IMPLEMENTATION OF GMP IN PHARMACEUTICAL MANUFACTURING FACILITIES IN SUDAN

Eltaib, S. A. Lina., ABDEL KARIM M. ABDEL KARIM., Dirar, H. Mawahib., Ali, A. Amani., Rikabi, A. Majeed. Hind

Department of Pharmaceutics, Faculty of Pharmacy, Omdurman Islamic University, Sudan
Corresponding author: Eltaib, S. A. Lina
B. pharm., M. pharm., PhD (Pharmaceutics)
Email: linasalaheldin@Gmail.com
Department of pharmaceutics, Faculty of Pharmacy, Northern Border University, P.O. Box 840, Rafha, 91911, Kingdom of Saudi Arabia

Abstract

Background:

This is a descriptive study design based on a survey form, to evaluate the manufacturing practice in Sudanese pharmaceutical manufacturing facilities and compliance to Good manufacturing Guidelines. Sixteen of the Sudanese pharmaceutical manufacturing facilities have been included in the study. There were twenty seven Sudanese pharmaceutical manufacturing facilities at the time this study was conducted two of the twenty seven factories were actually closed by the order of the regulatory authority and one closed for maintenance, Three factories were licensed for production but not started yet, only twenty one of the twenty seven factories were actually working and having products in the market.

Rationale for the study:

The present study aims at evaluating the current medicine storage practices in Sudanese pharmaceutical manufacturing facilities and their compliance to the recommended guidelines. Such information is useful in various ways:

I. To identify the critical issues of manufacturing practice in Sudanese pharmaceutical manufacturing facilities and its effect on the quality of pharmaceutical product.
II. To Identify and create the most coordinated and effective mechanisms required for responding and alerting key audiences, stakeholders the general public and regulatory bodies

about the importance of implementing the GSP guideline in Sudanese pharmaceutical manufacturing facilities.
III. To help evaluate and interpret national and international legislations and guidelines on GSP, and the possibility of implementing them in Sudanese pharmaceutical manufacturing facilities.
IV. To upgrade the quality of national pharmaceutical industry and this will support the national economy and decrease importation.

Results:

Only about 65 percent of the manufacturing facilities investigated comply with the GMP guideline. On the other hand, approximately 19 percent of the facilities investigated did not exactly comply with the guideline; compared to about 16 percent of the manufacturing facilities did not comply with the GMP guidelines.

{**Citation**: Eltaib, S. A. Lina., Abdel Karim M. Abdel Karim., Dirar, H. Mawahib., Ali, A. Amani., Rikabi, A. Majeed. Hind. Implementation of GMP in pharmaceutical manufacturing facilities in Sudan. American Journal of Research Communication, 2018, 6(5): 1-23} www.usa-journals.com, ISSN: 2325-4076.

1.1 Introduction:

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. The setting of global standards is requested in Article 2 of the WHO Constitution, which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products." Every government allocates a substantial proportion of its total health budget to medicines. This proportion tends to be greatest in developing countries, where it may exceed 40%. Without assurance that these medicines are relevant to تهand efficacy, any health service is evidently compromised. In developing countries considerable administrative and technical effort is directed to ensuring that patients receive effective medicines of good quality. It is crucial to the objective of health for all that a reliable system of medicines control be brought within the reach of every country. The supply of essential medicines of good quality was identified as one of the prerequisites for the delivery of health care at the International Conference on Primary Health Care in Alma-Ata in 1978. Similarly, the Conference of Experts on the Rational Use of Drugs, held in Nairobi in 1985, and WHO's Revised Drug Strategy, adopted by the World Health Assembly in

May 1986, identified the effective functioning of national drug regulation and control systems as the only means to assure safety and quality of medicines. Yet the World Health Assembly continues to express great concern about the quality, safety and efficacy of medicines, particularly those products or active pharmaceutical substances imported into, or produced in, developing countries. In recent years counterfeit products have infiltrated certain markets in disquieting proportions. Since the founding of WHO, the World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally. (Quality Assurance of Pharmaceuticals, 2006).

Many developing countries import a large proportion of their essential medicines requirements, as they do not have sufficient manufacturing facilities. Most of these countries also lack adequate, well established quality control authorities to routine verification of the quality of imported medicines. Therefore, they mainly rely on the expertise and integrity of the manufacturer for the quality and stability of the imported medicines. Problems can arise, especially in developing countries having a tropical climate due to the effects of a high temperature combined with a high humidity (to which the medicines are exposed during storage and transport) adversely affecting the biopharmaceutical properties of these medicines.

