	0	16.5
Generic product from high income countries	50.5	202	19.8
Generic product from low income countries	5.5	48.4	18.7
Generic product locally produced in Sudan	35.2	16.5	20.9

B. Providers consider: "the locally produced products were better than that produced in low income countries"

	Pharmacists n=82	Doctors n=95
Local product is better than low income countries products	45.6	29.7

Other specific indictors

A. Pharmacists:

1. **Physical appearance problems**

Observing change in the physical appearance of pharmaceuticals is not uncommon experience among the pharmacists. 99% of pharmacists experienced this problem at least once during their practice and cross the sample taken all categories of pharmacists experienced it equally. Amoxicillin & Multivitamins (especially capsules for both generics) were the generics in which there is obvious problem. Most of the pharmacists notice distinct physical changes in different dosage forms, whether this in the dosage unit and/or the inner packages and/or outer packages. From the results it was very difficult to judge whether the problem was mainly due to inappropriate storage conditions or it is related to poor

manufacturing specifications. In general capsules as dosage form (soft gelatin & hard gelatin) represents the major source of complaints under this heading.

Area type	Yes
All pharmacies (collective) n=82	99.2%
Centre – hospital St (n=11)	100%
Centre - Other (n=14)	100%
East (n=14)	100%
South (n=36)	98.1%
Peripherals (n=7)	100%

Generic Names:

Generic Name	% n=122
Multivitamins	21.1
Amoxicillin	17.1
Cough syrup	7.3
Ampiclox	4.9
Metronidazole	4.9
Chloroquine	4.1
Other antibiotics	4.1
Cephalexin	2.4
Azithromycin	2.4
Antihistamine	2.4
Mefenamic Acid	2.4

Other medicines:

Cotrimoxazole, Paracetamol, Diclofenac Na, Doxacycline, Tetracycline, Ar+SP, B6, Aspirin, Benzyl penicillin, Anti Flu, Clarithromycin, Furosemide, Gentamycin, K-citrate, Ketotifen, Metformin, Metoclopramide, Promethazine, Salbutamol, Timolol, Vit K

Pharmacological groups:

Groups	% n=122
Anti-infectives	42.3
Vitamins	22.0
Respiratory tract	4.8
NSAIDs	7.3
Anti-malarial	4.9
Blood preparations	1.6
Cardiovascular system	0.8
Central nervous system	0.8
Dermatology	0.8
Other	7.3

Dosage Forms:

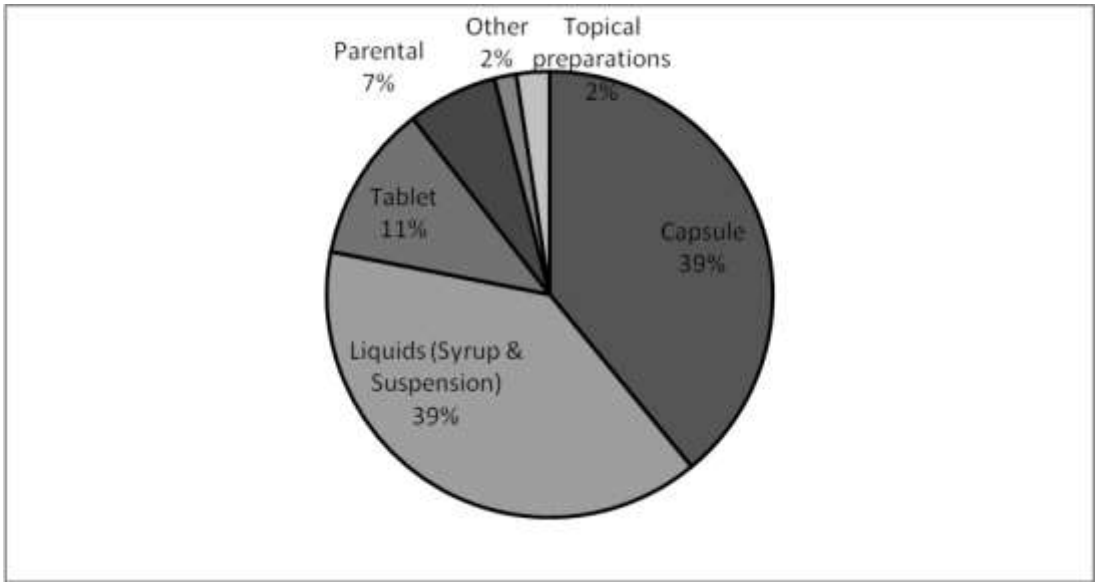

Figure 9: Classification of physical appearance problems

Observation source:

Observation source	% n=122
Himself / Herself	91.9
Doctors	2.4
Patients	4.1
Other	0.8

Problem classification:

Package type	Problem	% n=122
Stripe	Contents leakage	20.3
Stripe	Units missed	16.3
Bottle	Separation or precipitation	16.3
Bottle	Contents leakage	15.4
Stripe	Units crashed	9.8
Other	Color changes	4.9
Stripe	Deformation	3.3
Bottle	Color changes	2.4
Other	Contents leakage	1.6
Stripe	Color changes	0.8
Bottle	Crashed	0.8
Other	Crashed	0.8
Other	Other	7.3

2. Post Marketing Surveillance System

Post-marketing surveillance system has been developed by the Federal Directorate of Pharmacy in Sudan few years ago. Until this study was completed the system was well established only at the federal level. “NMPB” distributed some promotional posters and materials to raise the awareness about the existence of this system. The materials also aimed to open a sort of communication channel with pharmacies and pharmacists. Only 23% of surveyed pharmacies received these materials, and most of these pharmacies were located in the hospital street and in the eastern areas in Khartoum (no materials seen in other areas). Among different categories of pharmacists; those with more than 5 years of experience and those having experience between 1-2 years know about the system more than those in the range between 3-5 years of experience. Among pharmacists having adequate information in general about the system; 57% of them think that the system is effective and 22% have some concerns about the system efficacy.

A. Availability of drug safety poster:

Area type	Yes	No
All pharmacies (collective) n=82	22.8	64.6
Centre – hospital St (n=11)	50.0	37.5
Centre - other (n=14)	28.6	64.3
East (n=14)	42.9	50.0
South (n=36)	11.1	69.4
Peripherals (n=7)	0	100

B. Awareness about post-marketing surveillance system:

Area type	Yes	No
All pharmacies (collective) n=82	41.8	57.0
Centre – hospital St (n=11)	50.0	50.0
Centre - other (n=14)	42.9	50.0
East (n=14)	50.0	50.0
South (n=36)	41.7	58.7
Peripherals (n=7)	14.3	85.7

Category	Yes	No
All pharmacists (collective) n=82	4.8	57.0
1 year – 2 years (n=26)	44.0	56.0
3 years – 5 years (n=25)	33.3	62.5
More than 5 years (n=31)	64.7	53.3

C. Comments on the usefulness of the system:

Efficacy	Yes n=82
Effective	57.0
Partially effective	21.5
Not effective	16.5

Category	Effective	Partially Effective	Not Effective
All pharmacists (collective) n=82	57.0	21.5	16.5
1 year – 2 years (n=26)	60.0	24.0	12.0
3 years – 5 years (n=25)	58.3	25.0	12.5
More than 5 years (n=31)	53.3	16.7	23.3

3. Medicines recall

Most of the surveyed pharmacies experienced recall process at least once in the last period. All pharmacies in Hospital Street and those in the peripherals go through this process either through Pharmacy Directorate or through direct contact with the concerned companies. In 27% of recall cases “no official letter” was received from “NMPB" (previously it was Pharmacy Directorate which is the responsible body) to the pharmacies as endorsement to carry out the recall procedure. Upon the revision of the records from Pharmacy Directorate in comparison with the data obtained from the field, for 17% of the reported cases no records have been found. This was very critical and significant data.

A. Dealing with recall process:

Area type	Yes	No
All pharmacies (collective) n=82	92.4	6.3
Centre – hospital St (n=11)	100.0	0
Centre - other (n=14)	92.9	7.1
East (n=14)	85.7	14.3
South (n=36)	91.7	5.6
Peripherals (n=7)	100.0	0

	Recall	
	Yes	No
Deal with physical problems	74.0	100.0
Not deal with physical problems	13.7	0

B. Reference from the authorities for approving the recall:

Efficacy	Yes
With written letter	53.2
Without written letter	26.6
No comments	5.1

C. Examples of medicines recalled recently:

Generic name	% n=79
Cough syrup	40.5
Multivitamins	8.9
Ferrous preparation	8.9
Antihistamine	7.6
Aspirin	5.1
Ciprofloxacin	1.3
Other antibiotics	3.8
Other medicines	15.2

Other medicines:

Antacid, Bisacodyl, Chloramphenicol, Diclofenac, Indomethazine, Captopril, K-citrate, Metformin, Paracetamol and Salbutamol

Pharmacological Groups	% n=79
Respiratory tract	41.8
NSAIDs	10.1
Blood preparations	8.9
Vitamins	8.9
Cardiovascular system	5.1
Anti-infectives	3.8
Other	10.2

Dosage Form	% n=79
Liquids (syrup & suspension)	51.9
Tablet	25.3
Capsule	10.1
Parental	1.3
Other	2.5

Origin	% n=79
EAU	41.8
Europe	10.1
Jordan	8.9
India	8.9
Sudan	7.6
Other Arab countries	11.4
Other	2.5

4. Prioritization of pharmacological groups according to pharmacists

Pharmacists were asked about their prioritization for top 3 pharmacological groups they think it represents the most essential groups in their pharmacies in terms of consumption, importance and quality concerns. According to the results obtained; cardiovascular medicines, anti-infective medicines and gastrointestinal medicines represents the main groups. Pharmacists relatively prioritize these groups in their pharmacies and they think that the government should consider it carefully in its quality assurance plans.

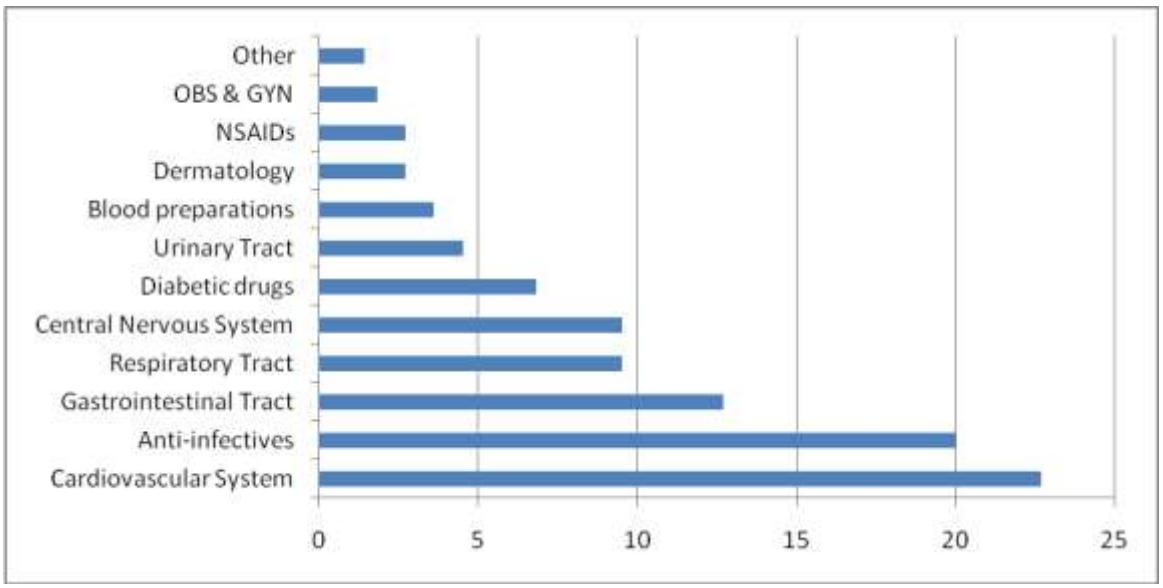

Figure 10: Prioritization of pharmacological groups according to pharmacists' feedback

B. Doctors:

1. Doctors' awareness & knowledge about substandard medicines

Some questions were asked to doctors for specific purposes; one of the questions designed to evaluate the knowledge of doctors about the problem of substandard medicines and its negative impacts. 40% of the doctors mentioned that the immediate effect of substandard

medicines could lead to patient's death. Same results to this one was also shown in another survey done by press newsletter in India about this area (Castro, 2005). In general results indicated that more educational interventions about substandard medicines should be developed and implemented; that aimed to increase their awareness by the impact of substandard medicines problem and how to deal with it (Palampur, 2003).

a) Substandard drawbacks:

What n=95	Yes	No	No comment
Additional cost for your patients	62.6	6.6	3.3
Prolong your patients' illness	59.3	7.7	5.5
Could be contributed to drugs resistance	54.9	11.0	5.5
Decrease your patients trust on your practice	52.7	11.0	8.8
Could lead to patient death	38.5	24.5	9.9
All of these	30.8	-	-
None of these	3.3	-	-

b) Reasons to recall (withdrawal) medicines from the market:

The awareness of doctors about recall system and what are the reasons for it showed very weak knowledge among them about it. Other suggested different reasons to take a recall decision.

Why n=95	Yes	No	No comment
Chemical problems (active and in-active contents problems)	58.2	3.3	11.0
Changes in color	58.2	3.3	11.0
Fracture of tablets or capsules	54.9	5.5	12.1
Repeated doctors and or patients complaints	54.9	6.6	12.1

2. Insistence to prescribe particular trade products

63% of doctors, particularly the specialists, report that they insist to prescribe certain trade products to their patients. Most of them refer this to the successful experience with these trades relative to other trades available in the market. On the other hand only 14% of doctors refer this to the price considerations as factor that could influence their decision to select certain reasonably affordable product.

	Yes	No	No comment
All Doctors (collective) n=95	62.6	9.9	5.5
Specialists n=53	64.7	9.8	3.9
Registrars n=24	60.9	4.3	3.0
General physicians n=18	58.8	17.6	0

Reasons if he/she insists to prescribe certain medicines:

Why	Yes	No	No comment
Success experience with those trades	50.5	21.1	2.2
Failure experience with other trades	18.7	44.0	2.2
Price considerations	14.3	48.4	2.2
Other	101	61.5	2.2

3. Availability versus Quality

"Available low quality drug is better than the drug is not available at all"

According to the results, 30% of the doctors agreed with the above concept. If no available alternative they may prescribe low quality product to safe the patients. This result was significant as many theories consider that low quality medicines could be regarded as not available for effective and safe human use under any circumstances (MSH, 2001), (Videau, 2001). This result could be evaluated only under the personal experiences of doctors in Sudan. Despite the fact this should be combined with consideration to that relatively there

are small number of registered medicines in Sudan [around 3700 trades] (NMPB, Sudan - National Medicines and Poisons Baord , 2010). This obviously affects the decisions of the doctors because of small available options to take. One third of the doctors will go for the unique drug drugs regardless its quality.

Category	Yes	No	Some times	No comment
All Doctors (collective) n=95	29.7	15.4	24.2	4.4
Specialists n=53	23.5	19.6	21.6	5.9
Registrars n=24	34.8	0	39.1	4.3
General Physicians n=18	41.2	23.5	11.8	0

I. Other

- **The problem of substandard medicines is worse in case of:**

Type of medicines	% n=95
OTC medicines	29.7
Rx medicines	28.6
Both types	4.4
No comment	11.0

- **Information sharing with pharmacists about quality:**

Why	Yes	No	No comment
All Doctors (collective) n=95	57.1	11.0	4.4
Specialists n=53	49.0	15.7	3.9
Registrars n=24	65.2	4.3	8.7
General physicians n=18	70.6	5.9	0

General discussion

Despite the fact that medicines inspection function in Sudan was improved largely in last few years, it is still true the unexpected failure of most inspectors to identify significantly substandard products put in question the training programs and/or testing protocols. The main concern whether these were adequate to build up the sufficient capacity for the inspectors to gain the skills required (WHO, 1999).

It has been mentioned before, there is a post marketing surveillance system implemented for registered medicines in Sudan. It aims to track different distribution channels of medicines through the country. It was designed to consider differential factors that affect the quality of marketed medicines. One of the basic conceptions for any PMS system, which considered as important anchor, is the sampling technique or methodology regarding the selection of targeted medicines or the collection of samples from the field. Both areas are critical so as to ensure that a representative sample of targeted medicines was collected from the distribution channels to support any future decision could be taken based on the results.

There are different approaches worldwide considering the PMS system development and some countries have unique system regarding the selection of medicines and its sample collection; as examples:

- In Australia complementary medicines and non-prescription drugs were routinely examined based on the Pharmacovigilance reports obtained from the field (Fracchia & others, 2000);

- In Malaysia all types of products were subjected to PMS analysis as the number of medicines available in the market was limited and easy to be tracked regarding it quality;
- In Cyprus products containing sensitive substances, products used for serious diseases and generic products posing interchangeability problems were considered as the primary targets for the system;
- In Cuba the PMS focuses on samples collected from manufacturers in connection with GMP inspection, rather than on samples collected directly from the "market base on the limited capacity of the quality control laboratory (USP, 2005).

It is valid that the conceptual believes of the medical professionals regarding the substandard medicines affect to large extent the curative process in any medical field (whether in the public or private sectors). Health professional believes could be of potential importance as it has been driven from years of experience and repeated practical knowledge. But this also could be of possible drawbacks effect on the health provision process when these pre-judgments weren't supported by evidence based indications (ICN, 2005). This survey aimed to express out the conceptual understanding of the health professionals in Khartoum city regarding the issue of substandard medicines circulated in the private market in Khartoum, and to link these thoughts to what was really taken place in the marketed medicines. Results of this survey showed the major issues regarding the professionals' ideas and how they deal with the substandard medicines. It was obvious there are different concepts regarding these issues among doctors surveyed and other significantly different concepts among the pharmacists. One of the possible reasons for that could be

referred to the basic educational background that allow the pharmacists to deal with medicines objectively regarding its quality despite its sources of origin, its prices or any other associated factors other than evidence based quality problems (Dodoo, 2007). This reflected the needs for developing educational programs to address the problems of counterfeit and substandard in the curriculums of pharmacy and medicines schools as part of essential medicines concept. On the other hand the judgment of doctors regarding the quality of any product used for the patients will be always concluded with slightly subjective evaluation which could be generated from their experiences in the field. As an example for that the use of substandard, narrow-spectrum antibiotics may lead practitioners to believe that the medicines are ineffective, and unnecessarily prescribing new/more expensive broad-spectrum antibiotic, which places additional financial pressures on the health care system and the patient as well (Andreotti & Crea, 2005). Another example with similar scenario applied for life saving drugs with narrow therapeutic index which were considered and taken seriously for patients with ischemic heart diseases and other life threatening diseases (Das, 1992) (Reaney, 2005).

It was obtained from the results that 80% and 70% of pharmacists and doctors respectively believes that there are substandard medicines available in the market. The awareness about the impact of this problem and its effects was different among health professionals. The educational background and the experience seem to play important role in these differences. The message that may be conveyed from medical professionals to the public, about the quality of medicines, sometimes become extremely misleading information and affect the overall handling of this issue. Concepts linked the quality of medicines to its price

and/or their origins are relevant in this case. It has been argued that increasing the awareness about poor quality drugs may cause patients to worry excessively about whether the medicines they are taking are genuine. On the other hand, lack of vigilance may generate a lack of trust in both consumers and professionals. Still the question about this matter will persist regarding the opinions to bring the issue of substandard medications to public attention as an essential first step towards reinforcing current methods of surveillance, with consideration to what extend this will affects the patients trust in the health system in general.

Based on the results obtained it was clear that the complaints received by the pharmacists from the patients were most likely due to factors related to the patients. Among the complaints received by pharmacists; the utmost issue of the complaints from the patients that they administer medicines that were not effective or, sometimes, the symptoms were not relieved after using some medicines. Although this was subjective issue, but still his was significant findings since that part of these medicines were medicines for chronic use e.g. antihypertensive anti-diabetic medicines.

Feedback about the quality

The following results obtained from the survey of health professionals. They were asked to account if they have any quality concerns regarding the selected generic names (refer to medicines selection criteria in pages 38&39). These results gives the overall summery of the feedback about the following medicines:

1. Ciprofloxacin
2. Amoxicillin susp/cap
3. Paracetamol
4. Metronidazole
5. Glibenclamide
6. Mefenamic Acid
7. Artesunate + SP
8. Chlorphenarmine
9. Chlorphenarmine
10. Ampiclox
11. Aspirin
12. Ethinylestradiol/levonorgestrel
13. Carbimazole tab
14. Cefuroxime
15. Atenolol
16. Co- trimoxazole
17. Furosemide
18. Nifedipine
19. Chloramphenicol
20. Hydrocortisone
21. Digoxin

1. General

Table 4: Overall summery of the feedback about surveyed generics

Order	Generics	Quality concerns	
		% Yes	% No
1	Ciprofloxacin	46.8	50.4
2	Amoxicillin susp/cap	43.2	53.2
3	Paracetamol	41.7	53.2
4	Metronidazole susp/tab	39.6	56.8
5	Glibenclamide tab	35.3	57.6
6	Mefenamic Acid	31.7	57.6
7	Artesunate + SP	30.9	69.1
8	Chlorphenarmine	25.9	61.2
9	Ampiclox	26.6	69.1
10	Aspirin	24.5	69.8
11	Ethinylestradiol/levonorgestrel	22.3	59.0
12	Carbimazole tab	23.7	68.3
13	Cefuroxime Inj	23.7	69.1
14	Atenolol tab	21.6	71.2
15	Co- trimoxazole	16.5	69.8
16	Furosemide	15.8	69.1
17	Nifedipine	15.1	72.7
18	Chloramphenicol	13.7	79.1
19	Hydrocortisone	11.5	83.5
20	Digoxin Inj/tab	7.2	82.7

* n=117

2. Classification of the feedback based on providers type

Table 5: Feedback about surveyed generics disaggregated by information provider

Order	Generics	Answering "Yes"	
		Pharmacists	Doctors
1	Ciprofloxacin tab	43.6	50.8
2	Amoxicillin susp/cap	46.2	39.3
3	Paracetamol	43.6	39.3
4	Metronidazole susp/tab	37.2	42.6
5	Glibenclamide tab	38.5	31.1
6	Mefenamic Acid	28.2	36.1
7	Artesunate +SP	28.2	34.4
8	Ampiclox	21.8	32.8
9	Chlorphenarmine	26.9	24.6
10	Cefuroxime sodium Inj	19.2	29.5
11	Aspirin	25.6	23.0
12	Carbimazole tab	24.4	23.0
13	Atenolol tab	17.9	26.0
14	Ethinylestradiol/levonorgestrel	34.6	6.6
15	Co- trimoxazole	6.4	29.5
16	Furosemide	6.4	22.9
17	Nifedipine	12.8	18.0
18	Chloramphenicol	14.1	13.1
19	Hydrocortisone	5.1	19.7
20	Digoxin Inj/tab	6.4	8.3

3. Classification of providers answers about ineffectiveness

Table 6: Feedback about surveyed generics disaggregated by problem category

Order	Generics	Answering the problem in	
		Drug itself	patients
1	Co- trimoxazole	69.6	30.4
2	Nifedipine	66.7	28.6
3	Aspirin	64.7	35.3
4	Atenolol tab	63.3	30.0
5	Ciprofloxacin tab	60.0	39.6
6	Digoxin Inj/tab	60.0	40.0
7	Paracetamol	56.9	43.1
8	Furosemide	59.1	36.4
9	Mefenamic Acid	59.1	38.6
10	Hydrocortisone	56.3	43.8
11	Glibenclamide tab	55.1	44.9
12	Amoxicillin susp/cap	55.0	45.0
13	Carbimazole tab	54.5	42.4
14	Metronidazole susp/tab	52.7	45.5
15	Ampiclox Inj	51.4	45.9
16	Cefuroxime sodium Inj	48.5	51.5
17	Ethinylestradiol/levonorgestrel	48.4	51.6
18	Artesunate	46.5	53.9
19	Chlorphenarmine	44.4	55.6
20	Chloramphenicol	36.8	63.2

Based on the above results which was obtained from the questionnaires; 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.

