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ASSESSMENT OF CROSS-CONTAMINATION PREVENTION PRACTICES IN PHARMACEUTICAL PRODUCTION: A COMPARATIVE CASE STUDY OF TWO PHARMACEUTICAL MANUFACTURING PLANTS IN ETHIOPIA

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December, 2017

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A thesis submitted to Addis Ababa University, Department of Pharmaceutics and Social Pharmacy, School of Pharmacy' in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics.

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This is to certify that the thesis prepared by Eyob Assefa, entitled **Assessment Of Cross-Contamination Prevention Practices in Pharmaceutical Production: A comparative case study of two pharmaceutical manufacturing plants in Ethiopia.** It is submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics and complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Acknowledgments

I would first like to thank my thesis advisors Prof. Tsige Gebre-Mariam and Dr. Anteneh Belete for their guidance and steering me in the right direction. Whenever I look for their help, they have been there for me.

I would also like to thank the pharmaceutical manufacturing companies involved in this study for their kind cooperation, the key respondents for their willingness and passionately participating in the study.

I am also gratefully indebted to the support I get from my family and friends throughout this study.

Finally my heart felt thank will go to Addis Ababa University and Addis Pharmaceutical Factory Sh. Co. for sponsoring My study

Eyob Assefa

December, 2017

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List of Acronyms

AHU	*Air Handling Unit*
API	*Active Pharmaceutical Ingredient*
EFMHACA	*Ethiopian Food Medicine and Health Care Authority*
EMA	*European Medicine Agency*
EU	*European Union*
FI	*Fully Implemented*
GMP	*Good Manufacturing Practices*
HEPA	*High Efficiency Particulate Air filter*
HPAPIs	*Highly Potent Active Pharmaceutical Ingredients*
HVAC	*Heating Ventilation and Air Conditioning*
ICH	*International Conference on Harmonization*
IPQC	*In-Process Quality Control*
LOD	*Limit of Detection*
LOQ	*Limit of Quantitation*
NA	*Not Applicable*
NI	*Not Implemented*
NRA	*National Regulatory Authorities*
OSD	*Oral Solid Dosage forms*
PMDA	*Pharmaceuticals and Medical Devices Agency*
PI	*Partially Implemented*
PIC/S	*Pharmaceutical Inspection Co-operation Scheme*
QC	*Quality Control*
QA	*Quality Assurance*
SOP	*Standard Operating Procedure*
TD	*Type Of Deficiency*
UNIDO	*United Nations Industrial Development Organization*
WHO	*World Health Organization*

Operational Definitions:

Analytical method validation: The process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use by means of well-documented experimental studies that establish documented evidence on accuracy and reliability of the analytical results.
Cleaning validation: Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.
Contamination: The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or onto a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.
Critical deficiency: An observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk.
Cross-contamination: Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.
Fully implemented (FI): All cGMP requirements regarding avoiding cross-contamination mentioned in the WHO and EFMHACA cGMP guidelines are in place and as required.
Good manufacturing practices: That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.
Installation qualification: The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.
Major deficiency: An observation describing a situation that may have an impact on the product but is not as significant as a critical observation.
Marketing authorization: A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.
Minor deficiency: An observation describing a situation that is a departure from cGMP but has no significant impact on the product quality.
Not applicable (NA): Those elements of cGMP included in the observation checklist, but not evaluated due to non-relevance in the companies.

Not implemented (NI): Non-execution of cGMP requirements regarding avoiding cross-contamination mentioned in the WHO and EFMHACA cGMP guidelines.
Operational qualification: Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.
Partially implemented (PI): Partial execution of cGMP requirements regarding avoiding cross-contamination mentioned in the WHO and EFMHACA cGMP guidelines.
Performance qualification: The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.
Risk assessment: Method to assess and characterize the critical parameters in the functionality of an equipment or process.
Standard operating procedure (SOP): An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection).