There are alarming and conflicting reports of substandard drug dosage forms in several developing countries cited in the literature (Hogerzeil., 1991; Hogerzeil,1992; Nazerali and Hogrezeil,1996). Furthermore, there is astounding scenario responsible for the emergence and dissertation of antimicrobial resistance and it is association to storage conditions (Mitema and Kikuvi, 2005; Planta, 2007; Kelesidis, 2007). This led to field studies on the stability of essential drugs during international transport to the tropics and to specific stability studies on drugs. Controlled longitudinal studies were performed to measure the quality of essential drugs within rural areas and to determine whether any failure were due to poor initial quality or to instability of the drugs during inland distribution and storage. All these studies focused on essential drugs and concluded that, even under the most adverse tropical conditions, clinically relevant instability of drugs is rare. In fact, poor initial quality poses a much more serious problem as it could, in principal, occur with any drug. The practical implication of this conclusion is that careful selection of suppliers and quality control at the entry point of the distribution chain are essential to ensure drug quality. Even in tropical climates subsequent quality checks at the district level are not necessary.(Assad Abdel Rafie, 2009)

GMP is a process employed to ensure a certain level of quality in a product. It may include whatever actions a business deems necessary to provide for the control and verification of certain characteristics of a product. The basic goal of Good storage practice is to ensure that the products, or processes provided meet specific requirements and are dependable, satisfactory, and fiscally sound. Product quality regulatory system was established many decades ago, with

incremental adjustments occurring over the years. However, due to constraints in this area in Sudan, and the policy of the ministry of industry to promote local industry and support pharmaceutical industry.

GMP is a major public health concern, particularly in light of growing cross-border health issues and international trade. Significant changes have occurred in the field of pharmaceutical sciences and manufacture over the last few decades. This warranted a systematic reappraisal of our national quality standard. Many international bodies and organizations redirected their approaches to product quality regulations. The GSP guidelines contains directions on receiving and arranging commodities; special storage conditions; maintaining the quality of the products; constructing and designing a medical store and waste management. Identify and create the most coordinated and effective mechanisms required to both respond and alert key audiences, stakeholders the general public and regulatory bodies about the importance of implementing these guidelines in pharmaceutical factory.

1.2 Literature review:

1.2.1 Organization and personnel:

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. (EU-GMP-1998).

1.2.2 Premises and Facilities:

Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals. Steps should be taken in order to prevent the entry of unauthorized people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.(EU-GMP, 1998).

1.2.3.2 Storage conditions

Storage conditions for pharmaceutical products should be in compliance with the instructions on the label, which are based on the results of stability testing.

1.2.3.2.1 Monitoring of storage conditions

Recorded temperature monitoring data should be available for review. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained. All monitoring records should be kept for at least the shelf-life of the stored pharmaceutical product plus one year, or as required by national legislation.(WHO,2003;2006) Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

Equipment used for monitoring of storage conditions should also be calibrated at defined intervals.

Failure to follow storage recommendations of pharmaceutical products can result in sub-potent products and potentially, therapeutic failure. As cited in the literature (Neeta, 2008). Hundreds of thousands of medications are discarded each year because of improper storage conditions. This can occur for a variety of reasons including improper shipping, failure to refrigerate or freeze a product upon receipt or after use, and in the event of a power failure. (Cohen, 2007). It is important to recognize when pharmaceutical products have not been stored according to the manufacturer's specifications and take appropriate action. Depending on the product, lot number and expiration date, time of exposure to temperatures outside of the recommended range and actual temperature of exposure, some medications may be deemed suitable for administration while others should be discarded. However, if a pharmaceutical product has not been stored according to the recommended conditions, it is important to contact the manufacturer and provide the specifics (lot number, expiration date, exposure temperature, length of time) to determine if the product is viable.

1.2.3.2.2 Storage and labelling conditions

Normal storage conditions

Storage in dry, well-ventilated premises at temperatures of 15–25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, other indications of contamination, and intense light must be excluded.

Defined storage instructions

Drug products that must be stored under defined conditions require appropriate storage instructions. Unless otherwise specifically stated (e.g. continuous maintenance of cold storage) deviation may be tolerated only during short-term interruptions, for example, during local transportation. Benchmarking the effects of prolonged storage is of paramount importance in

determining the retention time for plate storage, thereby ensuring a high-quality screening collection. (Barbara, 2003) provides the first published results on the effects of room-temperature storage on the stability of compounds in DMSO. The data presented in this study can be used to determine the maximum storage time at room temperature for an acceptable limit for compound loss.

The use of the following labelling instructions are recommended:

On the label	Means
"Do not store over 30 °C"	from +2 °C to +30 °C
"Do not store over 25 °C"	from +2 °C to +25 °C
"Do not store over 15 °C"	from +2 °C to +15°C
"Do not store over 8 °C"	from +2 °C to +8 °C
"Do not store below 8 °C"	from +8 °C to +25 °C
"Protect from moisture" to be provided to the patient in a moisture resistant container.	no more than 60% relative humidity in normal storage conditions;
"Protect from light" to be provided to the patient in a light resistant container.	

1.2.3.3 Storage condition and stability testing

Stability testing provides essential data on how the quality of a pharmaceutical varies over time under the influence of different environmental factors such as temperature, humidity and light. This enables recommended storage conditions, re-testing intervals and shelf-lives to be established. Comprehensive testing capabilities also include dissolution, Karl Fischer, hardness, disintegration, friability and characterization of impurities and degradants**.** Stability testing is interwoven through the entire fabric of the drug product lifecycle. A detailed knowledge of the stability requirements and the impact on other areas (e.g., container closure, process changes) is needed to properly design and evaluate stability studies in order to ensure minimal delays and minimize costs in developing a new drug product.