According to these criteria the following medicines came as a result if this appraisal:

Generics	Dosage	Assay	Pharmacology	Registered
Ciprofloxacin	Tablet	LC	Antibiotic	32
Amoxicillin	Capsule	LC	Antibiotic	48
Paracetamol	Tablet	UV	NSAIDs	22
Metronidazole	Tablet	Titration	Ant infective	18
Glibenclamide	Tablet	LC	Endocrinology	18
Mefenamic Acid	Tablet	Titration	NSAIDs	7
Artesunate +SP	Tablet	-	Antimalarials	6
Chlorphenarmine	Tablet	UV	Other	8
Ampiclox	Capsule	LC	Antibiotic	12
Aspirin	Tablet	Titration	NSAIDs	16
Cough Syrup	Syrup	-	Other	-
Erythromycin	Tablet	LC	Antibiotic	13
Ceftriaxone	Injection	LC	Antibiotic	12
Diclofenac	Tablet	Titration	NSAIDs	28
Amox-clav	Tablet	LC	Antibiotic	12

Table 7: Summery of primary selected medicines

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:

1. Ciprofloxacin
2. Aspirin
3. Metronidazole
4. Glibenclamide
5. Mefenamic Acid
6. Chlorphenarmine
7. Paracetamol
8. Diclofenac
9. Amoxicillin
10. Ceftriaxone

These 10 generics represent 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.

Countries of origin of selected generics were sorted out according to these classes, Annex no .6.

The following criteria were considered in the selection process:

1. Country income category;
2. Company of manufacturing and/or distribution;
3. Availability in other pharmaceutical dosage form;
4. Subjection of the trade product to Post Marketing Surveillance (PMS) analysis process by pharmacy directorate;
5. If any, the results of PMS;
6. Actual availability of the products in the market;
7. Most likely used products in the market (pharmacies' feedback);

According to this method 3 trade products were selected randomly for each generic with a total of 30 trade products as follows:-

Generic: Acetylsalicylic Acid

Concentration: 300 mg tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G02C13T01	C13	Sudan	Local	Yes	Yes/+
G02C17T02	C17	Lebanon	Low income	No	Yes/-
G02C06T03	C06	Sudan	Local	Yes	No

Generic: Amoxicillin Trihydrate

Concentration: 500 mg capsule

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G01C03T01	C03	Sudan	Local	Yes	No
G01C11T02	C11	India	Low income	Yes	Yes/+
G01C21T03	C21	Jordan	Higher-middle-income	Yes	No

Generic: Ceftriaxone sodium

Concentration: 1 & 0.5 gm powder for injection

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G03C10T02	C10	India	Low income	No	No
G03C14T03	C14	Jordan	Lower-middle-income	Yes	No
G03C20T01	C20	Switzerland	High income	Yes	No

Generic: Chlorphenarmine Maleate

Concentration: 4 mg tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G04C13T02	C13	Sudan	Local	No	No
G04C15T01	C15	Sudan	Local	No	No
G04C04T02	C04	Greece	High income	Yes	No

Generic: Ciprofloxacin

Concentration: 500 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G05C03T03	C03	Sudan	Local	Yes	NO
G05C19T02	C19	India	Low income	Yes	NO
G05C20T01	C20	Switzerland	High income	Yes	Yes/+

Generic: Diclofenac Sodium

Concentration: 25 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G06C06T01	C06	Sudan	Local	NO	NO
G06C14T03	C14	Jordan	Lower-middle-income	Yes	NO
G06C20T02	C20	Switzerland	High income	NO	NO

Generic: Glibenclamide

Concentration: 5 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G07C06T01	C06	Sudan	Local	NO	NO
G07C08T03	C08	Pakistan	Low income	NO	NO
G07C09T02	C09	England	High income	NO	NO

Generic: Mefenamic Acid

Concentration: 500 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G08C06T01	C06	Sudan	Local	Yes	NO
G08C08T03	C08	Pakistan	Low income	Yes	Yes/+
G08C09T02	C09	KSA	High income	Yes	NO

Generic: Metronidazole

Concentration: 250 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G09C22T03	C22	Sudan	Local	No	NO
G09C16T01	C25	Jordan	Lower-middle-income	Yes	NO
G09C16T01	C16	KSA	High income	No	NO

Generic: Paracetamol

Concentration: 500 mg Tablet

Trade	Company	Country of origin	Origin classification	Available in other form	PMS
G10C12T02	C12	Sudan	Local	No	No
G10C02T03	C02	UAE	High income	Yes	No
G10C07T01	C07	UK	High income	Yes	No

Collection of samples for chemical analysis

Sampling Quality Assurance

Sample collection process was considered as one of the critical steps in this study. For this reason a set of measures have been taken and applied based on the sampling protocol described previously.

The following measures were considered as quality assurance plan (Syhakhang & others, 2006). This included the following:

1. The sampling sites were only within Khartoum city;
2. The samples have been collected from the retail private pharmacies only;
3. The sampling technique considered different geographical areas;
4. The sampling process consider the following classification of locations:
   - Household areas.
   - Areas near clinics and hospitals.
5. The sampling process was based on the availability of the trade products authorized to be available in the market;
6. The samples were stored as indicated by the supplier before, during and after the laboratory analysis (USP, 2003).

Sample collection form

Pre-prepared sample collection form (see annex 7) was used to gather information about each sample. This was done to ensure the traceability of each sample collected during the whole process and to collect in-depth information regarding each samples. Accordingly

the following information was generated from such analysis to get clear background regarding each sample:

❖ **Distribution of sample:**

- By area:

Area	% n=46
Centre – hospital Street	26.1%
Centre - other	4.3%
East	15.2%
South	37.0%
Peripherals	17.4%

- By field:

Type	% n=46
Household areas	30.4%
Near clinics or hospitals	69.6%

❖ **Trade products:**

As it was mentioned that the availability of the selected medicines in the market was one of the important factors that affect the process of sample collection process from the retail pharmacies. It was planned to collect 30 different trade products, i.e. 3 trades per each generic. The list of the trade medicines was obtained from the registration department in National Medicines and Poisons Board as indictor for registration. But due to many reasons the availability of the selected trades was not found as expected, so the PIs decided to select alternative trades based on the same selection criteria described earlier. Out of 30 pre-determined trades 3 were not available in the market at the time of

sample collection and it was replaced randomly by other products within the same selected generics.

- **Suppliers:**

It is well understood that for each imported medicine there is a legally registered agent should be responsible for the distribution that product in the market. Different original oversees manufacturers could have the same distribution agent in Sudan. Accordingly, as expected there was difference between the number of manufacturers and the agents in the collected samples. The supplier classification was as follows:

Classification	No
Manufacturers (importation)	15
Manufacturers (local)	7
Distribution agents	10

- **Dosage form & concentrations:**

Form	%
Tablet	82.6%
Capsule	8.7%
Injection	8.7%

- **Pharmacological groups:**

The sample collected from different kinds of pharmacological groups, this includes the following:

Group	%
Anti-infectives	39.1%

NSAIDs	41.3%
Anti diabetic	10.9%
Anti histamine	8.7%

- **Number of batches:**

This part was also affected by the availability of each product in the market and the distribution power of each product. It is generally noted highly consumed products were characterized by the availability of several batches in the market and in different geographical areas through the study area. The sampling protocol was built on that; one batch for each trade product should be collected and on exceptions additional one could be collected to complete the total sample required units (USP, 2006). The total number of batches collected was 46, as on average one batch of each product was collected from the field.

- **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 manufacturing 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

❖ **Source of origin:**

Product type	**% n=46**
Products from high income countries	39%
Products from low income countries	24%
Products locally produced in Sudan	37%

❖ **Registered shelf life:**

Based on data obtained from "NMPB", it has been found that (16%) of batches collected from the market weren't complied with the registered period in "NMPB". The causes of this observation weren't clear. As example, some products were subjected to self life expansion, so, 2 batches from the same product with different shelf lives could be

available at the same time in the market. Still this indicates some degree of weaknesses in the ability of the inspection system to detect such kind of practices.

- **Shelf life expansion:**

Among the products collected from the field; 3 products were subjected to expansion of the shelf life periods as requested from "NMPB". Most of these products were manufactured in high income countries in its origin.

- **Registration number:**

FBPP as requirements was asking the manufactures to print the registration number (product specific) on the outer package. Upon analysis, and on average, 46% samples were distributed with pre-printed registration number.

Product with pre-printed registration number	%
Products from high income countries	50%
Products from low income countries	73%
Products locally produced in Sudan	24%

- **Pre-marketing test:**

The availability of reports regarding this part and according to "NMPB" was very limited for products targeted in this study. Especially the products subjected to pre-marketing test before its distribution in the market as pre-requisite for the first batch.

- **Post-marketing test:**

According to "NMPB" reports regarding the products targeted in this study; (22%) of the products under this study were subjected to post-marketing test considering different

product batches. Among these it was reported that in (94%) of products results obtained were satisfying the “NQCL” (NMPB, 2008).

- **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;
2. Temperature (degree or range);
3. Humidity (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.

Storage Conditions	% of products
Reach of Children	60.9%
Temperature	67.4%
Humidity	37.0%
Light	32.9%

- **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.

- **Laboratory storage period:**

Most of the samples were stored in the laboratory between the collection and the analysis. The storage was done based on the manufacturers constructions regarding the conditions required. This was considered so as to minimize that as possible confounding factor of the results. This was based on the type of generic products as follows:

Generics	No of days
Ciprofloxacin	36
Amoxicillin	33
Paracetamol	5
Metronidazole	13
Glibenclamide	32
Mefenamic Acid	11
Chlorphenarmine	12
Aspirin	13
Ceftriaxone	37
Diclofenac	35

Chemical analysis of selected medicines

After the completion of medicines selection process and sample collection, the medicines collected was subjected to different physiochemical tests regarding to evaluate its compliance with quality requirements and specifications according to pharmacopeia. The analysis done in collaborative manner between the study team, Faculty of Pharmacy – University of Khartoum and National Quality Control Laboratory - Federal Board of Pharmacy and Poisons. This study benefit also from such collaboration, because there is different capacity in each laboratory and this provided the opportunity to conduct different quality control tests in both organizations. This was reflected on the quality of the data obtained and the coverage of all targeted tests.

The study team developed the analysis plan based on the available capacity in each laboratory, this result in the following:

Generics	Dosage Form	Assay	Laboratory
Ciprofloxacin	Tablet	LC	National Lab
Glibenclamide	Tablet	LC	National Lab
Amoxicillin	Capsule	LC	National Lab
Diclofenac	Tablet	LC	National Lab
Ceftriaxone	Injection	UV	University Lab
Paracetamol	Tablet	UV	University Lab
Chlorphenarmine	Tablet	UV	University Lab
Mefenamic Acid	Tablet	Titration	University Lab
Aspirin	Tablet	Titration	University Lab
Metronidazole	Tablet	Titration	University Lab

Table 8: Finally selected generics for chemical analysis

Due to the sensitivity of the following results will be presented in blind manner the same prospect in which the laboratory analysis was conducted to shield the identity of the products and its results.

Overall & detailed results

The following were the overall results obtained from the assay examination of targeted medicines followed by detailed results.

Generic/Source	Local	Low income country	High income country
Amoxicillin	103.1%	100.1%	100.2%
	Comply	Comply	Comply
Aspirin	95.8% & 90.4%	92.7%	NA
	Comply & not comply	Not comply	NA
Ceftriaxone	NA	99.1% & 103.8%	99.8%
	NA	Comply & comply	Comply
Chlorphenarmine	95.6%	97.7%	98.9%
	Comply	Comply	Comply
Ciprofloxacin	99.3%	93.8%	99.1%
	Comply	Not comply	Comply
Diclofenac	98.5%	102.0%	104.7%
	Comply	Comply	Comply
Glibenclamide	95.3%	97.8%	98.2%
	Comply	Comply	Comply
Mefenamic Acid	99.4%	96.1%	104.7%
	Comply	Comply	Comply
Metronidazole	95.1%	98.5%	98.2%
	Comply	Comply	Comply
Paracetamol	98.4%	98.1%	99.1%
	Comply	Comply	Comply

Table 9: Overall results of chemical analysis

Detailed results by generic

Results of Acetylsalicylic Acid

Serial number	1
Generic name	Acetylsalicylic Acid
Product code	G02C13T01
Origin	Local product
Dosage form	Tablet
Concentration	300 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Damage in outer package
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Not comply with specifications
Chemical analysis	Comply with specifications

Serial number	2
Generic name	Acetylsalicylic Acid
Product code	G02C06T03
Origin	Local
Dosage form	Tablet
Concentration	300 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Not comply with specifications

Serial number	3
Generic name	Acetylsalicylic Acid
Product code	G02C17T02
Origin	Low income country
Dosage form	Tablet
Concentration	100 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Damage in outer package
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Not comply with specifications
Chemical analysis	Not comply with specifications

General comments:

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	

Results of Amoxicillin Trihydrate:

Serial number	4
Generic name	Amoxicillin Trihydrate
Product code	G01C03T01
Origin	Local
Dosage form	Capsule
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	92.5 to 110.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	5
Generic name	Amoxicillin Trihydrate
Product code	G01C11T02
Origin	Low income country
Dosage form	Capsule
Concentration	500 mg
Reference pharmacopeia	BP
Limits for contents	92.5 to 110.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

C. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	6
Generic name	Amoxicillin Trihydrate
Product code	G01C21T03
Origin	High income country
Dosage form	Capsule
Concentration	500 mg
Reference pharmacopeia	BP
Limits for contents	92.5 to 110.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Ceftriaxone sodium:

Serial number	7
Generic name	Ceftriaxone sodium
Product code	G03C10T02
Origin	Low income country
Dosage form	Powder for injection
Concentration	1 gm
Reference pharmacopeia	USP
Limits of contents	92.0 to 108.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No Leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	8
Generic name	Ceftriaxone sodium
Product code	G03C14T03
Origin	High income country
Dosage form	Powder for injection
Concentration	1 gm
Reference pharmacopeia	USP
Limits of contents	92.0 to 108.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	9
Generic name	Ceftriaxone sodium
Product code	G03C20T01
Origin	High income country
Dosage form	Powder for injection
Concentration	1 gm
Reference pharmacopeia	USP
Limits of contents	92.0 to 108.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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;	

Results of Chlorphenarmine Maleate:

Serial number	10
Generic name	Chlorphenarmine Maleate
Product code	G04C13T02
Origin	Local
Dosage form	Tablet
Concentration	4 mg
Reference pharmacopeia	BP
Limits of contents	92.5 to 107.5% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	11
Generic name	Chlorphenarmine Maleate
Product code	G04C15T01
Origin	Low income country
Dosage form	Tablet
Concentration	4 mg
Reference pharmacopeia	BP
Limits of contents	92.5 to 107.5% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	12
Generic name	Chlorphenarmine Maleate
Product code	G04C04T02
Origin	High income country
Dosage form	Tablet
Concentration	4 mg
Reference pharmacopeia	BP
Limits of contents	92.5 to 107.5% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and Comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Ciprofloxacin Hydrochloride:

Serial number	13
Generic name	Ciprofloxacin Hydrochloride
Product code	G05C03T03
Origin	Local
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	14
Generic name	Ciprofloxacin Hydrochloride
Product code	G05C19T02
Origin	Low income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	USP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	15
Generic name	Ciprofloxacin Hydrochloride
Product code	G05C20T01
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	USP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and Comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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 results	

Results of Diclofenac Sodium:

Serial number	16
Generic name	Diclofenac Sodium
Product code	G06C06T01
Origin	Local
Dosage form	Tablet
Concentration	25 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	17
Generic name	Diclofenac Sodium
Product code	G06C14T03
Origin	High income country
Dosage form	Tablet
Concentration	25 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	18
Generic name	Diclofenac Sodium
Product code	G06C05T02
Origin	High income country
Dosage form	Tablet
Concentration	25 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of Colour	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Glibenclamide:

Serial number	19
Generic name	Glibenclamide
Product code	G07C06T01
Origin	Local
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	Glibenclamide

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	20
Generic name	Glibenclamide
Product code	G07C08T03
Origin	Low income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	Glibenclamide

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	21
Generic name	Glibenclamide
Product code	G07C09T02
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	Glibenclamide

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of colour	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Mefenamic Acid:

Serial number	22
Generic name	Mefenamic Acid
Product code	G08C06T01
Origin	Local
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	23
Generic name	Mefenamic Acid
Product code	G08C08T03
Origin	Low income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	24
Generic name	Mefenamic Acid
Product code	G08C09T02
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Metronidazole:

Serial number	25
Generic name	Metronidazole
Product code	G09C22T03
Origin	Local
Dosage form	Tablet
Concentration	250 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	26
Generic name	Metronidazole
Product code	G09C16T01
Origin	High income country
Dosage form	Tablet
Concentration	250 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	27
Generic name	Metronidazole
Product code	G09C16T01
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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	

Results of Paracetamol:

Serial number	28
Generic name	Paracetamol
Product code	G10C12T02
Origin	Local
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	29
Generic name	Paracetamol
Product code	G10C02T03
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

Serial number	30
Generic name	Paracetamol
Product code	G10C07T01
Origin	High income country
Dosage form	Tablet
Concentration	500 mg
Reference pharmacopeia	BP
Limits of contents	95.0 to 105.0% of the stated amount

A. Physical properties:

Dosage form Status	Satisfactory
Packaging material status	Satisfactory
Leakage	No leakage
Uniformity of color	Satisfactory

B. Results and comments:

Physical properties	Comply with specifications
Chemical analysis	Comply with specifications

General comments:

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:-

- 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).

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).

Bioequivalence study of 2 products of Glibenclamide tab 5 mg

The products

Glibenclamide products included in this part are two products from part one & two of this research in which was selected based on the approach described under chapter 2 (methods and materials, please refer to page 67). These are one product under the code G07C09T02 which is the originator products and the other on is locally manufactured product under the code G07C06T01.

The volunteers

Twelve healthy volunteers; 6 men and 6 women, aged between 20 years and 36 years, and with a range of weight between 65 kg and 94 kg; were enrolled to participate in this study.

Pharmacokinetic analyses

The following parameters will be presented and discussed below:

1. The maximum plasma concentration (C_{max}) as indicator for absorption rate;
2. The time to reach the maximum plasma concentration (T_{max}) as indictor for the elimination rate;
3. The area under of curve (AUC) as it described the total amount of drugs available in plasma after the administration of the dose;
4. The elimination half life time ($T_{1/2}$) as indicator for the elimination;

Area Under the Curve (AUC)

The area under the curve (AUC_{0-t}) was calculated using the following formula:

$$\mathbf{AUC_{0-t}} = \sum_{i=1}^{t} \left(\frac{Ci + Ci-1}{2}\right)(ti - ti - 1)$$

The pharmacokinetic parameters were calculated as indicted before. Based on these parameters the elimination rate constant (KE) was obtained using the following formula.

$$\mathbf{(K_E) = 0.693 / T_{1/2}}$$

Based on the results obtained:

(K_E) Average slope for test product	0.104
(K_E) Average slope for reference product	0.194

Accordingly the elimination half life ($\mathbf{T_{1/2}}$) in hours for each product:

$\mathbf{T_{1/2}}$ of test product	6.663
$\mathbf{T_{1/2}}$ of reference product	3.572

The area under the curve to the last measurable concentration (AUC_{0-t}) was estimated by the linear trapezoidal rule. The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated by equation below.

$$\mathbf{(AUC_{0-\infty}) = AUC_{0-t} + C_t / k_E}$$

* Where C_t is the last measured concentration

The peak plasma concentration (C_{max}) and equivalent time to peak concentration (t_{max}) were determined directly using the data obtained from individual drug serum concentration-time profiles.

Statistical analyses

Note: the statistical analysis of this data was done using SPSS 16

After obtaining AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and T_{max} from the data, these parameters were further analyzed statistically as primary variables. This was basically carried out using the variance analysis for cross-over design. The data from this processing was used to evaluate the differences due to treatment, periods, sequences, and subjects. The AUC and C_{max} values were logarithmically transformed prior to the analysis. Paired samples analysis was used to compare the results of T_{max} of the test and the reference products. The results were considered statistically significant for a P value of less than 0.05. The 90% confidence intervals of parameters under testing were also estimated.

The inter-subject variation of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} parameters was also obtained by calculating the coefficient of variation (CV).

The results indicated that the mean "C_{max}" of the test product is 2.508 compared to 2.526 the reference product. On other hand the "$AUC_{0-\infty}$" of test product is 3.511 compared to 4.572 the reference product.

Parameters	Test product Mean ± SD	Reference product Mean ± SD	Intra- subject CV%
C max - (µg/ml)	2.508 ± 0.104	3.526 ± 0.118	2.8%

T_{max} - (hrs)	1.639 ± 1.024	2.167 ± 1.275	63.9%
AUC_{0-6} - (µg.h/ml)	0.490 ± 0.188	0.638 ± 0.252	55.7%
$AUC_{0-\infty}$ - (µg.h/ml)	3.511 ± 0.153	4.572 ± 0.202	2.4%

Table 10: Main pharmacokinetic parameters for test and reference products

The table below show the time interval for each of the test and reference products to reach the maximum concentration, the numbers showed the frequency of the volunteers.

Time interval (h)	Test	Reference
0,0 - 0,99	3	2
1,0 - 1,99	1	1
2,0 - 2,99	2	4
3,0 - 3,99	3	3
4.0 – 4.99	3	2

Figure 11 represents the mean serum Glibenclamide levels versus time profile following ingestion of a single dose of the test and reference tablet products to 12 healthy

volunteers

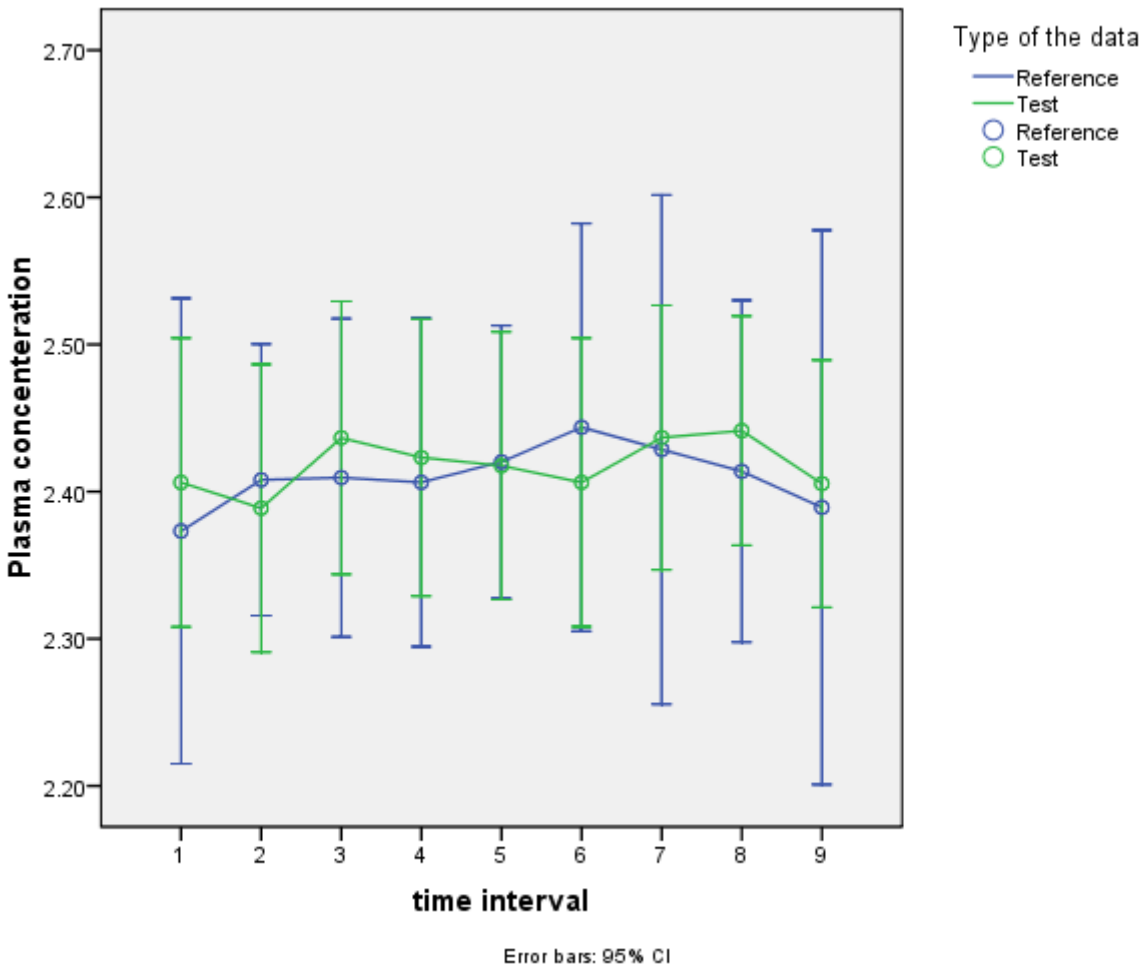

Figure 11: Mean serum Glibenclamide levels versus time profile

The AUC_{0-6}, $AUC_{0-\infty}$, C_{max}, and T_{max}, for each pair of products (test vs. reference) in this study were statistically different ($P<0.05$), suggesting that the serum profiles generated by reference tablets were relatively higher than those produced by the test product (Table 10).