Abstract

Introduction: It is vital for pharmaceutical manufacturing companies to protect their customers' health by manufacturing safe and quality medicines by adopting Good manufacturing practices (GMP), tools which help to ensure achieving this target sustainably. Among others, cross-contamination should be avoided by robust design of the premises, equipment and processes which take place within a manufacturing facility. The Food, Medicine, Healthcare Administration and Control Authority (FMHACA) has prepared a GMP roadmap for compliance of Ethiopian pharmaceutical manufactures by the Year 2018. Conducting scientific assessments on the companies' status of cross-contamination prevention can provide pertinent information for the companies to take appropriate interventions on cross-contamination aspects of GMP guidelines.

Objective: The aim of this study was therefore to assess, evaluate and compare the extent of cross-contamination prevention GMP guidelines implementation in the production areas of two Ethiopian pharmaceutical manufacturing companies, Company and Company B.

Methodology: This study was a descriptive study conducted with comparative case study approach. Comprehensive methods that have 2 phases were conducted in June and July 2016 in Ethiopia. Field observation using structured checklist adopted from WHO GMP guideline, data collection from the company's key personnel and chemical analysis of target residue on randomly selected equipment cleaned with the companies' existing procedures have been used.

Results: This study revealed that Company A has been operating with less compliance risk with 90.3% rating when compared to company B with 77.2% overall rating. The premises and Heating Ventilation and Air Conditioning (HVAC) system of the two companies were considerably different with critical deficiencies observed in company B. Moreover, the effectiveness of cleaning procedures in reducing active ingredient carryover was better in company A.

Conclusion and Recommendations: Company A exhibited better compliance with no critical deficiency while Company B operated with critical deficiencies and higher compliance risks. In order to achieve GMP compliance with respect to cross-contamination and protect the safety of its customers Company B has to upgrade the manufacturing site and shall focus on solving validation gaps this study revealed.

Keywords: Critical deficiency, Cross-Contamination, Good Manufacturing Practices, HVAC, Premises, Validation

1. Introduction

Today, more people than ever are taking pharmaceuticals. People prescribing or being prescribed medicines have little chance of detecting if the medicines are faulty or not. People who take medicines trust the doctor who wrote the prescription and the pharmacist who dispensed it. The doctor and pharmacist in turn put their trust in the manufacturer who has a fundamental role in ensuring that the medicine is fit for its purpose and is safe to use *(Learoyd, 2005).*

1.1. Good manufacturing practices (GMP) guidelines

For ensuring the safety and quality of the manufacturing process, pharmaceutical companies have to follow specific quality requirements which have an impact of the whole management and manufacturing process of the company. GMP ensures that quality is built into the organization and processes involved in manufacturing. It is intended to help ensure the safety and efficacy of all products *(WHO, 2007).*

Medicines are perhaps as old as mankind and the concepts how their quality has to be ensured has evolved gradually over the time (*Santoso and Rago, 2009*). More than from the growth of scientific knowledge, medicines regulation has been catalyzed by unfortunate events. A work by Patel and Chotai (2008) has outlined the history of GMP. Tragic incidents that trigger the establishment of GMP and chronological development are listed in Table 1.1.

GMP was initiated in 1978, since then it has been in a dynamic state and hence the name current GMP (cGMP) and to date various revisions and amendments have been made. For instance, the 1982 revision of GMPs made tamper resistant packaging a requirement for over the counter (OTC) drugs. This revision was triggered by 7 deaths which happened due to replacement of acetaminophen with cyanide in acetaminophen capsule and subsequent poisoning *(Immel, 2005).*

Since the establishment of GMP, the prime objectives set out in law and guidance has been to ensure that products are manufactured batch upon batch, year upon year, to the appropriate and consistent quality standards and in accordance with regulatory requirements. *(Nandhakumar et al., 2011& WHO, 2007)).*