Key factors to design quality stability program for drug product and API:

• Understand the Regulatory Requirements versus Scientific Requirements.

• Understand stability role in the drug development process.

• Stability profile needs to be established for drug product to assure safety, efficacy and quality.

• Design strategy for stability study based on data of development batches • Need to understand the product to design formal stability studies.

• Develop stability program and maximize efficiency . (Kim Huynh-Ba, 2008)

Publishing of the FDA- 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals established requirements concerning the expiration date on a drug product and stability testing to assure the appropriateness of that date. Each drug product may be a unique article because of, for instance, differences in (1) chemical and physical properties of the active ingredients or the excipients, (2) manufacturing procedures, (3) formulations, (4) containers and closures, (5) proposed storage conditions, and (6) the stability of the article to maintain its quality or purity through the use of antioxidants or preservatives. Because each drug product is unique, it is virtually impossible to provide one set of rules that can apply to all situations. The cGMPs were purposely written broadly to allow for such unique differences.

1.2.4 Equipments:

Manufacturing equipment should be designed, located and maintained to suit its intended purpose. Repair and maintenance operations should not present any hazard to the quality of the products.(EU-GMP, 1998).

1.2.5 Documentation

As stated (Quality assurance of pharmaceuticals, 2006), good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary; to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

1.2.6 Recall

There should be a system which includes a written procedure, to recall promptly and effectively pharmaceutical products known or suspected to be defective, with a designated person(s) responsible for recalls. Such procedures should be checked regularly validated and updated as necessary. The original manufacturer and/or marketing authorization holder should be informed in the event of a recall. Where a recall is instituted by an entity other than the original

manufacturer and/or marketing authorization holder, consultation with the original manufacturer and/or marketing authorization holder should, where possible, take place before the recall is instituted.

1.2.7 Retain Product

Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse.

1.2.8 Dispatch and transport:

Written procedures for the dispatch of pharmaceutical products should be established. Such procedures should take into account the nature of the product, as well as any special precautions to be observed.

Records for the dispatch of pharmaceutical products should be prepared and should include at least the following information:

- Date of dispatch;

- Name and address of the entity responsible for the transportation;

- Name, address and status of the addressee (e.g. retail pharmacy, hospital, community clinic);

- A description of the products including, e.g. name, dosage form and strength (if applicable);

- Quantity of the products, i.e. number of containers and quantity per container;

- Assigned batch number and expiry date;

- Applicable transport and storage conditions; and

- A unique number to allow identification of the delivery order.

1.2.8.3 Transportation and products in transit

The transportation process should not compromise the integrity and quality of pharmaceutical products. The manufacturer should communicate all relevant conditions for storage and transportation to those responsible for the transportation of pharmaceutical products. Such an entity should ensure adherence to these requirements throughout transportation and at any intermediate storage stages.

Pharmaceutical products should be stored and transported in accordance with procedures such that:

• The identity of the product is not lost;

• The product does not contaminate and is not contaminated by other products;

• Adequate precautions are taken against spillage, breakage, misappropriation and theft;

• Appropriate temperature and relative humidity conditions are maintained in the case of the pharmaceutical product, e.g. using cold chain for thermolabile products.

A batch tracking system should be used to enable specific batches to be traced during the distribution process.

The present study aims at evaluating the current medicine storage practices in Sudanese pharmaceutical manufacturing facilities and their compliance to the recommended guidelines. Such information is useful in various ways:

III. To identify the critical issues of manufacturing practice in Sudanese pharmaceutical manufacturing facilities and its effect on the quality of pharmaceutical product.
IV. To Identify and create the most coordinated and effective mechanisms required for responding and alerting key audiences, stakeholders the general public and regulatory bodies about the importance of implementing the GSP guideline in Sudanese pharmaceutical manufacturing facilities.
III. To help evaluate and interpret national and international legislations and guidelines on GSP, and the possibility of implementing them in Sudanese pharmaceutical manufacturing facilities.
IV. To upgrade the quality of national pharmaceutical industry and this will support the national economy and decrease importation.

2.1The study Objectives

The objective of the present study is to determine the following in the Sudanese pharmaceutical manufacturing facilities:

2.1.1 The personnel qualification, ongoing training in areas of store keeping, regulations and working condition .

2.1.2 The general appearance, premises and facilities.

2.1.3 Warehousing and storage conditions .

2.1.4 Equipment used in the stores.

2.1.5 The storage requirements including documentation, labeling and containers.

2.1.6 The procedure of handling returned products.

2.1.7 The procedure of handling recalled goods.

2.1.8 The procedure of dispatch and transportation.

2.2 Questions of the study:

In Sudanese pharmaceutical manufacturing facilities:
2.2.1Is there an adequate number of qualified personnel to achieve pharmaceutical quality assurance objectives?
2.2.2 Are storage areas (premises and facilities), of sufficient capacity to allow the orderly storage of materials and products?
2.2.3 Are warehousing and storage conditions in compliance with the good storage practice guidelines?
2.2.4 Are equipments in Sudanese manufacturing facilities designed, located and maintained to suit its intended purpose, and do not present any hazard to the quality of the products?
2.2.5 Do manufacturing facilities stores comply with the GSP guidelines in areas of storage requirements including documentation, labeling and containers?
2.2.6 Are returned pharmaceutical products, handled in accordance with approved written procedures?
2.2.7 Are recalled pharmaceutical products, handled in accordance with approved written and validated procedures?
2.2.8 Are dispatch and transportation of pharmaceutical products in compliance with the requirement of the GSP?