Moreover, 90% confidence intervals of the AUC_{0-6}, $AUC_{0-\infty}$, and C_{max} of the two formulations in the study were not found to be within the relative bioavailability

acceptable range of 80-125% (Table 10). Wilcoxon signed rank test showed distinct difference between the untransformed values of T_{max} of the test compared to the reference products. The intra-subject CV for AUC_{0-6}, $AUC_{0-\infty}$, and C_{max} appeared to be varied and relatively large for some AUC_{0-6} and T_{max}.

With a difference of about 24% between the test product and the reference product, the results indicate that the test product is not bioequivalent to reference product. The results indicated that, the probability that the true ratios with respect to C_{max} and AUC are not acceptable in bio-equivalence range (which is 80% - 120%). It is therefore clear that test product cannot be considered bio-equivalent to the reference product with respect to the extent of absorption as measured by AUC. The fact that the two products also differed with respect to C_{max} which is probably due to differences in the extent of absorption rather than the difference in the rate of absorption.

No hazardous side-effects or adverse reactions were noticed during the observation of the volunteers; however, several of them experienced unpleasant symptoms relevant to hypoglycemia. This was noticed in 2 volunteers after the test product and in 3 volunteers after the reference product.

The figure below showed the **serum glucose level** versus time for test and reference products.

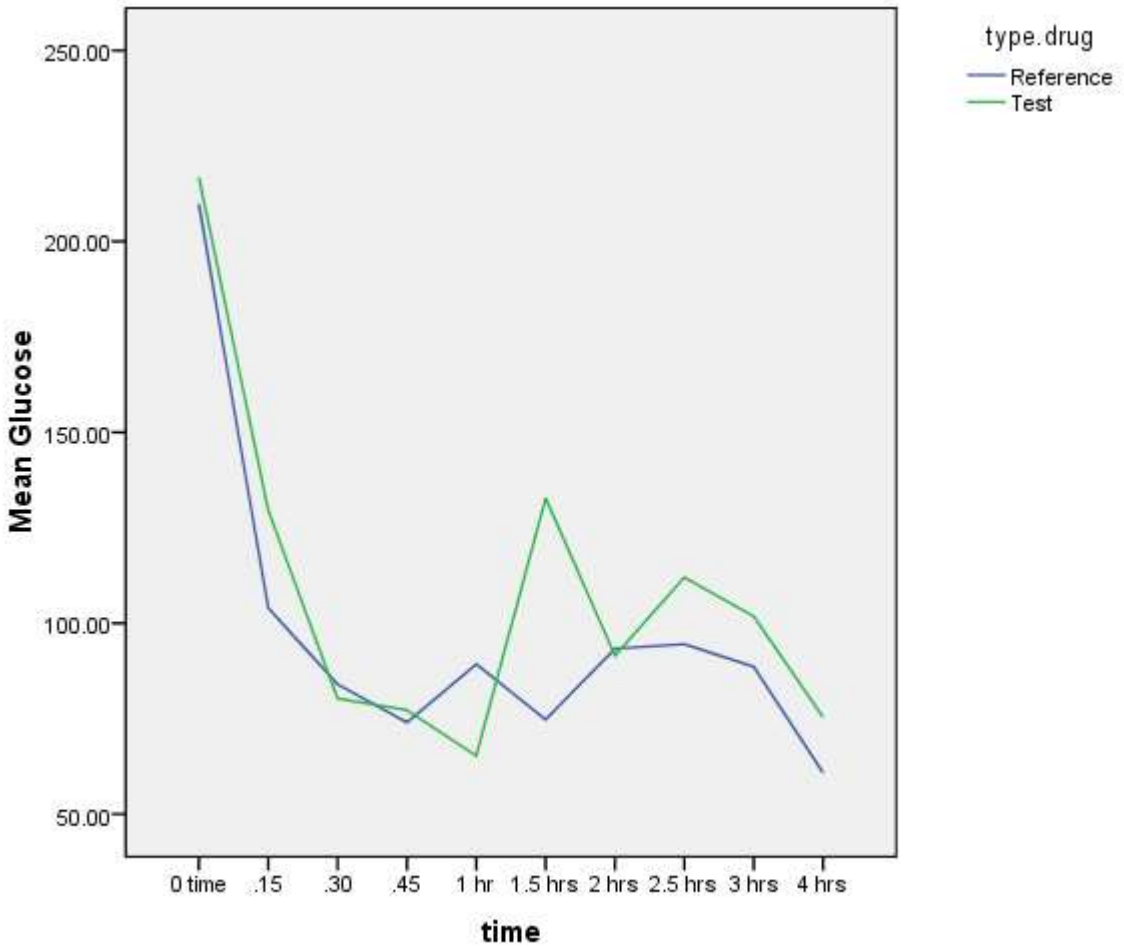

Figure 12: Serum glucose level for test and reference products

Summery discussion

In part one of this research and according to the results obtained from both data collection process and laboratory analysis, it was clear there are other reasons that contributed to ineffectiveness problems associated with specific Glibenclamide product in the market. This was reported as a problem in controlling blood glucose level among patients using this product. Conceptually, any dosage form should contain the amount of the drug equal to the dose necessary for clinical effectiveness. Along with that, the dosage form also should have the ability to deliver this amount into the body in order to ensure the achievement of the desire effects. For instance, the fulfilment of Glibenclamide formulations in its chemical contents based on the requirements of standard pharmacopeia is not a grantee for the effectiveness of Glibenclamide in controlling blood glucose. Glibenclamide is an example of drugs with unique characteristics regarding its high-quality formulations (Coppack & others, 1990). Some of these specifications need to be considered carefully when describing the product as of quality product, specifically talking about bioavailability of non-micronized formulations.

Glibenclamide is commonly used as a treatment of choice for type II diabetes mellitus. Using Glibenclamide in controlling blood glucose level known to be effective and patients using Glibenclamide products usually achieve satisfactory blood glucose level. However, currently there are 16 different pharmaceutical formulations authorized and available in Sudan and from different sources and very limited information about their bioavailability is known (NMPB, 2010). Due to lack of information about the interchangeability of these

products and lack of programs to inform and educate the patients; all of these highlight the concerns about the effectiveness of these products in managing the disease in more than (50,ooo) estimated cases of diabetes mellitus (type II) (FMOH, 2008). On the other hand, Glibenclamide is example of medicines that chronically used; in which the feedback from the patients and their doctors is highly important in order to evaluate the quality and therapeutic outcomes of the available products in the market.

As stated by Meredith PA (Meredith P. , 1996)*: "For economic reasons, the use of generic substitution is increasingly being supported by health authorities, ..., many developing countries do not have the resources or expertise to carry out appropriate quality control resulting in widespread distribution of substandard drugs, ..., a number of reports, largely anecdotal, of treatment failure or increased adverse events after switching brands have cast some doubts upon whether bioequivalence testing is sufficient in all cases. These reports have covered cardiovascular, respiratory, hormonal, psychotropic, anticonvulsant, anti-infective and anti-inflammatory drugs, ..., until such time as means can be provided-first, to enforce internationally accepted production standards, and second, to permit uniform testing of therapeutic agents-the safest clinical choice, particularly in countries where registration requirements and quality control are minimal, must remain the branded product*". On the other hand, Tschabitscher D and his colleagues urged: "*Since the introduction of generic drugs to the pharmaceutical market a sometimes emotional debate exists whether they are well-investigated and of high quality. There is some uncertainty about [whether evidence of bioequivalence is enough to guarantee efficacy and safety of generic drugs]. Some physicians ask the question if*

competent authorities are able to ascertain that the pharmaceutical quality of generics is acceptable. Doctors and patients sometimes are ill at ease about the interchangeability of innovator and generic products....., the importance of bioequivalence studies is increasing also due to the large growth of the production and consumption of generic products....., the registration of generic products does not demand complicated and expensive clinical study contrary to original product. The comparison of the original and the generic product via bioequivalence study is suggested as sufficient (Tschabitscher & others, 2008)

According to the results obtained both from the survey and from the laboratory analysis in this research; the risks associated with weak formulations of Glibenclamide products is the major cause behind the complaints reported about this drug. These observations and feedback about the specific locally manufactured product support the complaints received about the problem. It also supports the hypothesis behind the insufficiency of chemical analysis alone to verify the quality as it was shown in this bioequivalence study. Although, measuring the quality of pharmaceutical products was changed markedly in the last decade, nevertheless, chemical content of pharmaceutical products alone is no longer the most important indicator to measure the quality of some generics. As evidences showed, other important indicators that should be considered when we evaluate the quality of these drugs. The combined interpretation of QC results with data from clinical trials and feedback about therapeutic outcomes, for any drug, become highly important. This is particularly significant in order to include or exclude any potential risk factors that contribute to treatment failure or poor clinical outcomes (WHO, 1998).

Microbiological sensitivity testing of Amoxicillin

Sample characteristics

The total samples collected for this study were 102 specimens from 100 patients with median age of 34 years (minimum of 6 years and maximum of 65 years).

% of patients		% (± SD)	Notes
% of patients using Amoxicillin as first treatment for the current symptoms		64.3% (±2.6)	-
% of patients used other drug before Amoxicillin	used other beta-lactam antibiotics	44.5% (±3.2)	36 patients used other drug before the Amoxicillin
	Used other antibiotics	56.1% (±3.0)	

Of the 102 cases the following table showed the distribution of the cases according to the reason behind using the Amoxicillin:

Category of Patients	% (± SD)
Patients took Amoxicillin based on doctor's prescription	18.7 (±2.1)
Patients take Amoxicillin based on recommendation of the pharmacist	32.2 (±1.9)
Amoxicillin taken as requested by the patients themselves	49.1 (±1.8)

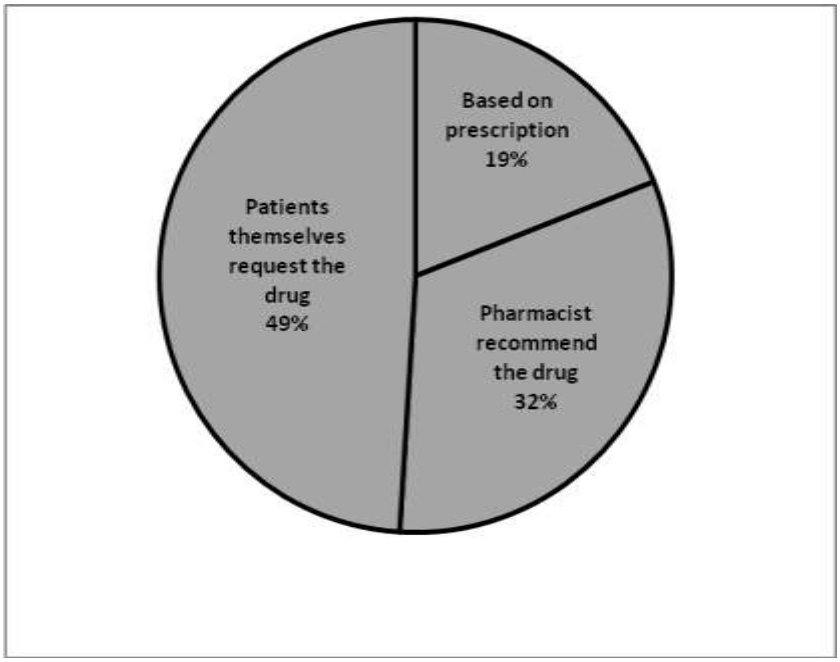

Figure 13: Classification of patients using Amoxicillin products

Follow-up of the patients

5 days after each patient received his/her medication (appropriate Amoxicillin dosage forms including capsules or suspension with different concentrations), the study team called back all of the patients those gave their contact numbers in the pharmacies. The purpose of these phone calls was to ask the patients about the following:

- Completion of the treatment fully as prescribed;
- Feeling about the relief of the symptoms

Patients' indicator		Results
Total number of patients with contact		86 patients
No. Patients responded		79 (91.9%)
No. Patients reported completion of the treatment		58 (93.4%)
% of patients feeling about the relief of the symptoms	Complete relief	22.7% (±2.1)
	Partial relief	46.9% (±2.6)
	No relief	30.4% (±1.8)

Microbiological sensitivity

For the purpose of this study, no typology identification was carried out for the isolates under testing. Rather the study team reported the presence or absence of microorganism growth before adding the Amoxicillin disks. In addition to that, the number of isolates with clear growth inhibition after the insertion of antibiotic disk was also reported. This data was linked to the demographic data above.

Isolates	%	Notes
% of isolates with clear growth on agar media before adding Amoxicillin disk	78.4% (±2.1)	On 22 plates no growth was detected
% of isolates with clear growth inhibition after adding the disk	48.9% (±2.1)	On 46 plates no clear growth inhibition was seen

Patients category	Total	Isolates	
		Clear Growth (%)	Growth Inhibited (%)
Total patient isolates	94	48 (51.1%)	46 (48.9%)
Patients using Amoxicillin as first treatment	64	25 (39.1%)	39 (60.9%)
Amoxicillin taken without professional advice	49	26 (53.1%)	23 (46.9%)
Patients feel complete or partial relief	55	31 (56.4%)	24 (43.6%)
Patients feel no relief	24	2 (8.3%)	22 (91.7%)

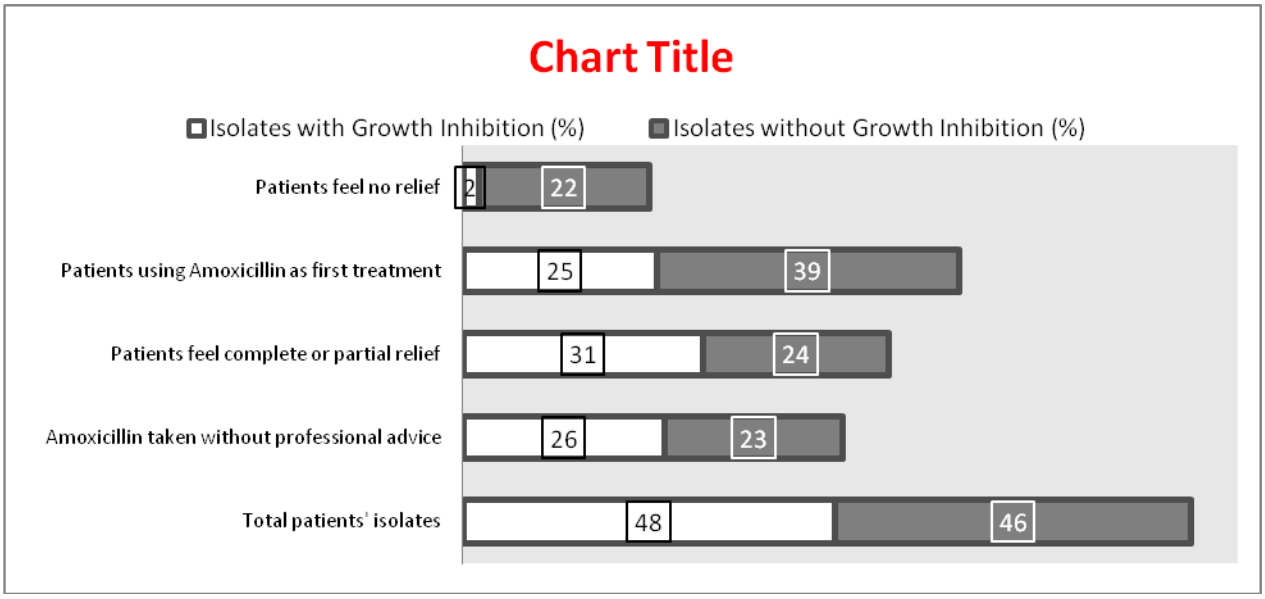

Figure 14: Summery of growth inhibition after using Amoxicillin discs

Summery discussion

Amoxicillin in Sudan has unique characteristics which make any study about its use and its quality is of considerable importance. These characteristics include the following:

1. Currently there are 77 products registered in Sudan between different dosage forms and concentrations (NMPB, National Medicines and Poisons Board, 2010);
2. It is the forth generic in terms of quantity (collectively exported and manufactured in the country) during the period 2006/2007 (FMOH, 2008);
3. It was among highly consumed products in the market, especially without prescription, which reflects the wide use of this drug in the community (FMOH, 2008);
4. It is a "symbol of antibiotic" in the community and it is culturally considered as one of the best accessible anti-infective drugs;
5. Based on the results obtained from part 1 of this research; it was the second generic that health professionals widely complain its effectiveness;
6. Based on the results obtained from part 1 of this research; it was the top generic that health professionals shift the patient from it to other antibiotics

On the contrary for the last two points, all assayed products were complying with standard specifications in its chemical contents. Based on the findings revealed from the primary investigation and analysis of targeted pharmaceutical products (among which "three" Amoxicillin 500 mg capsule products were tested); the results didn't respond to

concerns reported about Amoxicillin products circulated in the market. Although the products have been tested were chemically sounds but still they were clinically not effective (based on feedback of health professionals' survey). There are valid questions regarding the possibility of developing microbial resistance to this generic in Sudan. Taking into considerations the microbial resistance in such case is not an exclusive reason for therapeutic failure, as bioavailability problems and lack of appropriate use/administration may contribute also to these reported failures (Taylor & others, 1995).

Looking closely to the trend of Amoxicillin use both inside and outside the health system in Sudan (prescription based versus OTC treatment), it indicate the extent to which Amoxicillin is widely misused. Studies in Europe showed clear association between higher consumption of antibiotics and the rate of microbial resistance to it (Stephanie & others, 2001). This was especially noticed among the highly consumed antibiotics in the community similar to Amoxicillin in case of Sudan (WHO, 2009). In Sudan it is generally noticed that Amoxicillin is commonly, and mainly, used in both pediatric and adult patients for the treatment of upper and lower respiratory tract infections (U/LRTI), this usually besides other indications. Many studies confirmed the increasing prevalence of Streptococcus pneumoniae among patients with U/LRTI (beside other kinds of microorganisms) (Leesik & others, 2006). These facts critically raise the question about whether Amoxicillin is still an appropriate treatment of these kinds of infections. The implications of answering this question have great impact both at macro and micro levels in policy making process and at community level as well (Eerden & others, 2005). Currently there is no specific study in Sudan that "linked the usage of Amoxicillin with its

quality of effectiveness”; considering the large amount of Amoxicillin products consumed over the country.

In general, scientists agreed that the resistance of bacteria to certain antibiotic(s) is a matter of response from the bacteria towards the environmental changes due to the existence of the antibiotic “resistance as biological response”. This is valid regardless whether or not the antibiotic(s) were effective against the bacteria (Murray, 2007). This point supports the hypothesis about the possible contribution of microbial resistance against Amoxicillin. Upon the wide and extensive use of Amoxicillin in the community, there is considerable possibility of emerging resistance to this drug among microorganisms that were previously sensitive to it (Ball & others, 2002). Resistance for beta lactam antibiotics (Amoxicillin one of this group) were traditionally being associated with the bacteria that producing beta lactamase enzyme, as this leads to deactivation of the drug by breaking the beta lactam ring in its structure “the active part of the structure” (Katzung, 2001). Although the introduction of combination product, that include Clavulonic Acid beside Amoxicillin, lead to dramatic change in overcoming this problem, but still there is a wide use of Amoxicillin alone for treatment of some conditions. In comparison, it is clear that the combination mentioned before is more effective than the usage of Amoxicillin alone. However, due to some factors including the economic aspects and the shape of the market in Sudan still we can observe the wide use of Amoxicillin in different kinds of infections (especially in U/LRTI).

World Health Assembly Resolution in 1998 urged Member States to develop measures in to compact the development of microbial resistance for antimicrobials (WHO, 2009).

Countries were also encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures. For further details, World Health Assembly Resolution in 2005 urged Member States to “ensure the development of a coherent, comprehensive and integrated national approach to implementing the strategy for containment of antimicrobial resistance” and to “monitor regularly the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors” (WHO, 2009).

The above data gave clear indicators about the factors that may possibly influence the development of bacterial resistance for Amoxicillin products. That is unnecessary be linked to antibiotic use for viral respiratory infections as considered among the health professionals. In fact misdiagnosis the conditions and its symptoms lead to empirical and blind treatment of the case (in case of respiratory infections both viral and bacterial agents can cause similar clinical symptoms). Among other factors the extensive use of Amoxicillin and other similar products due to many reasons (e.g. patients’ pressure on health professional to obtain rapid treatment for their disease) also played important role. This was seen clearly in the results obtained from this study.

Based on the results generated from this study it becomes very obvious the needs to develop structured protocol to assess the quality of Amoxicillin and other similar products using microbiological assay approach. The step of this assay should be the starting point for in-depth analysis that aims to identify the possible causes for the treatment failure in patients using Amoxicillin and other similar products.

Biological assay of 3 products of Ceftriaxone powder for injection 1 g

The products

Three products of Ceftriaxone sodium (1 gm powder for injection) were included in this study. One of these is the originator's product which is "*Rocephin*", manufactured by Roche - Switzerland, and for the purposes of this study it was selected as reference product. The other two products were chosen basically in the first part of this research and were continued to be the same subject in this part. The details of the products were demonstrated in the table.

Trade	Company	Country of origin	Origin classification
G03C20T01	C20	Switzerland	High income
G03C10T02	C10	India	Low income
G03C14T03	C14	Jordan	Lower-middle-income

Statistical analysis

The range of concentrations of each product was statistically satisfactory to produce wide range of plotting points sufficient for producing clear statistical data. The concentrations prepared and used in this assay include 0.125, 0.5, 1.0, 4.0, 16.0 and 32.0 mg/ml (according to MIC of targeted bacteria, please see below). The assay was repeated using three concentrations of each antibiotic by triplicates for each microorganism.

Organism	MIC_{90} mg/ml
Streptococcus pneumoniae	0.060
Klebsiella pneumoniae	0.125
Staphylococcus aureus	4.000

For the purpose of this analysis, the linearity and precision of the method used were all determined. This was done by plotting the log-transformed concentrations of each product against inhibition zone in mm. The data followed the linear statistical model which was confirmed by the values of intercept and slope of the best straight line when applied in the equation (y = b + mx, b is the y-intercept and m is the slope). The x-intercept (log10 mg/L) and slope of the regression line with 95% confidence intervals (95% CI) were both calculated and used for regression approach to analysis of to determine the statistical significance of these variables.

The equivalencies of products under this experiment were concluded by comparing the slope and intersect of each product using a symmetrical parallel-line assay. In this analysis, and in accordance to the purpose of the study, potency was defined as the slope of the linear regression and concentration. In this case and if we assume that the test products and the innovator are equivalent, then the products must show a trend of parallel and overlaid curve with the cure of the innovator. At the same time, when there are parallel curves but it have different intercepts this may indicate the existence of same active ingredient but at different concentration above or below that of the innovator product. The relative potency for each product to the potency of the innovator was calculated using the distance between the innovator line and that of the test product.

The response values (diameter of inhibition zones) were calculated using the standard deviation and slope method and these were stated in term of means +/- the standard deviations and with the calculated coefficients of variation. To test the accuracy of the test; i.e. its ability to detect the differences in concentration significantly, standard curve was

obtained by using different concentrations of Ceftriaxone working standard solution with potency of 98.6%/L). This curve was compared with the curve of all products under assay.