Table 1. 1: Chronological development in the establishment of GMP

Year	Event	Result
1906	A book called "The Jungle" exposed adulteration and unsanitary conditions in Chicago meat packing industry	Pure Food and Drug Act passed by United States congress which in turn Created one of the first government regulatory agencies (now known as FDA)
1938	Sulfanilamide made with poisonous solvent diethylene glycol causes 107 deaths	Federal Food, Drug and Cosmetic (FD&C) Act introduced. It put proving the safety of products before marketing as a requirement.
1941	Nearly 300 deaths and injuries from distribution of sulfathiazole tablets tainted with phenobarbital.	FDA revises manufacturing and quality controls drastically, the beginning of what will later be called GMPs.
1962	Thalidomide causes birth defects in thousands of European babies.	Kefauver-Harris Drug Amendments introduced. It put a requirement for manufacturers to prove efficacy of products before marketing them and ensure stricter control over drug testing
1978		CGMPs Final rules for drugs and devices (21 CFR 210–211 and 820):Establishes minimum current good manufacturing practices for manufacturing, processing, packing, or holding drug products and medical devices.

Source: Patel and Chotai, 2008

Today, due to the emerging regulatory needs of pharmaceutical sector, the drug evaluation for the control of drug quality and trade has become highly sophisticated. Regulatory guidelines and standard tools provide a basis for implementation of laws, whereas laws provide a legal basis for drug control. The world covers more than 100 countries, where most of them have established pharmaceutical legislations and regulatory requirements. (*Santoso and Rago, 2009*).

The increase in global trade in pharmaceutical products, and growth in the complexity of technical regulations related to drug efficacy, safety, and quality. Efforts to harmonize various elements of drug regulatory activities have been initiated by various inter-governmental

organizations at regional and inter-regional level in the past decade and also subsequently paved the way to the establishment of International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan, and the United States with observers from WHO and Health Canada *(Rago,2004,).*

Implementation and enforcement of cGMP principles requires the involvement and interaction of stakeholders (e.g. regulatory bodies, manufacturers, traders, consumers, health professionals, researchers and governments) whose economic, social and political motives may differ, making implementation both politically and technically challenging *(Nandhakumar et al., 2011).*

Medicines regulation has administrative part but far more important is the scientific basis for it. All medicines must meet three criteria: be of good quality, safe and effective. The judgments about medicines quality, safety and efficacy should be based on solid science. There are several general and specific factors contributing to effective regulation by National Regulatory Authorities (NRA). General factors include political will and commitment to regulation, adequate availability of medicines that are accessible (to avoid smuggling and illegal use), strong public support for drug regulation, effective cooperation between NRA and other government institutions including those dealing with law enforcement (e.g. customs and police), and sufficient qualified and experienced pharmaceutical, medical and other professionals *(T.T. He et al., 2015)*.

Although even quality issues are still a problem (poor quality of starting materials including active pharmaceutical ingredients, quality problems with finished dosage forms, spreading of counterfeit medicines) it is likely that new technologies and new products will create new regulatory challenges*(Haleem et al., 2015).*

Recent scientific advances in fields as diverse as genomics and nanotechnology hold out the promise of major therapeutic breakthroughs. In parallel with innovations, a special set of standards must be gradually established in the global regulatory environment. In fact, some elements already do exist. To examine and predict environment impact is also a new task for pharmaceutical regulators (*Maynard et al., 2006*)

1.2. Cross-contamination as core element in GMP guidelines

Contamination from potentially harmful drugs such as steroids, hormones, cytotoxics, radio pharmaceuticals, and highly potent active pharmaceutical ingredients (HPAPIs) can cause severe side effects in workers, especially those who are exposed to them over long period of time, and have the potential to place patients at risk as well.In recent years, cross-contamination of medicinal products in shared facilities has come under increased regulatory scrutiny. Global regulations and guidelines for preventing cross-contamination have been published and have increasingly taken a risk-based approach *(Sargent et al, 2016).* Regulatory authorities across the world have created rules and guidelines as part of GMP to prevent cross-contamination and in order to protect patients and workers.