3.1.1 Study design

This is a descriptive study design based on a survey form, to evaluate the manufacturing practice in Sudanese pharmaceutical manufacturing facilities and compliance to Good manufacturing Guidelines.

3.1.2 Study population

Sixteen of the Sudanese pharmaceutical manufacturing facilities have been included in the study. There were twenty seven Sudanese pharmaceutical manufacturing facilities at the time this study was conducted two of the twenty seven factories were actually closed by the order of the regulatory authority and one closed for maintenance, Three factories were licensed for

production but not started yet, only twenty one of the twenty seven factories were actually working and having products in the market five of them

Study time and location

The study was conducted in the Sudanese pharmaceutical manufacturing facilities.

Sudanese pharmaceutical manufacturing facilities are mainly located in Khartoum state (the capital of Sudan) and Aljazera state, there are four of the Sudanese pharmaceutical manufacturing facilities in Aljazera state two of them were included in the study. Khartoum state consists three cities Omdurman, Khartoum and Khartoum Bahry. There are two manufacturing facilities in the city of Omdurman one of them was included in the study. There are seven manufacturing facilities in the city of Khartoum three of them were included in the study. In Khartoum Bahry there are fourteen manufacturing facilities in the city of ten of them are included in the study.

3.1.3 Data collection

The data were collected by the researcher using a designed questionnaire of 100 questions arranged under eight headings namely: organization and personal, premises, warehousing and storage conditions, equipment's, documentation, recall, retain product, and dispatch and transport.

3.1.4 Data analyses

The data were collected using a pretested questionnaire. The collected data was organized, tabulated, ordered, classified, and analyzed using statistical software program. Data entry and analyses took place once each data collection form (questionnaire) was reviewed for clarity and completeness using Statistical Package for Social Science (SPSS) version 12.0. The results were further tabulated, interpreted and discussed, figures were plotted using Microsoft excel program (2007). Descriptive statistics including frequency, mean, and standard deviation were used. To determine if there is a relationship between two nominal variables or whether they are independent of each other, non-parametric chi-square test was used. The non-parametric Krushal-Wallis test was used when more than two independent variables on ordinal data existed.

3.1.7 Ethical consideration

The managers of the manufacturing facilities and the person in charge of the store have been clearly informed about the academic purpose of the study, and assured that the data provided will not be used in any way to support a decision or harm against them.

3.1.8 Variables under the study

Based on the recommended guidelines of the WHO, united Arab emirate, food and drug administration, international conference of harmonization for pharmaceutical product preparation (ICH) and European union orange guide, and other health commodities, the following variables were used to carry out the study:

- The personnel qualification, hygiene and ongoing training in areas of store keeping, organizations, regulations and working condition.
- The general appearance, premises and facilities.
- Warehousing and storage conditions in the stores.
- Equipment used in the store.
- The pharmaceutical manufacturing facilities storage requirements including documentation, and labeling.
- The procedure of handling returned pharmaceutical products.
- The procedure of handling recalled pharmaceutical products.
- The procedure of dispatch and transportation.

A pilot test was done in five manufacturing facilities where the questionnaire was distributed by hand. The answered questionnaire copies were collected and analyzed. After the preliminary analyses, some questions were omitted, modified or rearranged.

The questionnaire was judged by professional experts in the area of pharmaceutics. According to their comments and guidance some questions were omitted, modified or rearranged.

The questionnaire in its final form was distributed by the researcher to the sixteen pharmaceutical manufacturing facilities, an interview was conducted with the managers of each of the pharmaceutical manufacturing facilities or the quality assurance manager on their behalf. The questionnaire was filled by the store keeper and in some parts by the quality assurance manager in presence of the researcher. In some of the pharmaceutical manufacturing facilities the documents, records and SOPs were actually checked by the researcher. A reliability test was conducted in each case.

3.1.9 Limitation of the study

The study was not intended to give a detailed evaluation of storage practice in Sudanese pharmaceutical manufacturing facilities.

4. Results

The personnel qualification, hygiene and ongoing training in areas of store keeping, organizations, regulations and working condition. This section consisted of eight questions. Only about 57 percent of the facilities investigated complied with the guidelines in areas organization, personnel qualification, ongoing training in areas of store keeping and regulations. In contrast, about 17 percent not exactly comply, compared to 26 percent don't comply with the guidelines.

The general appearance, premises and facilities of the pharmaceutical manufacturing stores. This section consisted of ten questions. About 75 percent of the facilities studied complied with the guidelines in areas of general appearance, premises and facilities of the pharmaceutical manufacturing stores. However, about 11 percent not exactly comply, compared to about 14 percent don't comply with the guidelines.