Results

The table below shows the potency estimates and other parameters derived from linear regression with their statistical comparison of test product versus innovator by Curve Fitting Analysis

Product	r2	Intercept ± SD	P-value	Slope ± SD	P-value	Potency estimate (%)
Organism: Staphylococcus aureus						
G03C20T01	0.97	2.401 ± 0.205	0.000	0.027	0.000	100.0%
G03C10T02	0.91	2.223 ± 0.187	0.000	0.026	0.000	84.3%
G03C14T03	0.78	2.172 ± 0.164	0.000	0.027	0.000	70.%
Organism: Klebsiella pneumoniae						
G03C20T01	0.97	2.198 ± 0.172	0.000	0.023	0.000	100.0%
G03C10T02	0.91	2.023 ± 0.124	0.000	0.025	0.000	89.4%
G03C14T03	0.78	2.089 ± 0.166	0.000	0.023	0.000	74.1%
Organism: Streptococcus pneumoniae						
G03C20T01	0.41	2.351 ± 0.311	0.000	0.022	0.000	100.0%
G03C10T02	0.52	2.325 ± 0.324	0.000	0.024	0.000	51.4%
G03C14T03	0.48	2.305 ± 0.452	0.000	0.024	0.000	47.1%

Table 11: Summery of relative potencies and other parameters of Ceftriaxone products

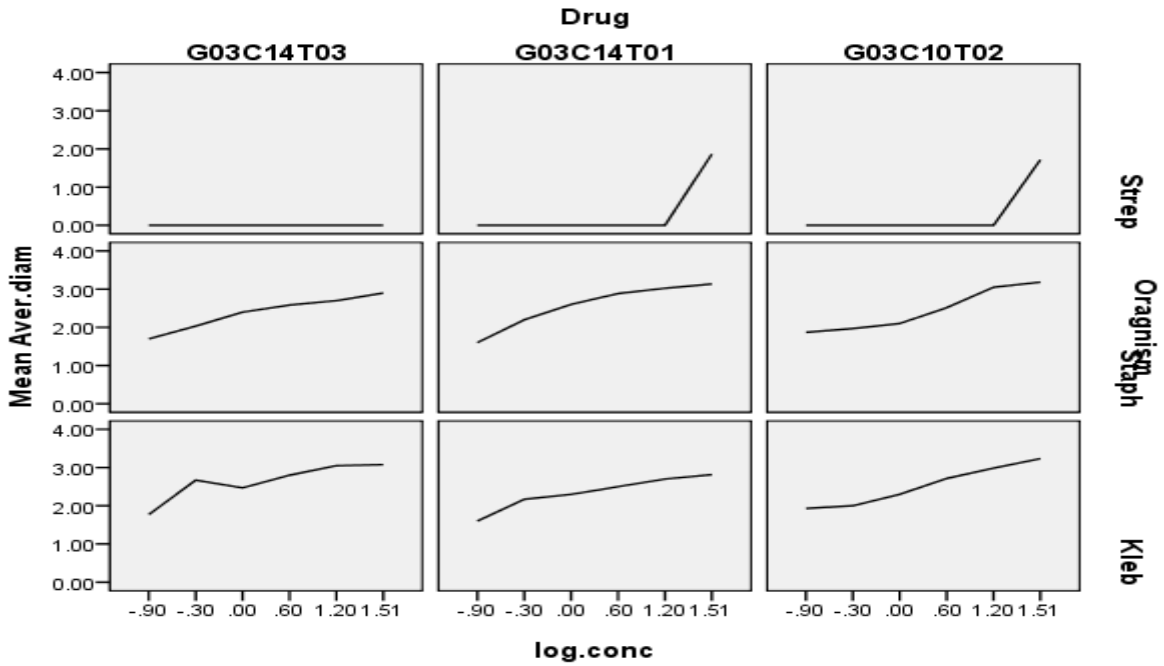

Figure 15: Single dose-response curves for Ceftriaxone products against targeted organisms

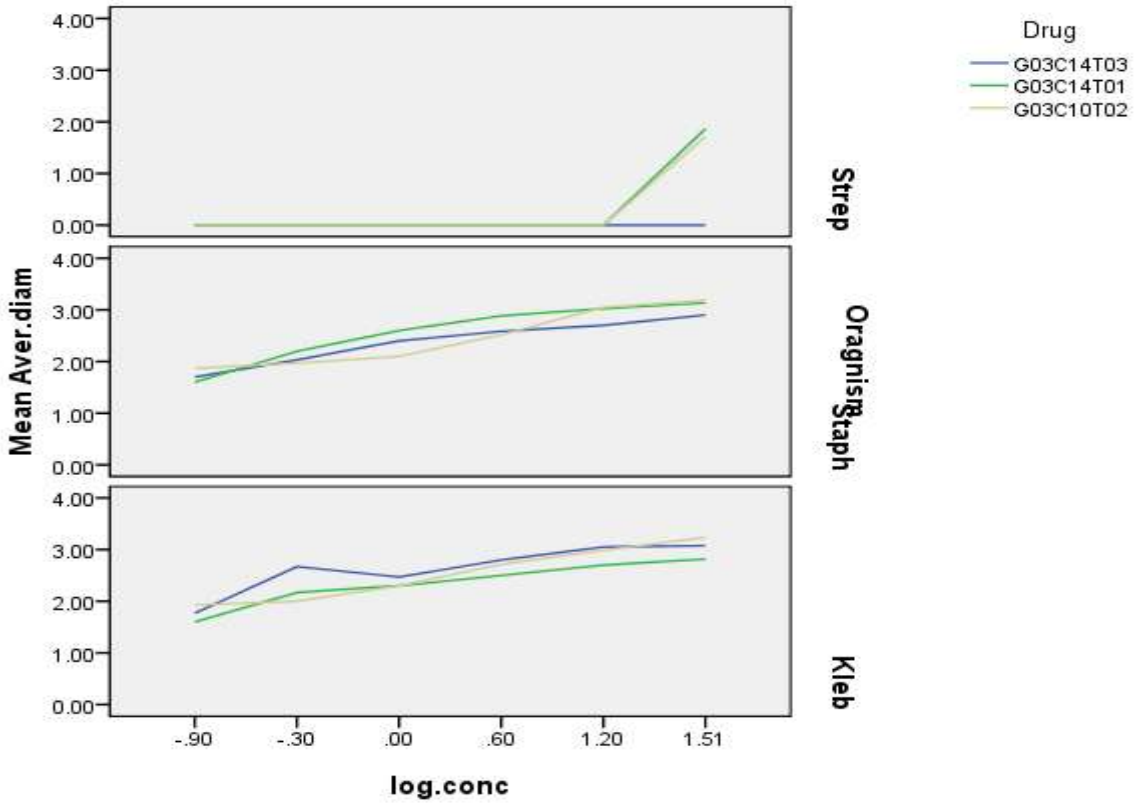

Figure 16: Combined dose-response curves for Ceftriaxone products against targeted organisms

Figure 15 and 16 above shows the log concentration-response relationship and the best straight line obtained from data from the microbiological assay of the innovator. The cases for Klebsiella pneumoniae and Staphylococcus aureus showed a linear relationship between the logarithm of the concentration (log10 mg/L) and the diameter (mm) of inhibition zones with relatively high coefficients of determination (r2 ranging from 0.97 to 0.78) and statistically significant intercept and slope ($P < 0.001$ by ANOVA). On the other hand the results for Streptococcus pneumoniae showed different trends. The main observation from the row data showed that the response of the organism (growth inhibition) was only appeared at higher concentration. That was appeared at a concentration 32 times the MIC90 for this organism, i.e. 2mg/ml, and this observed for all products tested. This was significant findings by its own under the fact that growth inhibition was expected to be at lower concentrations than that.

Excluding the data of Streptococcus pneumoniae and considering the data from other organisms, all of the products exhibited a different intercept ($P < 0.005$), the log concentration-response relationship for one of the generics (G03C20T02) was parallel and overlaid to innovator linear curve without significant difference ($P < 0.005$), while other generic (G03C20T03) was parallel but not overlaid to innovator linear curve. These findings signifying the facts that generic G03C20T02 and generic G03C20T03 had the same biologic activity (potency). On the other hand generic G03C20T02 and generic G03C20T03 showed relative estimated potency of 86.9% and 72.3% of the originator product respectively. All these data indicate that generic G03C20T02 is pharmaceutically equivalent to the originator product while generic G03C20T03 didn't prove the same relation.

Summery discussion

The results obtained from the chemical analysis tests, in part two of this study, weren't somewhat enough to answer the complaints from health professionals regarding the quality issues around Ceftriaxone powder for injection (especially certain products). Although these products complied with reference standard specifications in term of its chemical content limits. But considerably there are major concerns about its quality and even the clinical outcomes of these products. Ceftriaxone was the most generic in which the patients experienced shifting decisions by their doctors, either to shift them to other trade products or shift them to other different generics.

In this regard we have to consider the following facts:

1. All assayed products complied with reference standard specifications in its chemical contents;
2. The products are in an injectable form, so we can assume its bioequivalence because it isn't expected to experienced bioavailability problems especially as intravenous solution from

This will urge many questions regarding the reasons lead to these complaints and about that specific product. No single reason before this study could be considered as evidence for the primary cause of this observation.

As example, among the circulated Ceftriaxone products available in the market; there was specific trade product represent one of the major concerns received during the first part of

the study. This product was the main source of complaints and based on the results in this part it is clear that it is not equivalent to the other products.

Equivalency of pharmaceutical products becomes essential and basic criteria for proving the quality of any product (WHO, 1998). In general there are different methods could be used by the regulatory authorities to evaluate this characteristic. This may include the in-vitro/in-vivo bioavailability studies and other methods like bioassay. Using bioassay method is not new in different pharmaceutical sciences; however, it was used limitedly, and mainly, for pharmacokinetic studies (Simon & Yin, 1970). Late in 1980s the bioassay method has drew the attention as possible tool for establishing scientific judgment about pharmaceutical equivalence of certain categories of products like anti-infectives and vitamins (Humphrey & Lightbown, 1992). The method could help significantly in obtaining more conclusions about the similarity and the differences between products that supposed to contain similar and equivalent active ingredient. This is especially true when we consider the fact that any pharmaceutical formulation usually contains the active ingredient in addition to other substances (e.g. preservatives, impurities, etc). In most of the cases these materials were not considered in the assessment of the quality or the equivalency of generic products (Layloff, 1997).

Considering the critical importance of anti-infectives (especially Ceftriaxone) to public health in Sudan, it is now become very essential to investigate the assumption about the differences in therapeutic equivalent between the products available in the market. The equivalence and potency of intravenous/parenteral generic products of Ceftriaxone, away from clinical studies, can't be evaluated by using the conventional physical and chemical

methods only. It was proved that, after carrying out this study, using a well designed microbiological bioassay this should help the authorities to do such kind of re-evaluations. The statistical method adopted here was used for similar study done on other anti-infective intravenous preparations (Zuluaga & others, 2009). Previously it was believed that agar-diffusion assay is less reliable that other chemical methods (e.g. HPLC) because it implies on wide sourcing of biological errors. Still this method is statistically suitable to be used in such kind of studies (equivalence and potency evaluation studies). The logic behind the statistics used in this study (and similar studies in general) was based on the assumption that: if two Ceftriaxone products were equivalent to each other, so by obtaining two symmetrical and straight parallel lines (plotting of the mean zone size against the logarithmic concentration), then the relative potency of test product to the reference product could be derived by calculating the distance between the two lines (Zuluaga & others, 2009). In the same time these curves in their bioassay should not differ significantly from each other.

In conclusion, this simple method of analysis is very important for any regulatory authority to be considered as routine process. The method showed many advantages as it allows rapid, cost-saving, precise, and accurate determination of pharmaceutical equivalence of drugs in pharmaceutical dosage-form. This in fact is one of the considerable innovations for any quality monitoring system in the country related to injectable products.

Rapid observational study about the reconstitution practice of Ceftriaxone powder for injection

Effectiveness of Ceftriaxone

The participants see the drug and potent one and still effective as anti-infective. It is now the drug of choice for many conditions and doctors start with it in many cases. Part of the participants reported their observation about the efficacy of this drug, based on their experience early at its introduction phase it was very effective compared to other generics. But nowadays its efficacy started to decrease compared to that period. Some patients use Ceftriaxone and it they were not getting better so doctors shift them to other drugs. This shifting usually affects the psychological acceptance of the patients to their disease and they see that as difficult to cure infection. The drug is highly available in the hospital and more than 7 products usually used within the hospital from different origins.

Dissolution practices

There was common agreement between the nurses on how Ceftriaxone been reconstituted. All of the nurses only use water for injection or sometimes they use normal saline IV fluids. This point was agreed among all of the nurses participated in this session.

Concurrent administration with Calcium incorporated products

Despite the fact that the group came from different disciplines and with different years of experience in both the public and the private sector, the information about the cautions in mixing Ceftriaxone with Calcium (and other trivalent cations) is new to the entire group. One of the participants report one incident of prescribing both items for one patient, but she

couldn’t judge the therapeutic outcomes in this case and whether this affect the patients cure or not. Another participant pointed the situations related to renal dysfunction patients as they usually need anti-infectives and they also need Calcium Chloride. But this was not a concurrent administration in one IV line, rather it is usually separate.

Effect of origin on practice

Nursing community has preferences regarding which products to use over the other. Certain origins were used more frequently than others and this due to repeated experience with patients taking that specific products compared with other patient those administering the other products. Alternatives to preferred products usually give less therapeutic outcomes in the patients. There was other dimension raised during the discussion about the economic implications of using different products available in the market. The observation pointed out the fact that, the most likely used products is that with medium price compared with other products. 6 participants report their beliefs about the linkage between the sources of origin and the quality of medicines. They stated that they don’t advice the patients to take any drugs come for certain countries of origin.

Chapter 4: Discussion

Summary about this chapter

In the following chapter an overall discussion about the findings obtained different parts will be combined in a way that informed the improvement of quality monitoring systems of pharmaceuticals. This becomes essential in management science in which the use of evidence in building any interventions becomes the important feature of successful organizations. Moving from one strategy to another in any area usually needs supporting and scientific justifications for that step. In this specific context the proposed strategy is basically focus on how to move from testing a number of products blindly, towards more informed testing schemes based on available data.

In this chapter we will examine the practical approach of this proposed strategy to use a risk based post marketing surveillance system of medicines in Sudan. The strategy should inform the way by which the authorities should select medicines for regular and regular checks. To build such kind of systems this usually demands various kinds of information and data from different sources. The diversity of the data is useful under such kind of operational researches and its outcomes usually bring practical solutions. The data generated under this research indicates useful information and outlines about how to select effective strategy to improve the capacity of medicines regulatory authority to detect medicines of low quality. With the diversity of data generated from this research, and even though the routine data from the system, this should be a very helpful mean to enrich the decision taken at any level.

We will discuss in more details the shape and dynamics of the pharmaceuticals market in Sudan with some description about the current system of Post-marketing surveillance in the

country. Based on the findings obtained from this research a practical scheme will be proposed to expand the PMS system. The applications of risk assessment/management techniques in the areas relevant to quality management of pharmaceuticals will be discussed in brief. This will provide the base for building the model for expanding the PMS system in Sudan. The usefulness and expected applications of this model will be discussed later in this chapter.

Since the focus of this study was on the system in Sudan, the following details applied on the situation in Sudan. However, still the concept is valid to be applied in different settings.

1- Pharmaceuticals market in Sudan

National Medicines and Poisons Board in Sudan is the responsible body for granting market authorization of pharmaceuticals as a requirement for all medicines distributed in public and private sector in Sudan. Based on recent statistics, end of 2010, there are about 3709 registered products in term of trade names that has been authorized [of which 11% were locally produces]. Based on the regulations, the registration renewal is required for the registered medicines every 5 years (NMPB, National Medicines and Poisons Board, 2010).

The table below indicates the major indicators of pharmaceutical market in Sudan at the macro level (FMOH, 2007).

Table 12: The major market indicators

Indicator	2007	2006	2005
	All values are in millions US$		
Total Sudan market value (all sectors)	285	234	222
Total market growth	21%	5%	7%
Total medicines supply value (paid)	213	164	152
Public sector medicines supply value	49	39	41
Private sector medicines supply value	164	153	111
Local production share in paid market	24.9%	23.8%	NA
CMS share in paid market	22.6%	19.3%	17.6%

The growth rate of the market in Sudan, especially after pace agreement, was very clear and many of pharmaceuticals companies expanded (or plan to expand) its establishment into the market not only in pharmaceuticals but also in other medical products.

The market in Sudan is favorable environment for generic pharmaceutical companies that based mainly in low income countries (especially: India, China, Egypt, Jordan, Syria) that represents significant figures in the market (see table below) (FMOH, 2007).

Table 13: Major countries contributing to Sudan market

Country	Share %	Region
Egypt	7.8	Arab
India	6.1	Asia
United Kingdom	5.0	Europe
Switzerland	3.2	Europe
Jordan	3.0	Arab
Germany	2.8	Europe
China	2.0	Asia

Importers (agents) and local producers are the major players in private sector in Sudan in addition to the direct (special) importation which represents only small part of the market in this sector. The total importation in 2007 was about 104 million US$ (no noticeable growth from 2005) by 77 agencies from 200 different companies and manufacturers. Sudan pharmaceuticals market could be described generally as generic market, in which the generic trades represents about 90-95% of the market in terms of items. More than 70% of the total export value is from Arab and Asian countries and accordingly the total value of the market is consider not large compare to the volume in term of quantities. As mentioned before the local products represent about 11% of the total registered items (FMOH, 2008). When we consider all of this it will become clearly obvious that most of the products available in the market were imported from developing countries or countries with economies in transition. It will be very important to the "NMPB" to increase its capacity to detect and depict the existence of substandard medicines at different levels in the supply chain especially before it reach the end users (patients) to ensure safe and effective use of these medicines (Ratanawijitrasin & Wondemagegnehu, 2002).

Statistics showed that among the top 15 medicines, that entered the market in Sudan 2007, all items were in the national essential list of medicines in terms of generic names. But at the same time and among the top 50 medicines 20% (10 items) were not essential medicines and their major source in general is CMS. About 21% of the medicines supplied through the public sector are locally produced (compare to 8% only the year before) (FMOH, 2008).

Table 14: Top 15 medicines in the market 2006

Medicines			% of Share/Source		
Generic Name	**Strength**	**Dosage Form**	**Agents**	**CMS**	**Local**
1. Paracetamol	500 mg	Tablet	7	4	89
2. Metronidazole	250 MG	Tablet	2	10	88
3. Acetylsalicylic Acid	300 mg	Tablet	1	27	72
4. Amoxicillin	250 MG	Capsule	9	57	34
5. Diclofenac Sodium	25 mg	Tablet	15	14	71
6. Ampicillin + Cloxacillin	500 MG	Capsule	11	25	64
7. Chlorphenarmine Maleate	4 MG	Tablet	4	15	81
8. Chloroquine	200 mg	Tablet	0	0	100
9. Multivitamins & Minerals	-	Capsule	100	0	0
10. Folic Acid	5 MG	Tablet	86	0	14
11. Amoxicillin	500 mg	Capsule	15	20	65
12. Glibenclamide	5MG	Tablet	48	4	48
13. Mebendazole	100 mg	Tablet	4	4	92
14. Water for Injection	-	Injection	0	100	0
15. Ferrus salt	60-70mg	Tablet	0	100	0

Medicines registration outcomes in Sudan:

NMPB is the responsible body for issuing MA of different pharmaceutical products (beside poisons) and it is supported by standing committee that delegated from to approve the registration of human medicines (there is another committee for veterinary medicines). This committee consists of many experts in different sectors in health and pharmacy that approve or reject the submission request to register the pharmaceutical products. This is based adopted and published requirements and measures which were available in the department offices and on the federal pharmacy directorate web site. Up to this report there are about 3709 registered medicines in term of trade names (register by trade name using INN system). The following table summarized the registered items disaggregated by therapeutic groups versus the dosage forms:

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	212	21	38	18	8	3	300	08.1
Cardiovascular system	360	14	0	9	0	0	383	10.3
Respiratory system	33	3	34	5	20	0	95	02.6
Central nervous system	347	42	47	11	3	0	450	12.1
Infections	518	236	225	46	92	0	1117	30.1
Endocrine system	154	36	10	5	14	0	219	5.9
Obstetrics, gynaecology, & urinary-tract disorders	25	14	1	4	4	3	51	01.4
Nutrition and blood	135	50	37	85	0	0	307	08.3
Musculoskeletal and joint diseases	199	28	19	18	32	0	296	08.0
Skin	7	3	6	25	119	0	160	04.3
Other	67	98	40	97	28	1	331	08.9
Total	2057	545	457	323	320	7	**3709**	
%	55.5	14.7	12.3	08.7	08.6	00.2		

Table 19: Summery table of registered products in Sudan

2 - Current system of Post-marketing surveillance "PMS" in Sudan

The PMS system in Sudan is generally similar to many other systems in developing countries. Its main component, and may be the only one, is the routine sampling and testing of the authorized products distributed at different components of the supply chain. The following described briefly the outlines of the system.

2-1 Selection of medicines

Medicines selected for analysis and testing under the current system usually determined based on the following process:

1. Every month one pharmacological/therapeutic group normally targeted for testing based on the classification of BNF;
2. 40% of registered products within each group were randomly selected to be the major target for sample collection and the analysis. This usually represents 90% up to 95% of monthly analysis plan of PMS;
3. The remaining share of the products subjected to testing usually represents the items reported in the routine complaints receiving system. Normally assigned committee is responsible for the determination of products to be tested under this scheme out of all complaints received.

2-2 Complaint system

This system was established during 2006 and it used different communication tools including a hotline phone number (free of charge) in addition to direct acceptance of reports. These reports could arrive from different categories of the community including health

professionals and the public as well. Certain forms used to describe details about the product and reported problem(s). Since ..... a total of ..... reports have been received and discussed in the committee, (with average of ..... reports received annually). From these reports a total of..... products subjected for quality checks (NMPB, 2008).

2-3 Quality evaluation

The National Quality Control Laboratory "NQCL" is the responsible body for quality evaluation under this system. Certain communication plan usually applied between the PMS unit and the laboratory for follow-up and coordination. Quality evaluation checks under this system are basic physiochemical tests to evaluate the products under testing. The chemical analysis represents the main source of information to build the regulatory decisions (whether to recall, to revoke or any other decision). Studies indicated the weakness in NQCL mainly related to the capacity of the laboratory in different terms including human resources and the technical capacity (WHO, 2010). The capacity of the national laboratory to test medicines was a major component of plans during the last few years. In 2009 the total number of pharmaceutical products that have been tested (most of it were cosmetic products) was 2884 samples out of 2928 samples collected. According to results obtained 296 of items tested doesn't pass the quality specifications tests.

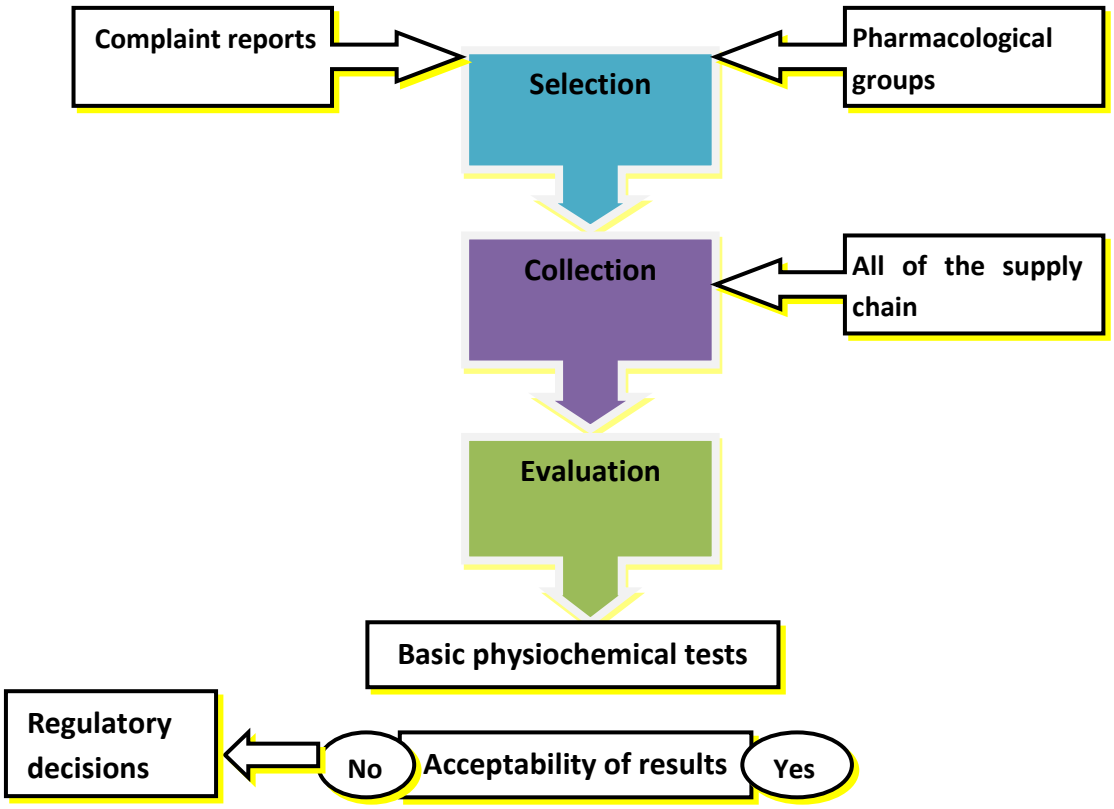

Figure 17: conceptual model of current PMS in Sudan

Looking at this system we can realize its passive nature, i.e. it depends basically on passive approach in selecting medicines/products for testing. There are no active measures in its components that adopt dynamic information to feedback the selection process of medicines and/or the regulatory decisions.