In 1978, the US Food and Drug Administration (US FDA) issued regulations pertaining to "minimum current GMP" for preparation of drug products for administration to humans or animals *(US FDA, 1978).* Subpart C of 21 CFR 211.42 broadly outlined requirements for the prevention of cross-contamination. It states "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures …" *(US FDA, 1978).* Other drug regulatory bodies including the European Medicines Agency (EMA) and the World Health. Organization (WHO), followed with similarly broad requirements *(Sargent etal, 2016).*

The lack of specificity as to the scope of guidance, different interpretations as to the classification of compounds, and the lack of agreement as to the acceptable level of controls required for the manufacture of highly hazardous compounds led to concerns about manufacturing pharmaceutical products in multi-product facilities. However, since the establishment of the Pharmaceutical Inspection Convention (PIC) in 1970 and Pharmaceutical Inspection Co-operation Scheme (PIC Sheme) in 1995 consensus has been enhanced globally on requirements that multi product manufacturers should implement to avoid cross-contamination *(Sargent etal, 2016).*

The International Conference on Harmonization (ICH), in its Q7 document which was also included in Part II of PIC/S GMP Guide in 2007 recommends using dedicated production areas, which can include facilities, air handling equipment and processing equipment, in the

production of highly sensitizing materials, such as Penicillins and *Cephalosporins (Rosa,2014. PIC/S, 2007& ICH, 2006)*

EU Guidelines for GMP Volume 4(2008) has put several points on measures to be taken to avoid cross-contamination which includes:

- The requirement to have appropriate design and operation of manufacturing facilities;
- The necessity to commensurate measures taken with the risks;
- To have adequate working and in-process storage space that can permit the orderly and logical positioning of equipment and materials;
- The requirement to have specific provisions that should be taken to avoid cross contamination and facilitate cleaning in cases where dust is generated; and
- The requirement to have dedicated facilities for manufacturing of medicinal products that can potentially present a significant risk including highly sensitizing materials such as beta lactams.

WHO (2007) has also given a direction on avoiding cross-contamination by taking appropriate technical or organizational measures, such as:

- Carrying out production in dedicated and self-contained areas for some hazardous products;
- Validating cleaning procedures & testing for residues;
- Providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems; and
- Using a "closed system" in production

USFDA guidance for industry published in 2013, while has focused on relative health risk of, and the potential for, cross-reactivity in the classes of sensitizing beta-lactams (including both penicillins and non-penicillin beta-lactams). Some of the directions provided by this guidance include:

- The requirement to have separate or defined areas or such other control systems for the firm's operations;

- The necessity to make the section of the manufacturing facility dedicated to manufacturing penicillin is isolated (i.e., completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured;
- Also, the requirement to have completely separate air handling systems for penicillin from those used for other drugs for human use; and
- Additionally, the requirement to test non-penicillin drug products for penicillin where the possibility of exposure to cross-contamination exists.

When we see the *EFMHACA (2014)* GMP guideline, it is similar to what mentioned by *WHO (2007)* including the requirement to have measures for preventing cross-contamination and checking the effectiveness of these measures.

In general, all GMP guidelines reviewed by this study seldom mention different requirements at the core and have indisputably indicated the necessity of preventing cross-contamination at every stage of manufacturing and following risk based approach.

The hazard that can be posed by beta lactams is potentially life-threatening and complex to prevent without dedicated facility, according to *USFDA (2013)* because it is difficult to define the minimal dose below which allergic responses are unlikely to occur in humans. There is a lack of suitable animal or receptor testing models that are predictive of human sensitivity and the threshold dose at which allergenic response could occur is extremely low and difficult to detect with current analytical methods.

1.3. Sources of cross-contamination

The reasons for cross-contamination can vary. WHO suggests that contaminants may result from inappropriate premises (e.g., poor design, layout or finishing), poor cleaning procedures, contaminants brought in by personnel, and a poor HVAC system *(WHO, 2007).* According to *Eudralex (2008),* factors for cross-contamination include facility/equipment design, personnel flow, physico-chemical characteristics of the API, process characteristics, cleaning processes and analytical capabilities.