Warehousing and storage conditions in the stores of pharmaceutical manufacturing facilities. This section consisted of thirty eight questions. Only about 59 percent of the facilities investigated, complied with the guidelines in areas of warehousing and storage conditions in the stores of pharmaceutical manufacturing facilities. In the contrary, about 16 percent not exactly comply with the guidelines compared to about 25 percent don't comply with the guidelines.

Equipment used in the store of pharmaceutical manufacturing facilities. This section consisted of eight questions. About 62 percent of the facilities surveyed comply with the guidelines in areas of equipment used in the store of pharmaceutical manufacturing facilities. On the other hand, about 26 percent not exactly comply, compared to about 12 percent of the facilities don't comply with the guidelines.

The storage requirements including documentation, and labeling. This section consisted of twenty three questions. About 73 percent of the facilities investigated comply with the guidelines in areas of documentation. In contrast, about 14 percent not exactly comply, compared to about 13 percent don't comply with the documentation guidelines.

The procedure of handling returned pharmaceutical products. This section consisted of four questions. About 83 percent of the facilities surveyed comply with the guidelines in areas of procedure of handling returned products. However, about 4 percent not exactly comply, compared to about 13 percent don't comply with the guidelines.

The procedure of handling recalled pharmaceutical products. This section consisted of six questions. About 60 percent of the facilities studied comply with the guidelines in areas of procedure of handling recalled products. In the contrary, about 20 percent of the facilities not exactly comply, compare to 20 percent don't comply with the guidelines.

The procedure of dispatch and transportation. This section consisted of three questions. Only about 38 percent of the facilities studied comply with the guidelines in areas of dispatch and

transport. On the other hand, about 6 percent not exactly comply, compared to about 56 percent don't comply with the guidelines.

To sum up, about 65 percent of the manufacturing facilities investigated comply with the good storage practice guideline. On the other hand, approximately 19 percent of the facilities investigated not exactly comply with the guideline, compared to about 16 percent of the manufacturing facilities don't comply with the good storage practice guidelines.

5.1 Discussion

This study is proposed to evaluate the implementation of good manufacturing practice guidelines in Sudanese pharmaceutical manufacturing facilities. To fulfill the objectives of the study, the researcher composed eight questions raised by its problem, accordingly the researcher hypothesized answers to these questions as stated in chapter two. Hereby, the discussion of results for each section then the eight hypotheses of the study will be reviewed individually against the results obtained by the data analysis.

5.1.1 The personnel qualification, hygiene, ongoing training in areas of GMP, and regulations.

The first hypothesis (*In some of Sudanese manufacturing facilities, no adequate number of qualified personnel to achieve pharmaceutical quality assurance objectives*.)

To test this hypothesis eight questions are used as shown in chapter 4. Only about 57 percent of the facilities investigated were found to be complied with the guidelines in areas of organization, personnel qualification, ongoing training in areas of store keeping and regulations. In contrast, about 17 percent did not exactly comply, compared with 26 percent did not comply with the guidelines.

Considering that the establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions. (Quality assurance of pharmaceuticals, 2006) To sum up, the results discussed above shows that a shortage of qualified personnel was cited as a major problem in some of the manufacturing facilities investigated. Consequently, the above hypothesis proved correct as it matches with the results discussion of the statistical analyses.

The results of a research done by (Assad, 2009.) surveillance of medicine storage practices in Khartoum state hospitals showed that personnel in charge of stores complied with requirement

of receiving proper training. These findings go in consistency with the results obtained by this study. Findings of Assad's study, did not discuss specifically the GSP as part of regular training, the results obtained by the present study shows that GSP was not part of regular training in most of the facilities investigated.

5.1.2 The general appearance, premises and facilities of the pharmaceutical manufacturing stores.

The second hypothesis **(***Storage areas (premises and facilities), in some of Sudanese pharmaceutical factories stores, are not of sufficient capacity to allow the orderly storage of materials and products*.)

To test this hypothesis ten questions are used as shown in chapter 4. About 75 percent of the facilities studied complied with the guidelines in areas of general appearance, premises and facilities of the pharmaceutical manufacturing stores. However, about 11 percent did not exactly comply, compared to about 14 percent did not comply with the guidelines.

Considering that the premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out (Quality assurance of pharmaceuticals,2006). The results discussed above shows that some of the manufacturing facilities investigated don't comply with the previous guideline. This strengthens the above and proves the hypothesis correct.

In the study done by (Sauwakon, 2002) (effective drug regulation multi-country study involved only 10 country out of the 191 WHO member states) the study results showed that problems related to the safety of personnel at manufacturing facilities exist in many places around the world today, in developing and developed countries alike. Some incidents have ended in tragedy, they are mostly caused by exposure to dangerous substance in open containers. These findings go in consistency with the results obtained by this study, shows that 50 percent of the manufacturing facilities did not have procedures in place ensuring good hygiene and safety of the personnel where exposure to material in open containers may occur.

5.1.3 Warehousing and storage conditions in the stores of pharmaceutical manufacturing facilities.

The third hypothesis **(***Warehousing and Storage conditions, in some of Sudanese pharmaceutical manufacturing facilities stores, does not comply with the good storage practice guidelines*.)