2-4 Detection rate & outcomes of the system

On average, through the last 5 years, 9% of the tested items under this system were found not complying with reference specifications and this was varies from one year to another. The non-compliance problems vary in its nature ranging from small physical problems up to critical chemical contents problems.

The following table indicates the summery of failed items per year:

Year	Number tested	% of non comply	Notes

The following table summarizes the details of medicines ***recalled*** from the markets during the last three years (NMPB, 2010):

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	3	0	1	0	0	0	4	09.8
Cardiovascular system:	4	2	0	0	0	0	6	14.6
Respiratory system	0	0	2	0	0	0	2	04.9
Central nervous system	0	1	0	0	0	0	1	02.4
Infections	6	1	3	5	0	0	15	36.6
Endocrine system	4	0	0	0	0	0	4	09.8
Obstetrics, gynaecology, & urinary-tract disorders	0	0	0	0	0	0	0	00.00
Nutrition and blood	2	0	0	0	0	0	2	04.9
Musculoskeletal and joint diseases	3	1	1	0	0	2	7	17.1
Skin	0	0	0	0	0	0	0	00.00
Other	0	0	0	0	0	0	0	00.00
Total	22	5	7	5	0	2	**41**	
%	53.7	12.2	17.1	12.2	00.00	04.9		

Table 20: Summery table of recently recalled products

The following table summarizes the details of medicines ***revoked*** from the markets during the last three years (NMPB, 2010):

Pharmacological groups	Solid oral	Parenteral	Liquid oral	other large liquid	Topical	Other	Total	%
Gastro-intestinal system	7	0	0	0	0	0	7	11.7
Cardiovascular system	7	0	0	0	0	0	7	11.7
Respiratory system	3	0	0	0	0	0	3	05.00
Central nervous system	1	0	0	0	0	0	1	01.7
Infections	10	1	0	2	0	0	13	21.7
Endocrine system	12	0	0	0	0	0	12	20.00
Obstetrics, gynaecology, & urinary-tract disorders	1	0	0	0	0	0	1	01.7
Nutrition and blood	0	0	0	0	0	0	0	0.00
Musculoskeletal and joint diseases	5	0	0	0	1	0	6	10.00
Skin	0	1	0	0	3	0	4	06.7
Other	4	0	0	0	0	2	6	10.00
Total	50	2	0	2	4	2	**60**	
%	83.3	03.3	0.00	03.3	06.7	03.3		

Table 21: Summery table of recently revoked products

Note: the products in table 20 & 21 were not necessarily similar to each other.

2-5 Awareness about the system

Getting back to the results obtained from health professionals' survey we found that only 42% of the pharmacists aware about this system. This relatively equal among different geographical areas surveyed, but it falls up to 14% in the peripheral areas in the city. Considering the experience of pharmacists responded, those with experience more than 5 years have more knowledge about the system better than other groups (especially those with 3-5 years of experience).

Category	Yes	No
All pharmacists (collective) n=82	42.8	57.0
1 year – 2 years (n=26)	44.0	56.0
3 years – 5 years (n=25)	33.3	62.5
More than 5 years (n=31)	64.7	53.3

Among all of these pharmacists 38% have reservations about this system and its outcomes in detecting the low quality medicines and how it responds to the challenges in the field.

3 - Expansion of the PMS system

Considering many facts that affect the value of current PMS system (such as the broad area in Sudan, capacity of NQCL and the limited financial resources) it become obvious that the current system need to be improved in an innovative way. The following graphical model indicates the suggested improvements of the system (compared to figure 17 of current model) by introducing more methods and approaches to get better outcomes.

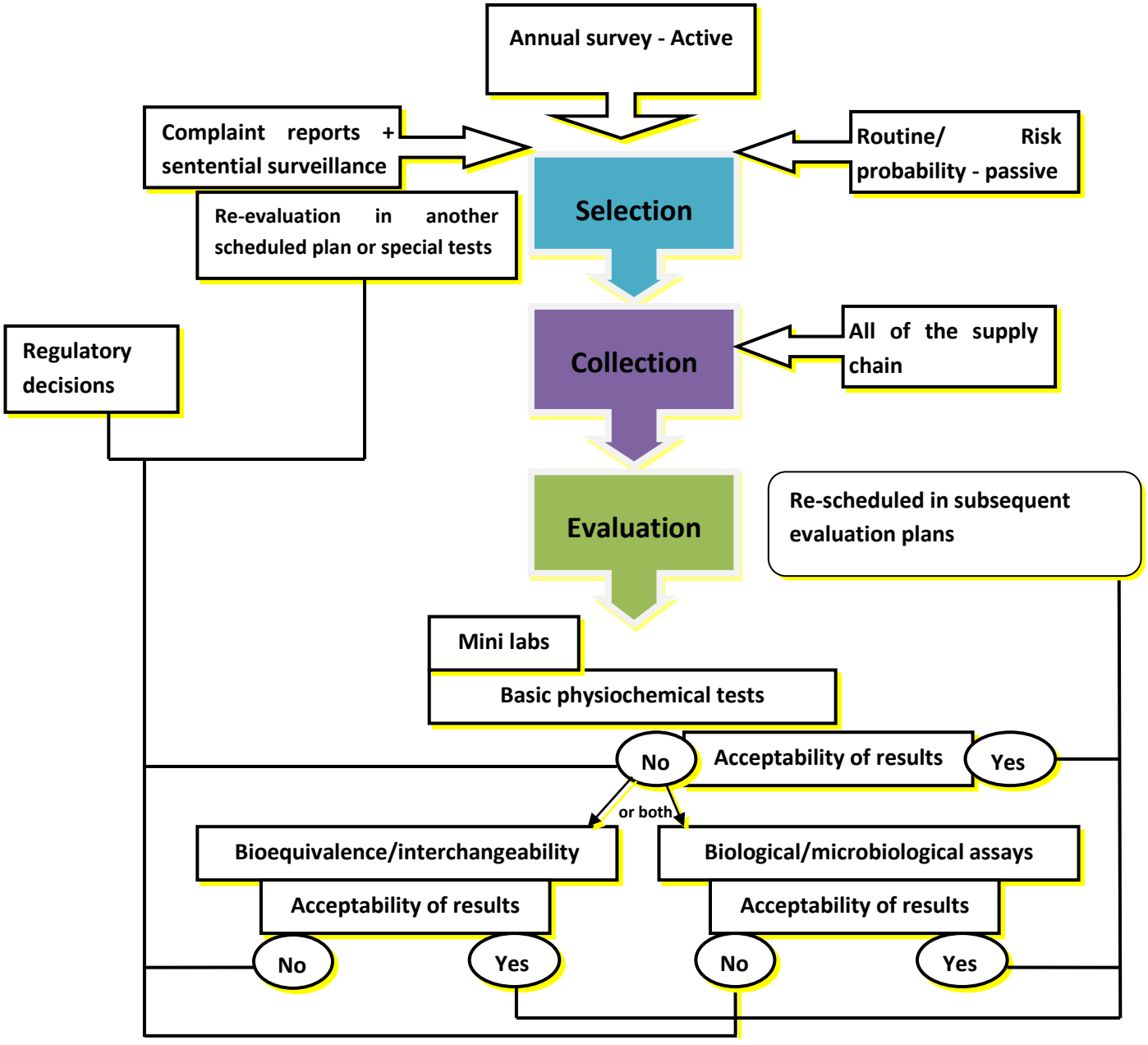

Figure 18: conceptual model of proposed expansion PMS in Sudan

According to the results obtained from previous study that investigated intensely the main causes of substandard medicines problem, the results pointed out different forms of problems with possibly different causes behind the detected cases. This started at the raw materials selection, through the manufacturing process, distribution and up to the storage (Nicholson, 2005). Accordingly, the way in which PMS system is designed should aim to reduce the manufacturing and trading of substandard. This form of such kind of vigilance should consider the process that checks the drug's identity, chemical integrity, physical stability, and biological activity, and exclude the possible damaging effects of inappropriate handling, packaging, and storage (Ndomondo-Sigonda & others, 2000). On the other hand the combined interpretation of quality control results with the clinical data or therapeutic outcomes of any product under this proposed scheme will support the regulatory decisions taken. This is particularly important in order to take overview picture for causes and effects of any problem and to include or exclude any potential factors that contribute to observed incident of substandard product.

Any strong PMS system should rely and based on strong drug monitoring information systems (Forzley, 2006). This information system should be able to track the problems up to patients' level including the feedback from healthcare providers at different levels. For example, the system should consider and monitor regularly the information about the shifting practices of treatments. This indicates important information about the efficacy part of any product under observation. With regard to the generics that usually included in the process of shifting are generally similar to those tested under this research which indicates

the importance and significance of this source of information. The proposed survey should also be able to bring such kind of information. In other aspect, the information system should differentiate between the complaints regarding the therapeutic process, that related to adverse reactions/events and that related to use of generics or any other sort of problems. By applying different reporting mechanisms the authorities will develop strong accumulated knowledge about the products, its manufactures and its distributors; what we can call “Product Profile”. This should become a routine part of quality management system of pharmaceuticals products. Beside all of these, there are other potential sources of information need to be collected and considered in taking the regularity decisions (not only the results of PMS). This includes the following:

1. Pre-marketing surveillance test results;
2. Acceptability of the remaining shelf-life at time of receipt;
3. The history of the drug and its agent at NQCL before distribution;
4. The quality status at time of collection in accordance to Pharmacopeia;
5. The quality at the end of the shelf-life;
6. Drugs most frequently failed the tests;
7. The lost of potency among the time;

In this system the authorities should emphasize more on building the relations with health professionals form different categories. The results shows that only 15% and 10% of pharmacists and doctors respectively have ever notified the authorities by any information related to medicines they deal with. Even those who ever notified the authorities, most of them never received a feedback on their reports or notice any kind of action done as

response to their reports (at least up to their knowledge). The role of pharmacy or health regularity bodies is very important and vital in the linkage between the professional practitioners and the products they use during their work. The feedback of the practitioners about the products efficacy, safety and quality should be communicated effectively between the two sides. Conducting the proposed survey "described in the above model" under the umbrella of the "NMPB" (and the dissemination of annual reports based on this survey) should help in building the trust of professional practitioners towards the authorities and it will encourage them to report more frequently. This will have direct impact on improving the detection rate of low quality products circulated in the market. The system in this part should specify clearly the decision making mechanism related to the reported cases. This should help the reporters to know exactly how their reports will be treated and they will acknowledge the process the authorities take under this reporting mechanism.

Considering the critical importance of anti-infectives to public health in Sudan (FMOH, 2006), it is now become very essential to investigate the problem around this therapeutic group as special part of the PMS system "specialized surveillance". All of the indicators from this research pointed out the volume of problems around products under this group. It is not only the resistance problems part but also its equivalence and other aspects. This proposed system appreciates the importance of establishing a monitoring system of "antimicrobials use" in the country including data about resistance (Blomberg, 2007). This system should ensure the development of strong mechanism that aim to monitor regularly the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors.

The reasons behind the recommendation to introduce the mini-labs strategy in this system was principally due to the fact that it could provide an inexpensive, low technology, non-laboratory-based testing option. It helps to assess product identity, disintegration, and drug content, which is of value in resource-limited settings like Sudan. When it is used by skilled persons, it provides an opportunity to identify substandard drugs in relatively inexpensive and quick process which is combined with other methods (Wondemagegnehu, 1999).

The approach by which this system designed and proposed is strong because it responds to problems that have been identified in most of PMS systems. In this regard the system will help the authorities because it is characterized by the following:

1. It is an effective quality monitoring system that use effectively the available resources;
2. It helps to increase the detection rate of substandard medicines;
3. It was based on improving the availability/sharing of information about the substandard medicines, the detected cases and the explanations behind that;
4. It provide advance and in-depth analysis of the detected cases;
5. It applies continuous improvement process (through research and development).

It is important to notice that handling of medicines quality judgments need to be combined with clinical outcomes analysis and ADRs surveillance and reporting. This should be a significant measure in order to avoid any subjectivity in the reported cases which need to be based on highly supported professionalism (Brewer & Colditz, 1999).

4 - Applications of risk assessment/management techniques

4.1 Theoretical background

When considering different risk analysis processes in any industry or services the risk definition is important step in order to manage the risk under analysis. In general it is know that risk defined as "*combination of the probability of occurrence of harm and the severity of that harm*" (ICH, 2005). This definition found to be valid for all field or areas and it cover wide range of risk categories including pharmaceuticals. In the context of medicines quality when considering the sampling and testing schemes the event in this case is any non-satisfactory testing outcome and the risk is sample selection that does not maximize the possibility of identifying this an outcome. So by identifying the best way to discover this "risk" the process will ensure the maximum detection rate of low quality products.

As discussed earlier we can find that many regulatory authorities started to apply the concepts of risk management in its regulatory decisions. ICH member states started to apply this concept few years ago and there are different guidelines about the application of this technique in the area of medicines quality control and quality assurance. Its applications in inspection and assessment activities had shown significant contribution in improving the management systems that applied this approach. However, its use in post marketing phase of products lifetime still limited and countries under process to develop and improve this application.

The following summarizes the experience of European Union countries about the usefulness of this approach (EMA, 2011):

- Risk management assisted in resources allocation among different activities including inspection planning, inspection intensity and in assessment intensity;
- It was useful in evaluating the significance of quality defects detected, evaluating the possibilities for potential recalls and significance of inspectional findings of manufacturing sites;
- It helps the authorities to determine the appropriateness and type of post-inspection regulatory follow-up;

In general, any quality risk management should be based on two fundamental principles. First; scientific knowledge should be applied when evaluating the risk and this should be linked to patient protection. Second; when decisions were taken to respond to identified risk(s) the efforts in this management process should be proportionate with the level of risk (Barone, 2008). The application of these principles in this research was considered as part of an analytical approach used to arrive to the conclusions made.

It is a common proactive practice to use both formal and informal risk assessment tools; both proven to be effective. The formal tools use well known techniques with more formal and structured process. This may includes Preliminary Hazard Analysis technique, Risk Ranking and Filtering technique and other techniques. The informal tools on the other hand may use more routine data in building models that help the organization to identify the potential risks in its systems. Whatever the tool used to evaluate the risk this should include clear identification of the vulnerability of outcomes under evaluation. In this process key set

of information need to be identified in any analysis. This includes information about the vulnerability of different aspects in the system (go wrong) and the possibilities for a getting that. In addition to this, the likelihood (probability) it will go wrong and the severity of that (FDA, 1999). Under the area of medicines quality, the triggering factors that might put the product under suspicious as substandard need to be identified. This process may include qualitative and/or quantitative methods of relating the probability of occurrence and severity of the risk if it happened. In other theories the use of "relative risk measure" to combine multiple levels of severity and probability into an overall estimate of relative risk is also acceptable (IEC, 2006). In this study the later technique was used to generate the model for selecting and detecting more low quality medicines among the authorized products in the system. The aim of any medicines authority, related to quality assurance, is to reduce the risk to public health if low quality medicines find its way to the markets. Accordingly, the purpose behind using this technique is to support the regularity authority in Sudan to make best use of the routine sampling and testing plans to increase the detection rate of these low quality medicines. The outcome of this process will help in selecting the products to be tested each year using a risk ranking approach that takes account of the available information to rank all categories of registered products.

4.2 Applications in quality monitoring

In EU countries the assessment of products to be included in post marketing evaluation for quality monitoring adopts the same technique. The selection of products usually based on the evaluation of a range of criteria that included, among others, therapeutic categories, market availability, stability and manufacturing process, experience with products. The

decision also combined these factors with some inputs from authorized staff in the regularly authorities and the GMP inspectorates (EMA, 2008). This ranking process made by considering the risk factors and its weight, then the selection of products for inclusion in any analysis plans will be based on the assigned risk level. After the completion of the assessment about the potential risk factors appeared in the analysis, these risk factors were critically evaluated considering the probability of achieving unsatisfactory testing results and the possible consequences of this outcome based on the profile of products under evaluation. Then the products (or its categories) were ranked against these factors, and the list of products to be tested every year should take account of this ranking. The important part of this system is its simplicity as it use the already existing information from different sources i.e. triangulation of available data (see model building section below for more details).

Management decisions in monitoring the quality and efficacy of pharmaceutical products in post marketing phase are usually difficult and complicated. The approach of using risk based management of quality monitoring, as described above, is one of the possible tools that can facilitate and support strong decision making process. Recently there was remarkable growing use of descriptive and analytical models for decision making in health services (Sanderson & Gruen, 2009). The models usually use the routine data and information generated from within the systems in order to increase the efficiency and to support quality improvement process. Different types of models could be used in this area depends on the objectives of the process and the available data. Considering the context under this research, risk-based model will be the most suitable and feasible approach.

Below we will discuss the possible use of risk based descriptive and analytical model to support the decisions related to monitoring the quality of medicines in post marketing phase.

5 - Logic of building the model

5.1 Theoretical background

The following graphical demonstration described the logic behind building any decision support model (based on (Sanderson & Gruen, 2009))

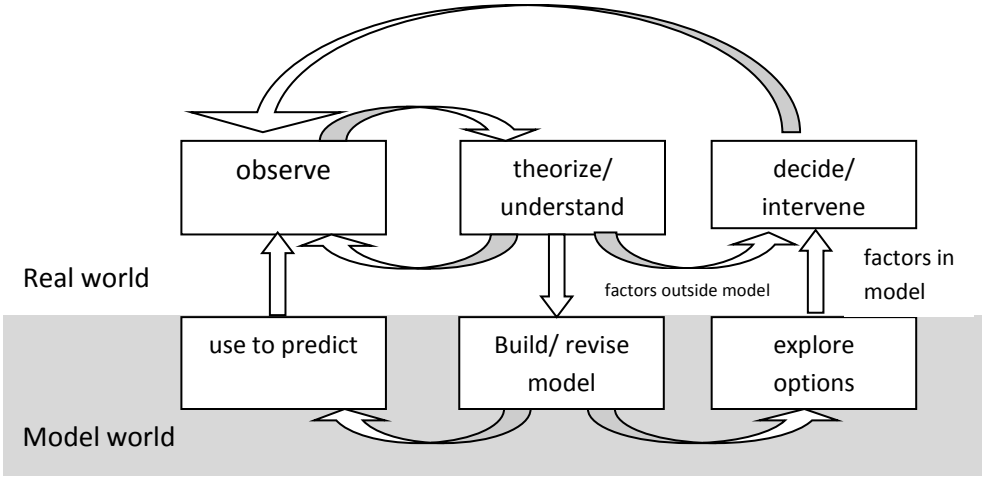

Figure 19: Logic of building a general decision support model

Upon the application of this concept, the proposed model to improve the post marketing surveillance of medicines was developed as described below. The general characteristics of this model include:

- The model came out of this process is basically a descriptive model in it nature, however, and based on the robustness analysis of the model, this provide a very strong starting point for advanced analytical model may be developed further in the future;

- The descriptive nature of the model is strong enough to show the relationships between the cause and outcomes of PMS system currently taken place in Sudan;
- The description generated from this model help greatly to build a hypothesis about the most at risk items that should be the subject of further quality evaluation or assessment (see details below);
- This model includes a framework for risk management for pharmaceutical quality which should contribute in more consistent and science-based decision-making;
- It will support the establishment and vision of quality related practices, guidelines, requirements and standards regarding the testing scheme of medicines in PMS system.

5.2 Model building process

In all risk identification procedures the core concept is the prioritization of large number of risk scenarios according to their individual contributions to the overall system risk (Yacov & others, 2002). According to that the basic assumptions in this model were developed based on the results generated from different components of this research. Besides that, the researchers utilized other data from different sources to estimate the overall risk probability. The following factors were considered in estimating the *severity of risk* of each category of products:

1. *Therapeutic groups*
2. *Dosage forms*
3. *Manufacturing origins*

1. **Therapeutic groups**: the following data was used to rank the risk associated with different therapeutic groups
    a) Feedback from health professionals about the probability of finding more items with quality/efficacy problems in these groups; (research)
    b) Feedback from health professionals about prioritization of these groups in contrast to other groups; (research)
    c) The statistics about physical problems have been experiences by the health professionals; (research)
    d) Statistics about the registered items in Sudan; (NMPB)
    e) Statistic about recalled medicines; (NMPB)
    f) Statistics about revoked medicines; (NMPB)
    g) The final selection of medicines under this research; (research)
    h) Outcomes from different tests and experiments; (research)

    Note: All of these were generated from the previous parts of this research (research); in addition to other sources of data from currently published reports by the "NMPB".

2. **Dosage forms**: the following data was used to rank the dosage forms
    - The statistics about physical problems have been experiences by the health professionals; (research)
    - Statistics about the registered items in Sudan; (NMPB)
    - Statistic about recalled medicines; (NMPB)

- Statistics about revoked medicines; (NMPB)
- The final selection of medicines under this research; (research)
- Outcomes from different tests and experiments; (research)

Note: All of these were generated from the previous parts of this research (research) in addition to other sources of data from currently published reports by the "NMPB".

3. **Manufacturing origins**: the following data was used to rank the origins of medicines
   - Feedback from health professionals about probability of finding items with quality/efficacy problems from certain origins; (research)
   - Feedback from health professionals about shifting practices of products cross different origins; (research)
   - The statistics about physical problems have been experiences by the health professionals; (research)
   - Statistics about the registered items in Sudan; (NMPB)
   - Statistic about recalled medicines; (NMPB)
   - Statistics about revoked medicines; (NMPB)
   - The final selection of medicines under this research; (research)
   - Outcomes from different tests and experiments; (research)

Note: All of these were generated from the previous parts of this research (research) in addition to other sources of data from currently published reports by the "NMPB".

To generate the probabilities related to the severity of risks for these 3 variables, the calculations were built on the weighting methods against the total of events reported under each variable considered (excel sheet for calculations in annex XXX).

The following are the outcome of this process:

Therapeutic groups	Probabilities
Infections	0.376
Respiratory system	0.144
Cardiovascular system	0.119
Nutrition and blood	0.091
Endocrine system	0.077
Central nervous system	0.035
Gastro-intestinal system	0.035
Obstetrics, gynaecology, and urinary-tract disorders	0.013

Note: since no data available for the other therapeutic groups they were excluded from this process.

Dosage form	Probabilities
Solid oral	0.756
other large liquid	0.136
Parenteral	0.080
Liquid oral	0.011
Topical	0.006

Origins	Probabilities
Local	0.374
Low&mid income countries	0.373
high income countries	0.254

Note: results didn't showed big differences between products produced locally or in low/middle income countries

In addition to these factors, it was fundamental in this process to consider the impact of identified risks on the public health. Since this was difficult without a precise data, it was decided to consider the "**consumption rate**" of the products as indicator for harm that may result from each product. Based on this, products with high consumption rate expected to entail more harm than products with low consumption rate. In this regard the eighty-twenty

rule (80:20) was applied (Juran, 1970). The concept is simple, 20% of registered items expected to have 80% of the market share and accordingly the expected harm represented by this ration.

After obtaining these outcomes, the same approach was applied in large scale decision tree (trail) that considered the different possible categories from the combinations of the 4 factors. The output of this process provides the primary data for the descriptive model. Then the Risk Ranking and Filtering technique was used to obtain the final outcomes of the model and this technique was found very useful to obtain the final results (MTC, 2010). The statistical package used for this process was the Cumulative Sum Charts "ISO-7871" (ISO, 1997). The results of this process generate the model that could be used to support the decision making to select specifically targeted medicines for quality checks based on the anticipated risks (detailed model in annex XXX).