To test this hypothesis thirty eight questions are used as shown in chapter 4. Only about 59 percent of the facilities investigated, complied with the guidelines in areas of warehousing and storage conditions in the stores of pharmaceutical manufacturing facilities. In the contrary, about 16 percent did not exactly comply with the guidelines compared to about 25 percent did not comply with the guidelines.

Considering that storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate. (Quality assurance of pharmaceuticals,2006) The results discussed above shows that some of the manufacturing facilities investigated does not comply with the previous guideline. This strengthens the above and to a very high degree proved that the hypothesis correct.

These findings were consistent with a study conducted at hospital pharmacy stores in Sudan (Assad, 2009).

5.1.4 Equipment used in the store of pharmaceutical manufacturing facility.

The fourth hypothesis: (Equipment's *in some of the Sudanese pharmaceutical manufacturing facilities are not designed, located and maintained to suit its intended purpose. And may present hazard to the quality of the products*.)

To test this hypothesis eight questions are used as shown in chapter 4. About 62 percent of the facilities surveyed comply with the guidelines in areas of equipment used in the store of pharmaceutical manufacturing facilities. On the other hand, about 26 percent did not exactly comply, compared to about 12 percent of the facilities did not comply with the guidelines.

Considering that equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.(Quality assurance of pharmaceuticals,2006). The results discussed above shows that some of the manufacturing facilities investigated does not comply with the previous guideline. Consequently, the above hypothesis proved correct as it matches with the results discussion of the statistical analyses.

5.1.5 The storage requirements including documentation, and labeling

The fifth hypothesis *(Some of Sudanese pharmaceutical manufacturing facilities stores, do not comply with the good storage practice guidelines in areas of storage requirements including documentation, labeling and containers.)*

To test this hypothesis twenty three questions are used as shown in chapter 4. About 73 percent of the facilities investigated comply with the guidelines in areas of documentation. In contrast,

about 14 percent did not exactly comply, compared to about 13 percent did not comply with the documentation guidelines.

Considering that good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate. (Quality assurance of pharmaceuticals, 2006) The results discussed above shows that some of the manufacturing facilities investigated does not comply with the previous guideline. This strengthens the above and to a very high degree proved that the hypothesis correct.

GSP is the need for clear documentation of the performance of significant steps in the handling of products. This documentation should include an auditable historical record of who performed the work at what time and on what date. Fortunately, this formidable task can be achieved by using validated computer software designed specifically for inventory maintenance.

5.1.6 The procedure of handling returned products

The sixth hypothesis (*Returned pharmaceutical products, in some of Sudanese pharmaceutical manufacturing facilities stores, are not handled in accordance with approved written procedures*.)

To test this hypothesis six questions are used as shown in chapter 4. About 83 percent of the facilities surveyed comply with the guidelines in areas of procedure of handling returned products. However, about 4 percent did not exactly comply, compared to about 13 percent did not comply with the guidelines.

Considering that Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded. A written programme for ongoing stability determination should be developed and implemented.(Quality assurance of pharmaceuticals,2006) To sum up, the results discussed above shows that some of the manufacturing facilities investigated don't comply with the previous guideline. Consequently, the above hypothesis proved correct as it matches with the results discussion of the statistic analyses.

It is commonly recommended that stability testing be performed initially, than every three months for the first year, then every six months for the second year, and then annually thereafter. However, more frequent testing near the end of the anticipated expiration date is often likely to give better information about the actual stability of the finished product. Nonetheless, testing at least annually is considered minimal for compliance with cGMPs. Some firms have chosen, for economical purposes, random dates to test all stability samples of a given product. As long as there is at least one test performed annually, this approach can be quite satisfactory.

5.1.7 The procedure of handling recalled products

The seventh hypothesis (*Recalled products in some of Sudanese pharmaceutical manufacturing facilities stores, are not handled in accordance with approved written procedures*.)

To test this hypothesis four questions are used as shown in chapter 4. About 60 percent of the facilities studied comply with the guidelines in areas of procedure of handling recalled products. In the contrary, about 20 percent of the facilities did not exactly comply, compare to 20 percent did not comply with the guidelines.

Considering that there should be a system to recall from the market, promptly and effectively, products known or suspected to be defective. (Quality assurance of pharmaceuticals,2006). The recall system should be routinely evaluated and systemically monitored in order to identify problems in the process and determine whether the activities actually carried out are consistent with the intended course of action, especially when considering the recall of serious or potentially life-threatening situations..

To sum up, the results discussed above shows that some of the manufacturing facilities investigated don’t comply with the previous guideline. Consequently, the above hypothesis proved correct as it matches with the results discussion of the statistical analyses.

5.1.8 The procedure of dispatch and transportation

The eighth hypothesis **(***Dispatch and Transportation of pharmaceutical product in some of the Sudanese pharmaceutical manufacturing facilities don't comply with the requirement of the good storage practice*).

To test this hypothesis three questions are used as shown in tables (98-100). Only about 38 percent of the facilities studied comply with the guidelines in areas of dispatch and transport. On the other hand, about 6 percent did not exactly comply, compared to about 56 percent did not comply with the guidelines.