5.3 Main outcomes of this model

From the model we can notice the following:

1. There are 360 different possible categories of products could be targeted for any quality monitoring scheme;
2. The final selection of medicines for evaluation in this research found to be within the first 64 categories (this represents 17.5% of the total). Even more, all of the items that were not complied with reference standards rest within the first 44 categories (it represents 11.20% of the total);

3. From the outcomes below, we can see the huge difference between the top five and the bottom five. In fact the probabilities in the first category are 21,400 times higher than the least group;
4. The top 52 categories represents about 80% of the whole probabilities in the model (i.e. by targeting these categories of medicines it may include 80% of the possibly low quality products);
5. The following showed the main features and outcomes of the model:

Top five categories with highest probabilities

Therapeutic groups	Dosage form	Origin	Consumption	Rank
Infections	solid-oral	Local	high consumption	8.505
Infections	solid-oral	Low&mid income countries	high consumption	8.482
Infections	solid-oral	high income countries	high consumption	5.776
Respiratory system	solid-oral	Local	high consumption	3.257
Respiratory system	solid-oral	Low&mid income countries	high consumption	3.249

Least five categories with the lowest probabilities

Therapeutic groups	Dosage form	Origin	Consumption	Rank
Obs, gyn and UT disorders	Other	high income countries	low consumption	0.001
Skin	topical	high income countries	low consumption	0.001
Obs, gyn and UT disorders*	topical	Local	low consumption	0.001
Obs, gyn and UT disorders	topical	Low&mid income countries	low consumption	0.001
Obs, gyn and UT disorders	topical	high income countries	low consumption	0.001

* Obstetrics, gynecology, and urinary-tract disorders

5.4 Statistical analysis of the outcomes

The outcomes analysis showed considerable diversity of its main statistical tests (correlation and significance). The following table summarizes these relations:

Correlations

		Risk	Summery
Risk	Pearson Correlation	1	.360
	Sig. (2-tailed)		.001
Summery	Pearson Correlation	.360	1
	Sig. (2-tailed)	.001	

This summery showed moderate correlation relationship between the anticipated risk of medicines category and the possibility of detecting (at least one) low quality product in that group. The summery also showed that when the risk increased, there is proportional increase of detected that product. Still there are some limitations of this model (based on this statistics). This includes the following:

1. Data about the outcome summery are very limited in number as only 40 results (outcomes) were used in this model. Nevertheless it also showed positive and relatively significant correlation factor as indicated above. Using more data in the future from the routine testing process should confirm the significance of using this model;
2. The model gives same weight for all factors under analysis (therapeutic groups, dosages ...etc) and doesn't consider its importance against each other (its weights). This is relatively an advance step in improving this model and it should be completed when more data is available

6 - Usefulness of this model and approach

The model provided scientific approach in checking the quality of pharmaceuticals circulated in the market. The proposed scheme to expand the quality/efficacy checks of medicines proven to be a useful strategy to ensure the availability of effective products and of good quality. This is new approach and it will help the decision-makers in a resources limited settings, in which it is well understood the challenges to make choices, to support their decisions.

By applying this approach the following factors need to be considered critically:

1. The market profiles of selected medicines is key determinant for the final selection;
2. The capacity of the quality control laboratories as it is critical to inform the selection process and the final decisions about the number to be picked under each category of products;
3. The availability of adequate financial resources at different levels of the system will limit the way by which the model is applied

Based on all of these points raised about this model we can see the usefulness of this proposed approach in the following aspects:

6.1 Selection decisions of medicines for quality/efficacy checks

The selection of products to be included in each annual programme should be based on rigorous criteria that maximize the outcomes of the testing and evaluation process. Based on this model the following selection protocol was proposed to be applied by the “NMPB”:

1. After the determination of the capacity of the authorized laboratories, the annual plan for testing/evaluation should consider the ranking of different categories. The selection of products for inclusion in any annual plans will be related to categories those ranked highest on the list at the time the products are selected, which is usually done in preceding year;
2. The selection mechanism may be done through two possible approaches:
   - Starting to target the categories of products one by one depends on its rank; or
   - Distributing the products in each month based on the weight of its categories (but again based on its rank)
3. If two categories were similar in their expected risk probabilities we can use either outranking technique or even swap technique (known statistical methods);
4. Products eligible for this selection process should be authorized at least two years prior to its selection. This will ensure that the product completed the distribution phase of its “product life” and the feedback from the system is sufficient for its inclusion;
5. Consideration should be made for products that authorized more than two years ago but which have never been tested. This indicate its market status (was not actually marketed) and it should be excluded;

6. The selection of products for inclusion in the annual plan that based on the proposed risk ranking should at least make up to 90% of the total targeted products. The remaining 10% may be allocated at random chance from the other categories outside the model. This will depend on the capacity of the authorized laboratories;
7. The selection process should consider different information that gathered from different sources to inform the evaluation plans. This include the following:
    a) Experts' opinion should be considered. For example the regular meeting of states inspectors plus the establishment of advisory group for quality monitoring that give its advice on the main test parameters in the product specifications;
    b) Health priorities in the country from the routine morbidity and mortality data;
    c) Bioequivalence information about the products (Midha & others, 2005);
    d) Market information about the product including its distribution pattern;
    e) Health and safety information about the product that indicate its impact on public health;
    f) Quality problems experienced in other countries and disseminated by the relevant authorities;
    g) The classification of medicines whether it is essential or not (based on the National Essential Drug List);
    h) The status of the remaining shelf life of selected products and if that is known to affect the outcomes of the testing/evaluation;
8. Sampling sites should be selected based on evidences about the structure of distribution channel in the country as two previous studied in Sudan provided important data about the vulnerability of different parts of the distribution system in

the country (Gamil, 2008). This should consider the climatic conditions, the equal share of sampling load between states, availability of targeted product/batch, size of the market, the clinical use of the product , etc;

9. As it was shown before, using questionnaire based-sampling of products this should provide more in-depth understanding of the samples collected and other related/associated factors;
10. Information should be sent in advanced to selected sampling sites to confirm the availability and the market status of targeted products and this could be done using any sort of data collection tool (i.e. questionnaires);
11. In addition to this process, the experience from other countries as we discussed before, may help to improve the system:
    i. In Australia complementary medicines and non-prescription drugs were routinely examined based on the pharmacovigilance reports obtained from the field
    ii. In Cyprus products containing sensitive substances, products used for serious diseases and generic products posing interchangeability problems were considered as the primary targets for the system;
    iii. In Cuba the PMS focuses on samples collected from manufacturers in connection with GMP inspection, rather than on samples collected directly from the "market based on the limited capacity of the quality control laboratory

6.2 Detection rate

As it was discussed before the adverse event the model tried to avoid in this case is the failure to identify a non-satisfactory testing outcome of the products (in other terms filature to detect the substandard drug). Accordingly, the other main use of this model is to maximize the possibility of identifying such product. As it was seen before, by apply this model practically the possibility of detecting 80% of low quality products will increased if the program focused on testing the firs categories of the model. In other terms 11% of the registered products represent the main source of substandard medicines in the system. This is significant finding and it could help the authorities to increase the detection rate of these low quality products.

In this regard, we should appreciate the role of the active surveillance in increasing the detection rate of these products. The proposed expansion of PMS system was built on this concept. By having more dynamic and active surveillance this will enable the interaction between different part of the system. The information system will become more able to indicate the potential problems and cases that may involve low quality products. The other advantage of this active approach is the involvement of health professionals in efforts to compact the problem of substandard medicines.

With no doubt, health care professionals are the major partners with potential importance and roles in improving the detection of substandard medicines. Since this category is well

oriented and educated about this problem, they should be essential part of any solution. This will add additional value for appreciating the detection of these medicines before it reaches the patients.

6.3 Improving the effectiveness of the system

The impact of substandard medicines on public health, resources utilization and its economic impacts all of these drives the need for such kind of interventions and innovations. The model provide good tool that help the development of effective plans that aim to compact this problem and decrease its effects on public health. This approach was considered effective for many reasons as it will assist in allocating the resources and in prioritization of the activities. Besides that, the model will help in creating optimal and cost-effective scheme for monitoring the quality/efficacy of pharmaceutical products.

To judge whether or not any system is effective or not, we should evaluate the system against its objectives and whether or not these we achieved. Although the hypothesis about the linkages between the model outcomes and the inputs need to be further studies, the model indicate the possibility to improve the PMS system as shown above regarding the selection process and the detection rate.

It will be highly recommended to observe the results of applying this approach after at least 5 years lifespan, as adequate data will be generated to develop more strong predictability tool to detect the possibility of getting certain results. The range of results and the outcomes anticipated from these results could inform more how the system dynamic showed directions and trends of risks. When analyzing the results from the findings, and its

associated factors, this should be very helpful for better understanding of the system. This includes results about products that complied with specifications, products associated with minor issues been identified, products found a out of specification and problems represent critical health risks.

As it was discussed above, the proposed system will help the relevant authorities to respond effectively to the concerns about the quality from different sources. This is important as the issue of low quality medicines is of interest for different parties including the consumers as it affects their cure and it has cost implications. The prescribers will be interested of effective system as low quality products affect their patient trust and their expected clinical outcomes. Besides that, the pharmaceutical companies will be concerned about the system as they are considering very much the reputation of their companies and the general trust on their products. Finally, the governments will highly appreciate effective stress in order to ensure the protection of public health and prevention of increased public expenditure for drugs (USP, 2004), (Bennett & others, 1999).

Conclusion

- This research ended by creating a risk-based model of Post marketing Surveillance System “PMS”;
- The proposed model aimed to improve the way the quality of medicines could be monitored. It is useful approach as it considered the risks associated with detecting low quality products;
- The model will enable the authorities to develop and apply dynamic and active approach in tracing the quality and efficacy problems in circulated products in the market;
- The experiments and sub-studies done under this research contributed significantly to strength the justifications for applying this model in this area. Compared to the conventional model of PMS, this model is cost-effective approach need to be considered in a resource limited settings in the developing countries;
- The application of this model will not be effective without the active involvement of health professionals form the healthcare field. This involvement will strengthen the outcomes of the model and at the same time it will help the implementing bodies to improve the model if the future;
- This research is small scale project and due to that still there are some limitations identified in its development. Still the findings showed statistically significant outcomes for measures to improve the PMS system;
- Further research and development efforts in this area need to be done in the future.

Recommendations

1. “NMPB” may consider the application of the proposed model for quality risk management in the practical field in the upcoming year to improve the post marketing system as key part of medicines regulation;
2. Implementation of medicines selection protocol proposed by this study to improve the outcomes of PMS system and to increase the detection rate of low quality medicines;
3. Development/enforcement of routine passive and active surveillance that bring more data about quality from different sources;
4. “NMPB” should consider the improvement of drug monitoring information systems as priority step. These systems should be able to track more problems in different levels;
5. Development of national database as central component for medicines quality management information system to support the formulation of strategic policy and plan to contain the incidence of low quality medicines;
6. “NMPB” should build strong relations with health professionals and should strength the communication and feedback systems with them;
7. Responsible authorities should develop practical mechanism to monitor the use of antimicrobial agents and the level of antimicrobial resistance in all relevant sectors;
8. Re-evaluating the outcomes of this model a 5 years after its implementation to assess its effectiveness and the improvement plan;
9. Expanding the PMS to check the quality and efficacy beyond the physiochemical analysis to include more tests including microbiological assay, bioassay, bioequivalence studies, minilabs, dissolution test, etc as routine tests.

10. Strengthening the capacity of National Quality Control Laboratory to implement the proposed expansion plan of PMS by securing additional resources in terms of human resources, capacity building programs, financial support and adequate workplace;
11. Development of educational programs targeting health professionals regarding the management of low quality medicines including substandard and counterfeit products.
12. Doctors and pharmacists should report more about the medicines they deal with and they should become the vigilant channels for counterfeit/substandard drugs;
13. "NMPB" or other relevant bodies should improve information dissemination to help in educating the consumers to be a part of medicines quality management channels;
14. Conduction of in-depth studies about the use of Amoxicillin inside and outside the health system in Sudan;
15. Further research is needed to assess the capacity of medicines regulatory system to identify the gaps that affect the detection of substandard medicines before and after entering the market and to develop an action plan to address these gaps;
16. More operational researches needed to determine the most effective regulatory mechanisms to reduce the circulation of substandard drugs in order to reduce the harm from substandard drugs

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Annexes

Annex 1: Pharmacists questionnaire

بسم الله الرحمن الرحيم

Questionnaire on Medicines Quality for pharmacists

Date……..	City: ……..…….……
State:-…….……	Province:-…….……
Area Type:-……..…….……..	
Code:-…….……	
Pharmacy name (optional):-……...……..	
Information provider:- □ Pharmacist □ assistant □ other	
Data collector:-…….……..	

Substandard Medicines:-

That are medicines not comply with the specifications including the active ingredient content

هي الادوية التي تعتبر غير مطابقة للمواصفات بما فيها محتوى المادة الفعالة

1. Did you think that there is problem of substandard (low quality) medicines found in the medicines market in Sudan?

☐ *Yes* ☐ *No* ☐ *No comments*

2. Did you think that it is major or minor problem?

☐ *Major* ☐ *Minor*

3. Did you deal with patients Complaints for ineffective medicines(s)?

☐ *Yes* ☐ *No*

4. If yes, did you think that the problem in the medicine itself or in the administration method (dosing, time, food interaction, etc)?

☐ *Majority in medicine itself* ☐ *Majority in Administration method*

5. What are the common Complaints did you receive?

☐ *Symptoms not relieved* ☐ *Side effects* ☐ *physical appearance*

☐ *Alternative medicine* ☐ *All of these* ☐ *other*

6. What are the common medicine(s) that you have experienced patient(s) Complaints:-

Generic name……

Trade Name……

Company/Source……

7. Did you think that this company have quality problem regarding its remaining range of products?

☐ *Yes* ☐ *No* ☐ *No comments*

8. Did you deal with medicine(s) have been physically changed?

☐ *Yes* ☐ *No*

9. If yes, what are the medicines if you experienced these?

Generic	Dosage Form	Changes	Notes Source

10. Did you have experience in shifting patient(s) from one product to another product (for same generic) because of uncontrolled patient(s) symptoms or complaints?

☐ *Yes* ☐ *No*

11. If yes, in this case(s) what is the:

Case (1):-

	Patient was on	Alternative	Your comment
Generic name			
Trade Name			
Company			

- If the locally manufactured drug is available in the market did you recommend it for the patient in this case?

  ☐ *Yes* ☐ *No*

Case (2):-

	Patient was on	Alternative	Your comment
Generic name			
Trade Name			
Company			

- If the locally manufactured drug is available in the market did you recommend it for the patient in this case?

  ☐ *Yes* ☐ *No*

12. Did you experienced if any: (your own observations) and/or (patients compliance) and/or (doctors comments) and/or (other college pharmacists) about the quality of the following generics regardless the trade name:-

* choose the number(s)

1- Your own observations 2- Patients compliance

3- Doctors comments 4- Other college pharmacists

Generics		Yes	No	If yes from *
21.	**Amoxicillin susp/cap**			
22.	**Ampiclox inj**			
23.	**Artesonate**			
24.	**Aspirin**			
25.	**Atenolol tab**			
26.	**Carbimazole tab**			
27.	**Cefuroxime sodium inj**			
28.	**Chloramphenicol cap/tab**			
29.	**Chlorpheniramine**			
30.	**Ciprofloxacin tab**			
31.	**Co- trimoxazole**			
32.	**Digoxin inj/tab**			
33.	**Ethinylestradiol/levonorgestrel**			
34.	**Furosemide**			
35.	**Glibenclamide tab**			

36.	**Hydrocortisone**			
37.	**Mefenamic Acid**			
38.	**Metronidazole susp/tab**			
39.	**Nifedipine**			
40.	**Paracetamol**			

13. From your experience what are the pharmacological groups (name 3) did you think that it should be monitored continually for its quality and you think that there are some problems in its medicines?

Groups	Yes	Why
Gastro-intestinal drugs		
Cardiovascular drugs		
Respiratory drugs		
Central Nervous system drugs		
Anti-infections drugs		
Urinary tract drugs		
Dermatological preparations		
Nutrition and blood preparations		
Obstetrics & gynecological drugs		

14. Is the Drug Safety poster from pharmacy directorate availability?

☐ *Yes* ☐ *No*

15. Are you familiar with the post marketing surveillance system in directorate of pharmacy?

☐ *Yes* ☐ *No* ☐ *No comments*

16. If yes, what is your comment upon the efficacy of the system to monitor drugs quality?

☐ *Very effective* ☐ *partially effective* ☐ *not effective*

17. Did you notify or report any compliance about drugs quality to the directorate of pharmacy?

☐ *Yes* ☐ *No* ☐ *No comments*

18. If yes, what is the response did you find in this case if any?

……....

……..

19. Did you deal with recall process done by one of the private companies (itself) in the market because of quality problems?

☐ *Yes* ☐ *No* ☐ *No comments*

20. If yes in this case what is the:-

Generic name……...

Trade Name……..

Company……...

Batch No……

21. Did this process is based on written letter from pharmacy directorate or just the company just recalls it by its self?

☐ *With* written letter ☐ *Without* written letter ☐ *No comments*

22. "The cheap item considerably of less in quality than the expensive item for the same generic", how did you evaluate this?

☐ *yes, always true* ☐ *yes, but not always* ☐ *not true*

23. How did you evaluate the following assuming all are available:-

Product type	*Good quality*	*Low quality*
The Innovator Brand name for generic		
Generic product from high income country for the same generic		
Generic product from low income country for the same generic		
Generic product Locally produced in Sudan for the same generic		

Annex 2: Doctors questionnaire

بسم الله الرحمن الرحيم

Questionnaire on Drugs Quality - Doctors

ظلت الادوية المتدنية الجودة (Low Quality) ومدى تواجدها في السودان هاجساً يؤرق جميع العاملين في الحقل الطبي وخاصة الاطباء، هذا الاستبيان يهدف الي تجميع معلومات حول اراء العاملين في الحقل الطبي (اطباء، صيادلة ومساعدين فنيين) في هذا الموضوع وذلك ضمن دراسة لنيل درجة الماجستير. ومع فائق الاحترام نقدر لك مساهمتك بالرائ في هذه القضية من خلال الاجابة علي هذا الاستبيان.

Information provider:- □ Specialist □ Registrar □ General Physician

☐ I am sorry I couldn't respond to this questionnaire

1. **Do you think there is a problem of low quality (substandard) drugs found in the drugs market in Sudan?**

   □ *Yes* ☐ *No* ☐ *No comments*

2. **Do you think that it is major or minor problem?**

   ☐ *Major* ☐ *Minor*

3. **Do you experience therapeutic failure with some patients?**

   ☐ *Yes always* ☐ *Not always* ☐ *No*

4. **If happened, do you think that the failure is due to the subjects' variability or due to the quality of medicines?**

   ☐ *Majority due to **subjects' variability*** ☐ *Majority due to **drugs quality***

What is the drug in this case (as example):-

Generic Name……..

5. **For you substandard drugs:**

☐*Prolong your patients' illness* ☐ *Yes* ☐ *No*

☐ *Additional cost for your patients* ☐ *Yes* ☐ *No*

☐ *Could be contributed to drugs resistance* ☐ *Yes* ☐ *No*

☐*Decrease your patients trust on your practice* ☐ *Yes* ☐ *No*

☐ *Could lead to patient death* ☐ *Yes* ☐ *No*

☐ *All of these*

☐ *None of these*

6. Comparably where did you think that the effect of substandard medicines will be worse in case of…..

☐ *Over the Counter Drugs (**OTC**)* **OR** ☐ *Prescribed Drugs (**Rx**)*

7. Are you sometimes insisting to prescribe certain trade names of drugs for the patients?

☐ *Yes* ☐ *No* ☐ *No comments*

8. If yes, the reason is?

☐ *Success experience with those trades* ☐*Price considerations*

☐ *Failure experience with other trades* ☐ *Other……..*

9. Did you have experience in shifting patient(s) from one product to another product (for same generic) because of uncontrolled patient(s) symptoms? ☐ *Yes* ☐ *No*

10. If yes, in this case(s) what is the:

	Patient was on	Alternative	Your comment
Trade name			

11. Assuming that the locally produced drug is available in the market, did you recommend it for the patient in this case?

☐ *Yes* ☐ *No*

12. "The cheap item considerably of less in quality than the expensive item for the same generic", how did you evaluate this?

☐ *yes, always true* ☐ *yes, but not always* ☐ *not true*

13. Is it valid that for your patients **"available low quality drug is better than that drug is not available at all"?**

☐ *Yes* ☐ *No* ☐ *Some times it is true*

14. Did you think that drugs should be recalled (withdrawal) from the market due to the following reasons?

☐*Chemical problems (active and in-active contents problems)* ☐ *Yes* ☐ *No*

☐*Changes in color* ☐ *Yes* ☐ *No*

☐*Fracture of tablets or capsules* ☐ *Yes* ☐ *No*

☐*Repeated doctors and or patients complaints* ☐ *Yes* ☐ *No*

15. Did you some times consult pharmacists about their view on the quality of certain drugs you want to prescribe?

☐ *Yes* ☐ *No*

16. Did you have any observations and/or patients complaints about the quality of the following generics regardless the trade name:-

Generics		Yes	No
41.	**Amoxicillin susp/cap**		
42.	**Ampiclox**		
43.	**Artesunate**		

44.	**Aspirin**		
45.	**Atenolol tab**		
46.	**Carbimazole tab**		
47.	**Cefuroxime sodium inj**		
48.	**Chloramphenicol cap/tab**		
49.	**Chlorpheniramine**		
50.	**Ciprofloxacin tab**		
51.	**Co- trimoxazole**		
52.	**Digoxin inj/tab**		
53.	**Ethinylestradiol/levonorgestrel**		
54.	**Furosemide**		
55.	**Glibenclamide tab**		
56.	**Hydrocortisone**		
57.	**Mefenamic Acid**		
58.	**Metronidazole susp/tab**		
59.	**Nifedipine**		
60.	**Paracetamol**		
61.			
62.			

Other medicines you note its problem

17. How did you evaluate the following assuming all are available:-

Product type	***Good quality***	***Low quality***
Original **Brand name** (international Companies)		
Generic product from **high income** countries		
Generic product from **low income** countries		
Generic product **Locally produced** in Sudan		

18. Did you notify or report any compliance about drugs safety or quality for any regularity body?

☐ *Yes* ☐ *No*

19. If yes; what is the drug, the problem and response in this case?

Drug	***Problem***	***Response***

Annex 3: Pilot study results

Substandard Medicines Study in Sudan

Pilot Study – Outcomes summary

The objectives of the Summery report:-

1. To identify the suitability of the proposed questionnaires to collect the needed data regarding the health workers directly deals with medicines (opinions in marketed medicines).
2. To identify the most appropriate methodology of data selection and sample identification and presentation.

- The pilot study was done in 10 private pharmacies in Khartoum locality and the sample was divided into the following categories:

Category	Type	No of pharmacies
Private pharmacy	Housing Area	**5**
Private pharmacy	Private Hospitals	**2**
Private pharmacy	Near Hospitals OR Doctors Clinics	**3**

- There is suggestion to include the public health facilities pharmacies in the survey but there are some problems especially in the criteria to select and whether this will affect the results or not.

Some notes from the pilot study:

1. There is some questions need to be reformulated to be clear (Q6, Q7)
2. There is need to introduce question about the observations of the pharmacists regarding the physical changes in medicines that they have been experienced in their work.
3. Doctor survey is seems to be difficult unless there is defined target doctors and the strategy to get access to them.
4. There is need to introduce the option of no comments in some answers options (Q6).
5. For deep analysis what type of data need to be concentrate on it?
6. To eliminate some of surveyed medicines and introduce another ones (e.g. Artesunate + Nifedipine + Some injectables).

Results:

This is only simple analysis for questions response without any interpretations of data or deep analysis:

Q1: The existence of substandard medicines in Sudan:-

Yes	90%
No	10%

Q2: To what extend:-

Major	22%
Minor	88%

Q3: Patient compliance of non effective medicine:-

Yes	100%
No	0

Q4: In his opinion the problem is in……

Drug itself	25%
Administration method	75%

Q5: What are the medicines in this case?

Medicines	Source	Type of pharmacy	Times
Amoxicillin	Sudan	Near Doctors Clinics	2
Amoxicillin	CMS	Housing Area	2
Artesunate	CMS	Near Hospital	1
Ciprofloxacin	India	Housing Area	1
Nifedipine	Lebanon	Private Hospital	1
Ibuprofen	India	Housing Area	1
Erythromycin	Sudan	Housing Area	1
Azithromycin	Jordan	Housing Area	1
Glibenclamide	Sudan	Private Hospital	1

Q6: The comment on the company products if have another quality problem:

Yes	33%
No	67%

Q7: Opinion evaluation regarding sources of medicines:

Product Type	Good Quality	Low Quality
Innovator Brand	10%	Zero
Generic from **High Income** countries	100%	Zero
Generic from **Low Income** countries	30%	70%
Generic **Locally** produced	50%	50%

Q8: Replacing generic from brand X to brand Y:

Yes	90%
No	10%

Q9A: Cases representing answer of Q8:-

Generic	Brand X	Source	Brand Y	Source
Amoxicillin	GMC	Sudan	Amipharma	Sudan
Amoxicillin	CMS	-	Amipharma	Sudan
Amoxicillin	Amipharma	Sudan	Clavox	KSA
Ceftrixone	CMS	-	Hikma	Jordan
Cephalexin	Shangahi	Sudan	Luka	India
Simvastatin	Blue Nile	Sudan	Pharmaline	Lebanon
Glibenclamide	Elie	Sudan	Euglycon	UK
Erythromycin	CMS	-	Amipharma	Sudan
Ciprofloxacin	-	Sudan	Mepha	Switzerland
Ciprofloxacin	-	India	Hikma	Jordan
Omeprazole	Gasec	UAE	Losec	Switzerland
Amilodipine	-	India	-	Egypt

Q9B: Suggesting the locally produced medicine as alternative:

Yes	58%
No	42%

Q10: Experience regarding quality problems:-

1- His own observations 2- Patients compliance

3- Doctors comments 4- other college pharmacists

Generics		Yes	Sources
63.	**Amoxicillin**	80%	2 – 4 – 1
64.	**Metronidazole**	70%	2 – 1
65.	**Paracetamol**	70%	1 - 2
66.	**Ceftrixone sodium**	60%	3
67.	**Ciprofloxacin tab**	60%	
68.	**Glibenclamide tab**	60%	3 - 2 - 4
69.	**Carbimazole tab**	40%	
70.	**Aspirin**	30%	2
71.	**Aminophyllin inj**	10%	
72.	**Ampiclox**	10%	
73.	**Atenolol tab**	10%	
74.	**Benzyl penicillin inj**	10%	
75.	**Digoxin inj/tab**	10%	
76.	**Adrenaline inj**	Zero	
77.	**Chloramphenicol oral**	Zero	
78.	**Chloramphenicol inj**	Zero	
79.	**Ferrous Sulphate**	Zero	
80.	**Gentamicin inj**	Zero	
81.	**Hydrocortisone inj**	Zero	
82.	**Methyl Ergometrine inj**	Zero	

Q11: Pharmacological groups in priorities:

Groups	Yes
Cardiovascular drugs	80%
Central Nervous system drugs	60%
Anti-infections drugs	50%
Gastro-intestinal drugs	30%
Respiratory drugs	30%
Nutrition and blood preparations	30%
Urinary tract drugs	20%
Dermatological preparations	0
Obstetrics & gynecological drugs	0

Q12: Post marketing Surveillance system awareness:

Yes	40%
No	60%

Q13: If aware, his opinion:-

Very effective	40%
partially effective	50%
Not effective	10%

Q14: "The cheap item considerably of less in quality than the expensive item for the same generic":-

yes, always true	10%
yes, but not always	60%
not true	30%

Q15: Report or compliance to pharmacy directorate:-

Yes	30%
No	70%

Q16: If yes, what is the medicines and what is the response:-

Medicines	Response
Ibuprofen	Not formal reporting
Seven Seas	Not formal reporting

Q17: Dealing with company recall process:

Yes	70%
No	30%

Q18: What is the cases:-

Generic	Trade	Company
Multivitamin	Vitamax	GSK
Vitamin B6	-	SPIC / Dar Eldoa
Carbamazepine	Epistron	Siho
-	Botelium	Mepha
Cough Syrup	Sedofan	Julphar
Promethazine	-	(Jordan)
Sildenafil	Agiel	

Annex 4: Samples information form

1- General & Primary Information
Date of collection…… ……
Area: □ Khartoum Hospital street pharmacies. □ Center of Khartoum pharmacies. □ East areas pharmacies. □ South areas pharmacies. □ Peripheral
Field of samples □ Near Hospital □ Household Retail pharmacy
Sample code……..
Company code……..
Medicine trade name code……..
Medicine generic name……..
Concentration……..
Dosage form □ Tablet □ Capsule □ Injection □ Suspension □ Syrup
Pharmacological group……..
Batch No……..
Date of receiving from the supplier……..
Manufacturing date……..
Expiration date……..
The remaining shelf-life at time of receiving……..
Quantity collected/units……..

Retail price in SDG……..

2- Other Information
Source of origin:- □ Multinational company □ High income country □ Low income country □ Local
Did the manufacturer have GMP certificate □ Yes □ N0
Number of other products register for this company……..
Registered Shelf life in Drug Regulatory Authority……..
Did this product subjected to shelf life expansion □ Yes □ N0
Did his batch subjected to pre-marketing test □ Yes □ N0
Did The government lab satisfy before distribution □ Yes □ N0
Did his batch subjected to post-marketing test □ Yes □ N0
Did product available in other form/concentration □ Yes □ N0 ……..
Date of importation……
Mean of importation □ By Air □ By Sea
Imported quantity/units in 2007……..
Product share in the market……..
Did this medicine on the national essential list □ Yes □ N0
Number of competitors (Foreign…….. Local……..)
Medicine Classification □ OTC □ Prescription

3- Storage form
Manufacturer storage condition: …… ……
Brief physical/visual description before storage: …… ……
Date of storing in the laboratory……
Starting Date for analysis……
Storage period……

Annex 5: Distribution of private retail pharmacies in Khartoum state

City	Administration Unit	Total number		% of the Total	
		Per Unit	Per City	Per Unit	Per City
Khartoum	Khartoum – Center	162	328	20	41%
	Khartoum – East	47		6	
	El Shohada – Soba	42		5	
	El Azhari	14		2	
	El Nasser	13		2	
	El Kalaklat	50		6	
Khartoum Bahri	Bahri	87	179	11	23%
	Bahri North	22		3	
	Eastern Nile	70		9	
Omdurman	Omdurman	131	282	1	36%
	Sothern City site	6		6	
	El Bokaa	46		3	
	El Ameer	27		3	
	El Thora	23		6	
	Karari	49		17	

Annex 6: Trade products selection process

Generic: Acetylsalicylic Acid **Concentration: 300 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
1.	**Aspicima**	Abd El Munim	Sudan	Local	Yes	Yes/+
2.	**Citypirin Adult**	City Pharma	Sudan	Local	No	Yes/+
3.	**Asprimax**	Climax	Sudan	Local	No	No
4.	**Eliprin**	Elie	Sudan	Local	No	No
5.	**Cafalgin Adult**	Humavite	Sudan	Local	No	No
6.	**Marwaprin**	Marwa	Sudan	Local	No	No
7.	**Samfpirin**	Salah	Sudan	Local	Yes	Yes/+
8.	**Asadin**	Chemical	Sudan	Local	No	No
9.	**Aspruna**	-	Sudan	Local	No	Yes/+
10.	**Aspro**	Bodrian	Kenya	Low income	No	No
11.	**Aspicot**	kerkisawi	Lebanon	Low income	No	Yes/-
12.	**Aspirin**	Development	Germany	High income	Yes	No

Mostly used (rows 1–2)

Mostly used (row 12)

Generic: Amoxicillin Trihydrate **Concentration: 500 mg Capsule**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
1.	**Cimoxil**	Abd Al Momin	Sudan	Local	Yes	No
2.	**Amixillin**	Amipharma	Sudan	Local	Yes	Yes/+
3.	**Epoxil**	Elie	Sudan	Local	Yes	No
4.	**Tauxil**	Sigma-Tau	Sudan	Local	Yes	No
5.	**Wafraxil**	Wafra	Sudan	Local	Yes	No
6.	**Amoxonil**	Shifa	Sudan	Local	Yes	No
7.	**G.M Amoxicillin**	GMC	Sudan	Local	Yes	No
8.	**Hipen**	Salmawit	India	Low income	Yes	Yes/+
9.	**Aramoxyl**	Samhar	Syria	Low income	Yes	No
10.	**Lamoxy**	Badr	India	Low income	Yes	No
11.	**Amoxydar Forte**	Kambal	Jordan	Lower-middle-income	No	No
12.	**Amoxicap**	-	Malaysia	Upper-middle-income	Yes	No
13.	**Moxen**	Hiba	Cyprus	High income	Yes	No
14.	**Amoxapen**	Siho	Cyprus	High income	Yes	No

Mostly used

Mostly used

Generic: Ceftriaxone sodium **Concentration: 0.5 gm Powder for injection**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
1.	**Rozifine**	Mahadi	Syria	Low income	Yes	No
2.	**Rociflex**	El Hussein	Syria	Low income	Yes	No
3.	**Onecef**	Rahma	India	Low income	No	No
4.	**Samixon**	Pharma exier	Jordan	Lower-middle-income	Yes	No
5.	**Triaxone**	Kambal	UAE	High income	Yes	No
6.	**Rocephin**	Dal	Switzerland	High income	Yes	No
7.	**Mesporin**	Nabil	Switzerland	High income	Yes	No

Mostly used

Mostly used

Generic: Chlorphenarmine Maleate **Concentration: 4 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
Most used	**1. Cimalurg**	Abd El Munim	Sudan	Local	No	No
	2. Amihistin	Amipharma	Sudan	Local	Yes	No
	3. Citramin	City Pharma	Sudan	Local	No	No
	4. Epohist	Elie	Sudan	Local	No	No
	5. Marwastine	Marwa	Sudan	Local	No	No
	6. Wafrastin	Wafra	Sudan	Local	No	No
	7. Allerfin	Pharma	Jordan	Lower-middle-income	Yes	No
Most used	**8. Istamex**	El atlanti	Greece	High income	Yes	No
	9. Chlorohistol	Kambal	UAE	High income	No	No

Generic: Ciprofloxacin **Concentration: 500 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
Most used 1.	**Amiciprox**	Amipharma	Sudan	Local	NO	Yes/+
2.	**G.M Proxal**	GMC	Sudan	Local	Yes	NO
3.	**Ciproflex**	El Hussien	Syria	Low income	NO	NO
4.	**Roxin**	Dar Dawa	Pakistan	Low income	Yes	NO
5.	**Microflox**	Fast	India	Low income	Yes	NO
6.	**Ciprobid**	Salmawit	India	Low income	Yes	NO
7.	**Ciproquin**	Omdurman	India	Low income	NO	NO
Most used 8.	**Ciprolet**	Pharma care	India	Low income	NO	Yes/+
9.	**Ciplox**	Marwaco	India	Low income	Yes	NO
10.	**Ciprodar**	Kambal	Jordan	Lower-middle-income	Yes	NO
Most used 11.	**Ciprolon**	Pharma Exier	Jordan	Lower-middle-income	Yes	Yes/+

	12.	**Ciproflox**	Pharma	Jordan	Lower-middle-income	NO	NO
	13.	**Siprobel**	Comprehensive	Turkey	Upper-middle-income	NO	NO
Most used	**14.**	**Bactiflox**	Nabil	Switzerland	High income	Yes	Yes/+
	15.	**Ciprinol**	EPICO	Slovenia	High income	Yes	NO
	16.	**Ladinin**	M&M	Greece	High income	Yes	NO

Generic: Diclofenac Sodium **Concentration: 25 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
Most used	**Amifenac**	Amipharma	Sudan	Local	NO	NO
2.	**Epofenac**	Elie	Sudan	Local	NO	NO
3.	**G.M Diclofenac**	GMC	Sudan	Local	NO	NO
4.	**Yesenac**	Shangahi	Sudan	Local	NO	NO
Mostly used	**Votrex**	Pharma Exier	Jordan	Lower-middle-income	Yes	NO
6.	**Diclogesic**	Kambal	Jordan	Lower-middle-income	Yes	NO
7.	**Olfen - 25**	Nabil	Switzerland	High income	Yes	NO
Mostly used	**Voltaren**	Siusoba	Italy	High income	Yes	NO
Mostly used	**Taks**	Mabara	Cyprus	High income	NO	NO
10.	**Remethan 25**	Siho	Cyprus	High income	Yes	NO

Generic: Glibenclamide **Concentration: 5 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
1.	**Cimanil**	Abd Munim	Sudan	Local	NO	NO
Mostly used	**Epoclamide**	Elie	Sudan	Local	NO	NO
3.	**Wafranil**	Wafra	Sudan	Local	NO	NO
Mostly used	**Glicon**	Dar Dawa	Pakistan	Low income	NO	NO
5.	**Glibamid**	Kerkisawi	Lebanon	Low income	NO	NO
6.	**Betanase**	Salmawit	India	Low income	NO	NO
7.	**Glibil**	Pharma exier	Jordan	Lower-middle-income	NO	NO
8.	**Glibesyn**	Kambal	Cyprus	High income	NO	NO
9.	**Gliban**	Mabara	Cyprus	High income	NO	NO
10.	**Glitisol 5**	Siho	Cyprus	High income	NO	NO
11.	**Euglucon**	Dal	Italy	High income	NO	NO
Mostly used	**Glibenclamide**	Dal	England	High income	NO	NO

Generic: Mefenamic Acid **Concentration: 500 mg Tablet**

		Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
Mostly used	1.	**G.M Menapon**	GMC	Sudan	Local	Yes	Yes/+
	2.	**Elifan**	Elie	Sudan	Local	Yes	NO
Mostly used	3.	**Mefnac DS**	Dar Dawa	Pakistan	Low income	Yes	Yes/+
	4.	**Pangesic Forte**	kanar	Jordan	Lower-middle-income	Yes	Yes/+
Mostly used	5.	**Fendol D.S**	Fast	Jordan	Lower-middle-income	Yes	Yes/+
	6.	**Mafepain**	Dal	KSA	High income	Yes	NO

Generic: Metronidazole **Concentration: 250 mg Tablet**

	Trade	Company	Country of Origin	Origin Classification	Available in other form	PMS
Mostly used 1.	**Aminidazole**	Amipharma	Sudan	Local	Yes	Yes/+
2.	**Epindazole**	Elie	Sudan	Local	Yes	NO
3.	**G.M Metrozal**	GMC	Sudan	Local	Yes	NO
Most used 4.	**Marwazole**	Marwa	Sudan	Local	No	NO
5.	**Yesazol**	Shangahi	Sudan	Local	No	NO
6.	**Wafrazole**	Wafra	Sudan	Local	No	NO
7.	**Metrozole**	Development	Jordan	Lower-middle-income	Yes	NO
Mostly used	**Nidazole**	Fast	Jordan	Lower-middle-income	Yes	NO
9.	**Supplin**	Arabi	Astoria	High income	No	NO

Generic: Paracetamol

Concentration: 500 mg Tablet

	Trade	Company	Country	Classification	Available in other	PMS
1.	**Amidol**	Amipharma	Sudan	Local	Yes	No
Mostly used	**Clmamol**	Climax	Sudan	Local	No	No
3.	**Elidol**	Elie	Sudan	Local	No	No
Mostly used	**Citymol**	City Pharma	Sudan	Local	No	No
5.	**G.M Paracetamol**	GMC	Sudan	Local	No	No
6.	**Humadol**	Humavite	Sudan	Local	No	No
7.	**Marwadol**	Marwa	Sudan	Local	Yes	No
8.	**Wafradol**	Wafra	Sudan	Local	Yes	No
9.	**Regamol**	Africa	India	Low income	No	No
10.	**Zerin**	Dar Dawa	Bangladesh	Low income	No	No
Mostly used	**Dolomol**	Fast	Jordan	Lower-middle-income	No	No
12.	**Ultramol**	Rahma	Syria	Low income	Yes	No
Mostly used	**Panadol**	Bodrian	Ireland	High income	Yes	No
14.	**Adol**	Kambal	UAE	High income	Yes	No

Annex 7: Plan for medicines sample collection

Package A

	Generics	Product A - High	Product B - Low	Product C - Local
1.	Amoxicillin			
2.	Paracetamol			
3.	Metronidazole			
4.	Glibenclamide			
5.	Diclofenac			

Package B

	Generics	Product A - High	Product B - Low	Product C - Local
1.	Ciprofloxacin			
2.	Mefenamic Acid			
3.	Chlorphenarmine Maleate			
4.	Aspirin			
5.	Ceftriaxone			

Annex 8: Samples analysis form

Lab wok revision

Physical			
Test	**Limits**	**Results**	**Comments**
Unit dose per container			□ The sample pass. □ The sample fails.
Description			□ The sample pass □ The sample fails.
Color and Uniformity of Color			□ The sample pass □ The sample fails.
Odor			□ The sample pass □ The sample fails.
Melting behavior			□ The sample pass □ The sample fails.

Water solubility			□ The sample pass □ The sample fails.
Chloroform solubility			□ The sample pass □ The sample fails.
Dissolution test			□ The sample pass □ The sample fails.
Disintegration test			□ The sample pass □ The sample fails.
Weight			□ The sample pass □ The sample fails.
Hardness			□ The sample pass □ The sample fails.
pH test			□ The sample pass □ The sample fails.
Optical rotation			□ The sample pass □ The sample fails.

Uniformity of dosage units			□ The sample pass □ The sample fails.
Dosage form status (Damage)			□ The sample pass □ The sample fails.
Packaging material status			□ The sample pass □ The sample fails.
Label			□ The sample pass □ The sample fails.
Presence of contamination			□ The sample pass □ The sample fails.

Chemical Tests			
Test	**Limits**	**Results**	
Identity test			□ The sample pass □ The sample fails.
%of stated concentration			□ The sample pass □ The sample fails.
Degradation			□ The sample pass □ The sample fails.
IR			□ The sample pass □ The sample fails.
TLC			□ The sample pass □ The sample fails.

Annex 9: Amoxicillin Sensitivity Study

Sample collection form

Dear colleague,

Please note that, this form and the sample as well are targeting the patients those will take Amoxicillin only as the main drug indicated for upper respiratory infections.

A am	

Annex XXX Ranking outcome

Therapeutic groups	Risk probability	Dosage form	Risk probability	Origin	Risk probability	Consumption rate	Risk probability	Overall risk	Rank
Anti	0.376	solid-oral	0.756	Local	0.374	high consumption	0.8	0.08505	8.505
Anti	0.376	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.08482	8.482
Anti	0.376	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.05776	5.776
RT	0.144	solid-oral	0.756	Local	0.374	high consumption	0.8	0.03257	3.257
RT	0.144	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.03249	3.249
CVS	0.119	solid-oral	0.756	Local	0.374	high consumption	0.8	0.02692	2.692
CVS	0.119	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.02685	2.685
RT	0.144	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.02212	2.212
Anti	0.376	solid-oral	0.756	Local	0.374	low consumption	0.2	0.02126	2.126
Anti	0.376	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.02121	2.121
NUT	0.091	solid-oral	0.756	Local	0.374	high consumption	0.8	0.02058	2.058
NUT	0.091	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.02053	2.053
MUS	0.088	solid-oral	0.756	Local	0.374	high consumption	0.8	0.01991	1.991
MUS	0.088	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.01985	1.985
CVS	0.119	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.01828	1.828
END	0.077	solid-oral	0.756	Local	0.374	high consumption	0.8	0.01742	1.742
END	0.077	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.01737	1.737
Anti	0.376	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.01530	1.530
Anti	0.376	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.01526	1.526
Anti	0.376	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.01444	1.444
NUT	0.091	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.01398	1.398
MUS	0.088	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.01352	1.352
END	0.077	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.01183	1.183
Anti	0.376	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.01039	1.039
Anti	0.376	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00900	0.900

Anti	0.376	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00898	0.898
RT	0.144	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00814	0.814
RT	0.144	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00812	0.812
GIT	0.035	solid-oral	0.756	Local	0.374	high consumption	0.8	0.00792	0.792
CNS	0.035	solid-oral	0.756	Local	0.374	high consumption	0.8	0.00792	0.792
GIT	0.035	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.00790	0.790
CNS	0.035	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.00790	0.790
CVS	0.119	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00673	0.673
CVS	0.119	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00671	0.671
Anti	0.376	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00611	0.611
RT	0.144	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00586	0.586
RT	0.144	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00584	0.584
RT	0.144	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00553	0.553
GIT	0.035	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.00538	0.538
CNS	0.035	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.00538	0.538
NUT	0.091	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00515	0.515
NUT	0.091	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00513	0.513
MUS	0.088	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00498	0.498
MUS	0.088	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00496	0.496
CVS	0.119	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00484	0.484
CVS	0.119	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00483	0.483
SKN	0.021	solid-oral	0.756	Local	0.374	high consumption	0.8	0.00475	0.475
SKN	0.021	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.00474	0.474
CVS	0.119	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00457	0.457
END	0.077	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00435	0.435
END	0.077	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00434	0.434
RT	0.144	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00398	0.398

Anti	0.376	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00382	0.382
Anti	0.376	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00381	0.381
NUT	0.091	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00370	0.370
NUT	0.091	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00369	0.369
MUS	0.088	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00358	0.358
MUS	0.088	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00357	0.357
NUT	0.091	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00349	0.349
RT	0.144	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00345	0.345
RT	0.144	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00344	0.344
MUS	0.088	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00338	0.338
CVS	0.119	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00329	0.329
SKN	0.021	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.00323	0.323
END	0.077	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00313	0.313
END	0.077	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00312	0.312
END	0.077	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00296	0.296
OBS	0.013	solid-oral	0.756	Local	0.374	high consumption	0.8	0.00294	0.294
OBS	0.013	solid-oral	0.756	Low&mid income countries	0.373	high consumption	0.8	0.00293	0.293
CVS	0.119	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00285	0.285
CVS	0.119	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00284	0.284
Anti	0.376	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00260	0.260
NUT	0.091	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00251	0.251
MUS	0.088	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00243	0.243
RT	0.144	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00234	0.234
Anti	0.376	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00225	0.225

Anti	0.376	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00224	0.224
NUT	0.091	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00218	0.218
NUT	0.091	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00217	0.217
END	0.077	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00213	0.213
MUS	0.088	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00211	0.211
MUS	0.088	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00210	0.210
OBS	0.013	solid-oral	0.756	high income countries	0.254	high consumption	0.8	0.00200	0.200
GIT	0.035	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00198	0.198
CNS	0.035	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00198	0.198
GIT	0.035	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00197	0.197
CNS	0.035	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00197	0.197
CVS	0.119	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00193	0.193
END	0.077	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00184	0.184
END	0.077	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00184	0.184
Anti	0.376	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00153	0.153
NUT	0.091	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00148	0.148
RT	0.144	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00146	0.146
RT	0.144	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00146	0.146
MUS	0.088	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00143	0.143
GIT	0.035	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00142	0.142

CNS	0.035	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00142	0.142
GIT	0.035	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00142	0.142
CNS	0.035	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00142	0.142
GIT	0.035	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00134	0.134
CNS	0.035	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00134	0.134
END	0.077	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00125	0.125
Anti	0.376	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00124	0.124
Anti	0.376	other	0.011	Local	0.374	high consumption	0.8	0.00124	0.124
Anti	0.376	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00123	0.123
Anti	0.376	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00123	0.123
CVS	0.119	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00121	0.121
CVS	0.119	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00121	0.121
SKN	0.021	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00119	0.119
SKN	0.021	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00118	0.118
RT	0.144	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00099	0.099
GIT	0.035	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00097	0.097
CNS	0.035	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00097	0.097
NUT	0.091	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00093	0.093
NUT	0.091	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00092	0.092
MUS	0.088	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00090	0.090
MUS	0.088	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00089	0.089
RT	0.144	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00086	0.086
RT	0.144	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00086	0.086

SKN	0.021	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00085	0.085
SKN	0.021	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00085	0.085
Anti	0.376	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00084	0.084
Anti	0.376	other	0.011	high income countries	0.254	high consumption	0.8	0.00084	0.084
GIT	0.035	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00084	0.084
CNS	0.035	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00084	0.084
GIT	0.035	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00084	0.084
CNS	0.035	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00084	0.084
CVS	0.119	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00082	0.082
SKN	0.021	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00081	0.081
END	0.077	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00078	0.078
END	0.077	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00078	0.078
OBS	0.013	solid-oral	0.756	Local	0.374	low consumption	0.2	0.00074	0.074
OBS	0.013	solid-oral	0.756	Low&mid income countries	0.373	low consumption	0.2	0.00073	0.073
CVS	0.119	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00071	0.071
CVS	0.119	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00071	0.071
Anti	0.376	topical	0.006	Local	0.374	high consumption	0.8	0.00067	0.067
Anti	0.376	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00067	0.067
NUT	0.091	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00063	0.063
MUS	0.088	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00061	0.061
RT	0.144	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00059	0.059
SKN	0.021	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00058	0.058