Considering that transportation process should not compromise the integrity and quality of pharmaceutical products. The manufacturer should communicate all relevant conditions for storage and transportation to those responsible for the transportation of pharmaceutical products. Such an entity(-ies) should ensure adherence to these requirements throughout transportation and

at any intermediate storage stages. (WHO,2006). The results discussed above shows that some of the manufacturing facilities investigated does not comply with the previous guideline. This strengthens the above and to a very high degree proved that the hypothesis correct.

5.2 Conclusion

The potential justification behind conducting this research is to evaluate the current medicine good manufacturing practices in Sudanese pharmaceutical manufacturing facilities and their compliance to the recommended guidelines. Sixteen manufacturing facilities have been included in the study. These were the only working manufacturing facilities at the time these study was conducted.

Eight hypotheses are established as shown in chapter one, and later tested against the results of the study. The main hypothesis are built around the idea that some Sudanese manufacturing facilities does not comply with the GMP guidelines.

The findings of the present study contribute to the growing concern over the storage practice, and the importance of implementation of GMP guideline.

Results of the study proved all the study hypotheses correct as they reveal that:

Only about 57 percent of the facilities investigated were found to be complied with the guidelines in areas of organization, personnel qualification, ongoing training in areas of store keeping and regulations.

About 75 percent of the facilities studied complied with the guidelines in areas of general appearance, premises and facilities of the pharmaceutical manufacturing stores.

Only about 59 percent of the facilities investigated, complied with the guidelines in areas of warehousing and storage conditions in the stores of pharmaceutical manufacturing facilities.

The choice of temperature has been dictated by common practice rather than scientific investigation. There is clearly a need for further research to investigate the long-term effects of storing products at various temperatures.

Only about 62 percent of the facilities surveyed comply with the guidelines in areas of equipment used in the store of pharmaceutical manufacturing facilities.

About 73 percent of the facilities investigated comply with the guidelines in areas of documentation.

About 83 percent of the facilities surveyed comply with the guidelines in areas of procedure of handling returned products.

Only about 60 percent of the facilities studied comply with the guidelines in areas of procedure of handling recalled products.

Only about 38 percent of the facilities studied comply with the guidelines in areas of dispatch and transport.

To sum up, only about 65 percent of the manufacturing facilities investigated comply with the GMP guideline. On the other hand, approximately 19 percent of the facilities investigated did not

exactly comply with the guideline, compared to about 16 percent of the manufacturing facilities did not comply with the GMP guidelines.

5.3 Recommendations

Manufacturing facilities have to provide regularly updated Job descriptions, should have qualified key person at the manufacturing facility, an evaluation should be made of all activities to identify training needs, and should have good storage practice as part of regular training.

Manufacturing facilities should have procedures ensuring good hygiene and safety of the personnel where exposure to material in open containers may occur, adequate ventilation at the warehouse, and heating/air-conditioning system installed.

Stores outside the facility have to get inspected by the regulatory authority, manufacturing facilities have to provide written procedures for warehousing, authorized release procedures in place in the warehouse, written procedure for documentation of product reception, appropriate intake control procedures in place, written procedures and documentation for unloading of products, and records for cleaning activities.

Manufacturing facilities should ensure that the storage temperature is always kept within a defined range and controlled. A retest should be conducted to pharmaceutical products in the stores of manufacturing facilities.

Manufacturing facilities have to maintain waste materials awaiting disposal stored safely and properly, store containers of sensitive products under adequately monitored storage conditions, storage requirements for dangerous goods met on site and during transportation, and ensure that equipment for bulk storage is designed according to product requirements.

Manufacturing facilities should have a process in place to consider if deviations of calibration of quality critical equipment have had an impact on the quality of product since the last successful calibration, written procedure for the maintenance, preventive maintenance plan, maintenance record, and have to clean and maintain each piece of equipment in contact with the product according to written procedures.

Manufacturing facilities should have a quality manual and written procedures describing all GMP related processes, provide the retest date or expiry date and storage conditions (where applicable) with each shipment, either on the label or on the COA, and should have written procedure for segregation or prevention of cross contamination, if hazardous (e.g. toxic, corrosive) products are present on the site.
COAs of the original manufacturer should only be used for originally sealed and properly stored products.

Manufacturing facilities should have procedure ensuring all customers and authorities are informed in case of serious or potentially life-threatening situations, and effectiveness of the recall system should be evaluated.

Manufacturing facilities should have appropriate system (physical or computerized), to control materials in segregated areas.

Manufacturing facilities should have procedure in place, to ensure controlled conditions during transportation of products where necessary.