GIT	0.035	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00057	0.057
CNS	0.035	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00057	0.057
NUT	0.091	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00054	0.054
NUT	0.091	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00054	0.054
END	0.077	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00053	0.053
OBS	0.013	liquid-oral	0.136	Local	0.374	high consumption	0.8	0.00053	0.053
OBS	0.013	liquid-oral	0.136	Low&mid income countries	0.373	high consumption	0.8	0.00053	0.053
MUS	0.088	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00053	0.053
MUS	0.088	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00053	0.053
SKN	0.021	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00050	0.050
SKN	0.021	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00050	0.050
OBS	0.013	solid-oral	0.756	high income countries	0.254	low consumption	0.2	0.00050	0.050
CVS	0.119	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00048	0.048
RT	0.144	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00047	0.047
RT	0.144	other	0.011	Local	0.374	high consumption	0.8	0.00047	0.047
RT	0.144	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00047	0.047
RT	0.144	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00047	0.047
END	0.077	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00046	0.046

END	0.077	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00046	0.046
Anti	0.376	topical	0.006	high income countries	0.254	high consumption	0.8	0.00046	0.046
CVS	0.119	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00039	0.039
CVS	0.119	other	0.011	Local	0.374	high consumption	0.8	0.00039	0.039
CVS	0.119	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00039	0.039
CVS	0.119	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00039	0.039
NUT	0.091	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00037	0.037
OBS	0.013	liquid-oral	0.136	high income countries	0.254	high consumption	0.8	0.00036	0.036
MUS	0.088	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00036	0.036
GIT	0.035	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00036	0.036
CNS	0.035	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00036	0.036
GIT	0.035	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00036	0.036
CNS	0.035	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00036	0.036
SKN	0.021	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00034	0.034
RT	0.144	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00032	0.032
RT	0.144	other	0.011	high income countries	0.254	high consumption	0.8	0.00032	0.032
END	0.077	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00031	0.031
OBS	0.013	small-parenteral	0.08	Local	0.374	high consumption	0.8	0.00031	0.031
OBS	0.013	small-parenteral	0.08	Low&mid income countries	0.373	high consumption	0.8	0.00031	0.031

Anti	0.376	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00031	0.031
Anti	0.376	other	0.011	Local	0.374	low consumption	0.2	0.00031	0.031
Anti	0.376	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00031	0.031
Anti	0.376	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00031	0.031
NUT	0.091	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00030	0.030
NUT	0.091	other	0.011	Local	0.374	high consumption	0.8	0.00030	0.030
NUT	0.091	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00030	0.030
NUT	0.091	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00030	0.030
MUS	0.088	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00029	0.029
MUS	0.088	other	0.011	Local	0.374	high consumption	0.8	0.00029	0.029
MUS	0.088	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00029	0.029
MUS	0.088	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00029	0.029
CVS	0.119	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00027	0.027
CVS	0.119	other	0.011	high income countries	0.254	high consumption	0.8	0.00027	0.027
RT	0.144	topical	0.006	Local	0.374	high consumption	0.8	0.00026	0.026
RT	0.144	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00026	0.026
END	0.077	other large-	0.011	Local	0.374	high consumption	0.8	0.00025	0.025

		liquid							
END	0.077	other	0.011	Local	0.374	high consumption	0.8	0.00025	0.025
END	0.077	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00025	0.025
END	0.077	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00025	0.025
GIT	0.035	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00024	0.024
CNS	0.035	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00024	0.024
CVS	0.119	topical	0.006	Local	0.374	high consumption	0.8	0.00021	0.021
SKN	0.021	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00021	0.021
SKN	0.021	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00021	0.021
CVS	0.119	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00021	0.021
OBS	0.013	small-parenteral	0.08	high income countries	0.254	high consumption	0.8	0.00021	0.021
Anti	0.376	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00021	0.021
Anti	0.376	other	0.011	high income countries	0.254	low consumption	0.2	0.00021	0.021
GIT	0.035	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00021	0.021
CNS	0.035	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00021	0.021
GIT	0.035	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00021	0.021
CNS	0.035	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00021	0.021
NUT	0.091	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00020	0.020
NUT	0.091	other	0.011	high income countries	0.254	high consumption	0.8	0.00020	0.020
MUS	0.088	other	0.011	high income countries	0.254	high consumption	0.8	0.00020	0.020

		large-liquid							
MUS	0.088	other	0.011	high income countries	0.254	high consumption	0.8	0.00020	0.020
RT	0.144	topical	0.006	high income countries	0.254	high consumption	0.8	0.00018	0.018
END	0.077	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00017	0.017
END	0.077	other	0.011	high income countries	0.254	high consumption	0.8	0.00017	0.017
Anti	0.376	topical	0.006	Local	0.374	low consumption	0.2	0.00017	0.017
Anti	0.376	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00017	0.017
NUT	0.091	topical	0.006	Local	0.374	high consumption	0.8	0.00016	0.016
NUT	0.091	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00016	0.016
MUS	0.088	topical	0.006	Local	0.374	high consumption	0.8	0.00016	0.016
MUS	0.088	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00016	0.016
SKN	0.021	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00015	0.015
CVS	0.119	topical	0.006	high income countries	0.254	high consumption	0.8	0.00015	0.015
GIT	0.035	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00014	0.014
CNS	0.035	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00014	0.014
END	0.077	topical	0.006	Local	0.374	high consumption	0.8	0.00014	0.014
END	0.077	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00014	0.014
OBS	0.013	liquid-oral	0.136	Local	0.374	low consumption	0.2	0.00013	0.013
OBS	0.013	liquid-oral	0.136	Low&mid income countries	0.373	low consumption	0.2	0.00013	0.013
SKN	0.021	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00013	0.013
SKN	0.021	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00013	0.013
RT	0.144	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00012	0.012

RT	0.144	other	0.011	Local	0.374	low consumption	0.2	0.00012	0.012
RT	0.144	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00012	0.012
RT	0.144	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00012	0.012
GIT	0.035	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00012	0.012
GIT	0.035	other	0.011	Local	0.374	high consumption	0.8	0.00012	0.012
CNS	0.035	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00012	0.012
CNS	0.035	other	0.011	Local	0.374	high consumption	0.8	0.00012	0.012
GIT	0.035	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00011	0.011
GIT	0.035	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00011	0.011
CNS	0.035	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00011	0.011
CNS	0.035	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00011	0.011
Anti	0.376	topical	0.006	high income countries	0.254	low consumption	0.2	0.00011	0.011
NUT	0.091	topical	0.006	high income countries	0.254	high consumption	0.8	0.00011	0.011
MUS	0.088	topical	0.006	high income countries	0.254	high consumption	0.8	0.00011	0.011
CVS	0.119	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00010	0.010
CVS	0.119	other	0.011	Local	0.374	low consumption	0.2	0.00010	0.010
CVS	0.119	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00010	0.010

CVS	0.119	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00010	0.010
END	0.077	topical	0.006	high income countries	0.254	high consumption	0.8	0.00009	0.009
OBS	0.013	liquid-oral	0.136	high income countries	0.254	low consumption	0.2	0.00009	0.009
SKN	0.021	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00009	0.009
RT	0.144	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00008	0.008
RT	0.144	other	0.011	high income countries	0.254	low consumption	0.2	0.00008	0.008
GIT	0.035	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00008	0.008
GIT	0.035	other	0.011	high income countries	0.254	high consumption	0.8	0.00008	0.008
CNS	0.035	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00008	0.008
CNS	0.035	other	0.011	high income countries	0.254	high consumption	0.8	0.00008	0.008
OBS	0.013	small-parenteral	0.08	Local	0.374	low consumption	0.2	0.00008	0.008
OBS	0.013	small-parenteral	0.08	Low&mid income countries	0.373	low consumption	0.2	0.00008	0.008
NUT	0.091	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00007	0.007
NUT	0.091	other	0.011	Local	0.374	low consumption	0.2	0.00007	0.007
NUT	0.091	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00007	0.007
NUT	0.091	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00007	0.007
MUS	0.088	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00007	0.007

MUS	0.088	other	0.011	Local	0.374	low consumption	0.2	0.00007	0.007
MUS	0.088	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00007	0.007
MUS	0.088	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00007	0.007
SKN	0.021	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00007	0.007
SKN	0.021	other	0.011	Local	0.374	high consumption	0.8	0.00007	0.007
SKN	0.021	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00007	0.007
SKN	0.021	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00007	0.007
CVS	0.119	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00007	0.007
CVS	0.119	other	0.011	high income countries	0.254	low consumption	0.2	0.00007	0.007
RT	0.144	topical	0.006	Local	0.374	low consumption	0.2	0.00006	0.006
RT	0.144	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00006	0.006
END	0.077	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00006	0.006
END	0.077	other	0.011	Local	0.374	low consumption	0.2	0.00006	0.006
END	0.077	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00006	0.006
END	0.077	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00006	0.006
GIT	0.035	topical	0.006	Local	0.374	high consumption	0.8	0.00006	0.006
CNS	0.035	topical	0.006	Local	0.374	high consumption	0.8	0.00006	0.006
GIT	0.035	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00006	0.006
CNS	0.035	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00006	0.006

CVS	0.119	topical	0.006	Local	0.374	low consumption	0.2	0.00005	0.005
CVS	0.119	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00005	0.005
OBS	0.013	small-parenteral	0.08	high income countries	0.254	low consumption	0.2	0.00005	0.005
NUT	0.091	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00005	0.005
NUT	0.091	other	0.011	high income countries	0.254	low consumption	0.2	0.00005	0.005
MUS	0.088	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00005	0.005
MUS	0.088	other	0.011	high income countries	0.254	low consumption	0.2	0.00005	0.005
SKN	0.021	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00005	0.005
SKN	0.021	other	0.011	high income countries	0.254	high consumption	0.8	0.00005	0.005
RT	0.144	topical	0.006	high income countries	0.254	low consumption	0.2	0.00004	0.004
END	0.077	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00004	0.004
END	0.077	other	0.011	high income countries	0.254	low consumption	0.2	0.00004	0.004
OBS	0.013	other large-liquid	0.011	Local	0.374	high consumption	0.8	0.00004	0.004
OBS	0.013	other	0.011	Local	0.374	high consumption	0.8	0.00004	0.004
GIT	0.035	topical	0.006	high income countries	0.254	high consumption	0.8	0.00004	0.004
CNS	0.035	topical	0.006	high income countries	0.254	high consumption	0.8	0.00004	0.004
OBS	0.013	other large-liquid	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00004	0.004
OBS	0.013	other	0.011	Low&mid income countries	0.373	high consumption	0.8	0.00004	0.004

NUT	0.091	topical	0.006	Local	0.374	low consumption	0.2	0.00004	0.004
NUT	0.091	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00004	0.004
MUS	0.088	topical	0.006	Local	0.374	low consumption	0.2	0.00004	0.004
MUS	0.088	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00004	0.004
SKN	0.021	topical	0.006	Local	0.374	high consumption	0.8	0.00004	0.004
SKN	0.021	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00004	0.004
CVS	0.119	topical	0.006	high income countries	0.254	low consumption	0.2	0.00004	0.004
END	0.077	topical	0.006	Local	0.374	low consumption	0.2	0.00003	0.003
END	0.077	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00003	0.003
OBS	0.013	other large-liquid	0.011	high income countries	0.254	high consumption	0.8	0.00003	0.003
OBS	0.013	other	0.011	high income countries	0.254	high consumption	0.8	0.00003	0.003
GIT	0.035	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00003	0.003
GIT	0.035	other	0.011	Local	0.374	low consumption	0.2	0.00003	0.003
CNS	0.035	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00003	0.003
CNS	0.035	other	0.011	Local	0.374	low consumption	0.2	0.00003	0.003
GIT	0.035	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00003	0.003
GIT	0.035	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00003	0.003
CNS	0.035	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00003	0.003
CNS	0.035	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00003	0.003
NUT	0.091	topical	0.006	high income countries	0.254	low consumption	0.2	0.00003	0.003
MUS	0.088	topical	0.006	high income countries	0.254	low consumption	0.2	0.00003	0.003

SKN	0.021	topical	0.006	high income countries	0.254	high consumption	0.8	0.00003	0.003
END	0.077	topical	0.006	high income countries	0.254	low consumption	0.2	0.00002	0.002
OBS	0.013	topical	0.006	Local	0.374	high consumption	0.8	0.00002	0.002
OBS	0.013	topical	0.006	Low&mid income countries	0.373	high consumption	0.8	0.00002	0.002
GIT	0.035	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00002	0.002
GIT	0.035	other	0.011	high income countries	0.254	low consumption	0.2	0.00002	0.002
CNS	0.035	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00002	0.002
CNS	0.035	other	0.011	high income countries	0.254	low consumption	0.2	0.00002	0.002
SKN	0.021	other large-liquid	0.011	Local	0.374	low consumption	0.2	0.00002	0.002
SKN	0.021	other	0.011	Local	0.374	low consumption	0.2	0.00002	0.002
SKN	0.021	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00002	0.002
SKN	0.021	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00002	0.002
OBS	0.013	topical	0.006	high income countries	0.254	high consumption	0.8	0.00002	0.002
GIT	0.035	topical	0.006	Local	0.374	low consumption	0.2	0.00002	0.002
CNS	0.035	topical	0.006	Local	0.374	low consumption	0.2	0.00002	0.002
GIT	0.035	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00002	0.002
CNS	0.035	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00002	0.002
SKN	0.021	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00001	0.001
SKN	0.021	other	0.011	high income countries	0.254	low consumption	0.2	0.00001	0.001
OBS	0.013	other large-	0.011	Local	0.374	low consumption	0.2	0.00001	0.001

		liquid							
OBS	0.013	other	0.011	Local	0.374	low consumption	0.2	0.00001	0.001
GIT	0.035	topical	0.006	high income countries	0.254	low consumption	0.2	0.00001	0.001
CNS	0.035	topical	0.006	high income countries	0.254	low consumption	0.2	0.00001	0.001
OBS	0.013	other large-liquid	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00001	0.001
OBS	0.013	other	0.011	Low&mid income countries	0.373	low consumption	0.2	0.00001	0.001
SKN	0.021	topical	0.006	Local	0.374	low consumption	0.2	0.00001	0.001
SKN	0.021	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00001	0.001
OBS	0.013	other large-liquid	0.011	high income countries	0.254	low consumption	0.2	0.00001	0.001
OBS	0.013	other	0.011	high income countries	0.254	low consumption	0.2	0.00001	0.001
SKN	0.021	topical	0.006	high income countries	0.254	low consumption	0.2	0.00001	0.001
OBS	0.013	topical	0.006	Local	0.374	low consumption	0.2	0.00001	0.001
OBS	0.013	topical	0.006	Low&mid income countries	0.373	low consumption	0.2	0.00001	0.001
OBS	0.013	topical	0.006	high income countries	0.254	low consumption	0.2	0.00000	0.000

Glossary

Some of the terms used within this repot were defined below based on the reference definition for all terms.

1. **Active Pharmaceutical Ingredient (API):**

   A substance or compound intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

2. **Adverse Drug Reactions (ADRs):**

   Any unwanted effect(s) produced by a drug that is harmful to the patient. Onset may be sudden or develop over time.

3. **Assay:**

   The monograph standard test, with associated method of analysis, which is designed to determine the strength of a drug product

4. **Basic Tests:**

   Simplified analytical tests that do not require complex methodologies and equipment. Basic tests may be used to verify the identity of a drug or to ascertain the absence of gross degradations or contamination.

5. **Batch:**

   A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that the product could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a de.ned fraction of the production, characterized by its intended homogeneity. A batch may need to be divided into smaller batches, which are later combined to form final homogeneous batch.

6. **Batch Certificate:**

   A document containing information that is usually issued for each batch by the manufacturer, or validated or issued by the competent authority of the exporting country, particularly for vaccines, sera, and other biological products. The batch certificate accompanies every major consignment.

7. **Batch Number:**

A distinctive combination of numbers, letters, or both that specifically identifies a batch on the labels, the batch records, and the certificate of analysis, etc.

8. **Bioavailability:**

The rate and extent of availability of an active ingredient from a dosage form as measured by its concentration/time curve in the systemic circulation or its excretion in the urine.

9. **Bioequivalence:**

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent, and their bioavailability, after administration in the same molar dose, is similar to such a degree that their effects can be expected to be essentially the same.

10. **Certificate of Analysis:**

Report of the analytical test results obtained, including the analysis conclusion of the examination of a sample issued by the manufacturer, repackager or trader.

11. **Counterfeit Drug:**

A pharmaceutical product that is deliberately and fraudulently mislabeled with respect to identity or source. Both branded and generic products can be counterfeited. Counterfeit drugs can include products with the correct ingredients, with the wrong ingredients, without active ingredients, with insufficient quantity of active ingredients, or with fake packaging. A counterfeit drug can be a deliberate imitation or a copy of a genuine product.

12. **Disintegration:**

The breaking up of a tablet or a capsule into granules or aggregates in an aqueous fluid.

13. **Dissolution:**

The process by which a solid substance is separated into molecules or ions that homogeneously disperses in an aqueous fluid to form a solution. The rate of dissolution is determined by the interaction between the substance and the medium.

14. Dosage Form:

The form - tablet, capsule, injection - of a completed pharmaceutical preparation.

15. Dosage (or strength):

The content of the active ingredient per dosage unit is determined by the assay of the specific monograph and expressed, generally, in milligrams or units per dosage unit.

16. Drug:

Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

17. Drug Product:

A Finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance generally, but not necessarily, in association with one or more other ingredients.

18. Efficacy (of a Medicine or Treatment):

The maximum ability of a medicine or treatment to produce a result regardless of dosage. A medicine passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed.

19. Essential Medicines:

Medicines that satisfy the priority health care needs of a population. Essential medicines are selected with due regard for public health relevance, evidence of efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price that individuals and communities can afford.

20. Expiry (or Expiration) Date:

The date up to which a product is expected to remain within specifications, if stored correctly. Expiry date is established by the manufacturer for each batch by adding the shelf-life period to the date of manufacture.

21. Generic Drug:

A generic drug is the same as a brand name drug is dosage, safety, strength, how it is taken, quality, performance, and intended use. Before a generic drug is approved, an MRA should require many rigorous tests and procedures to assure the generic drug can be substituted for a brand name drug.

22. Generic Name:

The approved or International Nonproprietary Name of a drug given by the World Health Organization.

23. Generic Products:

A pharmaceutical product - usually intended to be interchangeable with the innovator product - is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

24. Good Manufacturing Practices (GMP):

The part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled by the quality standards appropriate to their intended use and as required by the marketing authorization. These standards include criteria for personnel, facilities, equipment, materials, manufacturing operations, labeling, packaging, quality control, and in most cases, stability testing.

25. Identity:

The correct chemical substance and formula of an active ingredient in a drug product.

26. Identity Test:

The selected test in the monograph to verify that the API is correct for that drug product.

27. International Nonproprietary Names:

International nonproprietary names facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name. Proposals for recommended international nonproprietary names are submitted to the World Health Organization on a form provided by WHO

by the purpose. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

28. Label:

All finished drug products should be identified by labeling, as required by national legislation, bearing at least the following information:

a) The name of the drug product.
b) A list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each active ingredient present, and a statement of the net contents (number of dosage units, mass, or volume).
c) The batch number assigned by the manufacturer.
d) The expiry date and manufacturing date in un coded form.
e) Special storage conditions or handling precautions that may be necessary.
f) Directions for use, and any warnings or precautions that may be necessary.
g) The name and address of the manufacturer or the company or person responsible for placing the product on the market.

29. Marketing Authorization:

An official document issued by a competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. The certificate must set out, among other things, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INN or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. The document speci.es the information on which authorization is based. The license also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization.

30. Medicines Regulatory Authority (MRA):

A national body that administers the full spectrum of regulatory activities associated with pharmaceuticals, including at least all of the following functions: marketing authorization of new products and variation of existing products; quality controlled laboratory testing (although in some countries, the laboratory may not be part of the

MRA); adverse drug reaction monitoring; provision of medicine information and promotion of rational medicine use; good manufacturing practice inspections and licensing of manufacturers, wholesalers, and distribution channels; enforcement of operations; and monitoring of drug utilization.

31. Method Validation:

A demonstration of the suitability of the analytical procedure for its intended use. The characteristics of the analytical procedures to be considered in method validation are accuracy, precision, robustness, linearity and range, selectivity, limit of detection, and limit of quantization.

32. Monograph:

A set of properly selected standardized tests with associated methods of analysis that can be used to assess the integrity of drugs (including dosage forms) and starting materials. These standards, when met, assure the quality of the drug with respect to identity, purity, strength, packaging, storage, and labeling. Monographs are published in pharmacopeia.

33. Over-the-Counter (OTC) Medicine:

Medicines that can be sold from licensed retail pharmacies or outlets without professional supervision and without a physician's prescription. OTC medicines are considered safe and effective for use by the general public. OTC medicines are suitable for self-medication for minor diseases and symptoms.

34. Pharmacopeia:

A book containing an official list of monographs and internationally acceptable standards for the potency, purity, quality, packaging, and labeling of pharmaceutical products. The major pharmacopeias in the world are the International Pharmacopeia, the United States Pharmacopeia, the British Pharmacopoeia, the Japanese Pharmacopeia and the European Pharmacopoeia. Other countries have their own pharmacopeias.

35. **Pharmacovigilance:**

All science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or other drug-related problems. In general, Pharmacovigilance aims to reevaluate the safety and efficacy of pharmaceutical product in the market. This encompasses spontaneous adverse drug reactions, drug information reporting, promotion of rational use of drugs, risk management, and crisis preparedness.

36. **Post marketing Surveillance:**

Monitoring the quality of drugs by inspection and laboratory testing to assure that the storage is correct and that drugs are stable within their labeled shelf-life.

37. **Potency:**

The extent to which a drug contains the specified amount of the active ingredient.

38. **Premarketing Surveillance:**

Monitoring the quality of medicines by inspection and laboratory testing to assure that medicines conform to the quality standards and specifications before their marketing authorization.

39. **Product Certificate:**

A document containing the information set out in Form 5.1. The certificate is validated and issued for a specific product by the competent authority of the exporting country and intended for use by the competent authority in the importing country, or, in the absence of such an authority, by the drug procurement authority.

40. **Product Recall:**

A process for withdrawing or removing a pharmaceutical product from the distribution chain because of defects in the product or complaints of serious adverse reactions to the product. A recall may be initiated by an MRA, a manufacturer, or by an importer/distributor or a responsible agency.

41. **Quality:**

All characteristics—purity, strength, packaging, labeling—that allow the drug product to deliver its intended treatment.

42. Quality Assurance (QA):

All matters that individually or collectively influence the quality of a product. The objective of QA is to ensure that pharmaceutical starting materials and pharmaceutical products meet quality standards.

43. Quality Control (QC):

All measures taken—including setting specifications, sampling, testing, and analytical clearance—to ensure that raw materials, intermediates, packaging materials, and finished pharmaceutical products conform to established specifications for identity, strength, purity, and other characteristics.

44. Recall:

The process of withdrawing a medicine from the market because of a quality, safety, or efficacy problem.

45. Safety:

Not causing harm or injury, having a low incidence of adverse reactions and significant side effects when adequate instructions for use are given, and having a low potential for harm under conditions of widespread availability.

46. Sample:

A portion of material collected according to a de.ned sampling procedure. The size of any sample should be sufficient to carry out all anticipated test procedures, including all repetitions.

47. Sampling Procedure:

A detailed and complete sampling operation to be applied to a de.ned material for a specific purpose. A detailed, written description of the sampling procedure is provided as sampling protocol.

48. Shelf-Life:

The period of time during which a drug product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life establishes the expiry date of each batch.

49. Specification:

A detailed document describing the requirements with which the pharmaceutical products used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

50. Stability:

The ability of a pharmaceutical product to retain its chemical, physical, microbiological, and biopharmaceutical properties within specified limits throughout its shelf-life.

51. Standard:

A technical specification that addresses a business requirement, is implemented in viable commercial products, and to the extent practical, complies with recognized standards organizations such as (ISO).

52. Starting Material:

Any substance of de.ned quality used in the production of a pharmaceutical product, excluding packaging material.

53. Substandard Drug:

A legal branded or generic drug that does not meet national or international standards for quality, purity, strength, or packaging.

54. Validated Method:

A method of analytical performance demonstrated by experimental data that has proven its suitability as analytical support of a specification proposed for particular drug. The nature of the method and the type of drug test determine the characteristics that should be considered to validate the method.