References

1. Assad Abdel Rafie, 2009. Surveillance of medicine storage practices in Khartoum state hospitals *(un published).*
2. *Barbara A. Kozikowski, Thomas M. Burt, Debra A. Tirey, Lisa E. Williams, Barbara R. Kuzmak, David T. Stanton, Kenneth L. Morand and Sandra L. Nelson J Biomol, 2003,* The Effect of Room-Temperature Storage on the Stability of Compounds in DMSO 8: 205. *Screen 2003 Journal of Biomolecular Screening.*
3. Clark J., 2006. Risk management in the biomaterial cold chain. Contract Pharma..*http://www.contractpharma.com/articles/2006/11.*
4. Cohen V, Jellinek sp, Teperikidis L, et al., 2007. Room temperature stability of medications labeled for refregration. *Am J Health Syst Pharm;64:1711-5.*
5. Elamin et al, 2010. Availability of Essential Medicines in Sudan, *Sudanese Journal of Public Health, January, 2010, Vol.5 NO1.*
6. European Medicines Agency (EMA),2011. a concept paper on storage conditions during transport.
7. EU-GMP, 1998. Good manufacturing practices Medicinal products for human and veterinary use, EUROPEAN COMMISSION Directorate General III – Industry Pharmaceuticals and cosmetics, *The rules governing medicinal products in the European Union Volume 4 Edition EU-GMP-Vol4_ (Orange guide).*
8. Federal Ministry of Health, 2010. SUDAN PHARMACEUTICAL COUNTRY PROFIL, world health organization *www.who.int/medicines/areas/coordination/Sudan*
9. Food and Drug Administration, 2009. Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). Rockville, MD: Author;2009.

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm062693.htm.

10. Food and Drug Administration, 2010. Guidance for Industry: Current Good Manufacturing Practice for Finished Pharmaceuticals *ORA/ORO/DEIO/IB* Number: 41 EXPIRATION DATING AND STABILITY TESTING FOR HUMAN DRUG PRODUCTS- 21 CFR Part 211 -.*

11. Food and Drug Administration, 2004. Department of Health and Human Services. Current good tissue practice for human cell, tissue, and cellular and tissue-based product establishments; *Inspection and enforcement (21 CFR Parts 16, 1270, and 1271). Fed Regist 2004;69:68612–68688.*

12. Ginsburg, 2008. TW Burke, P. Febbo Centralized biorepositories for genetic and genomic research. *JAMA 2008;299:1359–1361.*

13. ICH, 1993-2001. GUIDELINE STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS, *International Conference of Harmonization ICH.*

14. ISBER, 2008. Best practices for repositories. Cell Preservative Tech. *2008;6:3–58.*

15. John Mills F., 2009. Chairman of the Board, BioStorage Technologies,The Need For Good Storage Practice — Biopreservation and Biobankin, *http://www.liebertpub.com.*

16. Kim Huynh-Ba (ed.), 2008. Springer Science and Media Publishing, available November 2008, "Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies and Best Practices", *ISBN:978-0-387-85626-1, www.springer.com or www.amazon.com.*

17. Mitchell Bl, Y Yasui, CI Li, et al., 2005. Impact of freeze-thaw cycles and storage time on plasma samples used in mass spectrometry based biomarker discovery projects. *Cancer Infor. 2005;1:98–104.*

18. National drug policy 2005-2009. Sudanese National Ministry of health, *www.fmoh.com.*

19. Neeta Bahal O'Mara, Pharm.D., BCPS, October 2008. Stability of Refrigerated and Frozen Drugs, *PHARMACIST'S LETTER / PRESCRIBER'S LETTER Volume 24~Number 241001.*

20. Planta MB, 2007. the role of poverty in anti-microbial resistance. *J Am Board Fam Med; 20:533-39.*

21. Quality assurance of pharmaceuticals, 2006. a compendium of guidelines and related materials, Vol.2, Good manufacturing practices and inspection. –2nd edition, *WHO Library Cataloguing-in-Publication Data.*

22. United Arab Emirates, 2006. Good pharmaceutical storage and distribution practice(GS&DP). *Ministry Of Health Drug Control Department.*

23. U.S. Department of Health and Human Services,2007. Centers for Disease Control and Prevention, and National Institutes of Health. Biosafety in Microbiological and Biomedical Laboratories (BMBL), *5th ed. Washington, DC: US Government Printing Office.*

24. World Health Organization, 1992. Expert Committee on Specifications for Pharmaceutical Preparations. Good Manufacturing Practices for pharmaceutical products. *Geneva, (WHO Technical Report Series, No. 823), Annex 1.*

25. World Health Organization, 1992. Expert Committee on Specifications for Pharmaceutical Preparations, Validation of analytical procedures used in the examination of pharmaceutical materials. *Geneva, (WHO Technical Report series No.32).*

26. World Health Organization, 1996. WHO technical report series No. 863.

27. World Health Organization, 1999. WHO technical report series No. 885.

28. World Health Organization, 1999. Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. *Volume 2. Good manufacturing practices and inspection. Geneva.*

29. World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations, 2002. Model certificate of analysis, Thirty-sixth report. Geneva, *(WHO Technical Report Series, No. 902).*

30. World Health Organization, 2003. Expert Committee on Specifications for Pharmaceutical Preparations, 2003, Good Manufacturing Practices for pharmaceutical products: main principles, Thirty-seventh report. Geneva,*(WHO Technical Report Series, No. 908), Annex 4.*

31. World Health Organization, 2006. Expert Committee on Specifications for Pharmaceutical Preparations, Good distribution practices for pharmaceutical products *(WHO Technical Report Series, No. 937),Annex 5.*

32. World Health Organisation, 2007. Receipt and storage of purchased products.