The contamination at unsafe levels of one product with another can happen through 4 mechanisms i.e., mix up which may come due to inadequate plant and process design or human error, retention that cause carryover of material on product contact surfaces from one product to another in the same equipment used in a sequential or campaign manner, mechanical transfer

which can arise through inappropriate personnel and material flows and air borne transfer which is the generation and subsequent movement of a stable aerosol to another area where it is deposited in unsafe quantities on another exposed product *(ISPE, 2010)*

1.4. Pharmaceutical manufacturing in Ethiopia

With an estimated population of 92 million in 2016, Ethiopia has the potential to become a significant market for pharmaceutical products in sub-Saharan Africa *(World Bank,2011)).*According to Ernst &Young (2009) Ethiopia is expected to become the third-largest sub-Saharan economy by 2023 following South Africa and Nigeria.

Since the GMP Roadmap was made official, the factories have been working towards implementing GMP elements by 2018. With only less than 1 year is left for the deadline, only 3 of the 9 manufacturing plants are able to get PIC/S Certification. Ethiopian industry policy focuses on encouraging self-reliance on local production so that essential medicines are affordable in the country. However, most Ethiopian companies are staggering for existence due to compliance with the regulatory standards and other issues. Moreover, dependence on foreign companies for technology and knowledge sources has been one of the shortcomings of the local manufacturers *(Gebre-Mariam et al. 2015).*

1.5. Statement of the problem

If certain sensitizing compounds, such as penicillins and beta-lactam antibiotics, make their way into production of other drugs, they can trigger allergic reactions, even at low levels. The risks range from inconvenient (hives, a rash, or itchy eyes) to dangerous immune responses, including full-blown anaphylactic reactions, which may be fatal.

According to *Sargent (2016),* beyond having an unintended effect, a cross-contaminated drug may not have its desired effect. This means the people taking the medication won't receive the treatment that they need. Even if there are cases where ineffective medications are merely harmless to the people who take them; they can result in product recall for the manufacturer.

Pharmaceutical manufacturers follow different practices to prevent risks of cross-contamination and to prove that no cross-contamination has occurred by delivering detailed documentation. However, there are certain challenges when it comes to adopting actions designed to avoid cross-contamination. One of these difficulties derives from the fact that, in order to keep costs low and manufacturing efficient often pharmaceutical manufacturers run

different pharmaceutical products in parallel. While this is cost effective, it increases the risk of cross-contamination, where active ingredients from one line can be carried across to the other: through the air, on workers' clothing, via contaminated equipment or through poorly designed facilities. This can place both workers and patients at risk *(David, 2014 & ISPE,2010).*

Cross contamination prevention could not be ensured without putting in place at least the minimum standards of GMP guidelines. Thus far, out of the nine Pharmaceutical manufacturing factories in Ethiopia only 3 are able to acquire PIC/S GMP Certification. To date, there is no any study-based evidence that can be used as an insight to implement the prevention of cross-contamination in Ethiopian pharmaceutical manufacturing factories.

1.6. Research questions

In line with the above general introduction on the subject matter and description of statement of the problem, the main research questions were:

- Do premises, HVAC systems and production area equipment design, construction and maintenance in the two local pharmaceutical manufacturing companies prevent risk of cross-contamination? And how similar/different are the maintenance practices in the two companies?
- How is the overall awareness of personnel in the two companies with regard to prevention of cross-contamination? And how similar/different is the awareness in the two companies?
- Do the cleaning processes in the two local pharmaceutical manufacturing companies prevent risk of cross-contamination? And how similar/different

1.7. Significance of the study

This study envisages the provision of an insight to local pharmaceutical manufacturers about the effectiveness of cross-contamination prevention practices in two sampled factories, when weighed against the GMP requirements. It also attempts to assess practices in the two different manufacturing companies- how the manufactures identify areas where intercompany best practices transfer is possible ultimately showing the underlying gaps that impede non-GMP compliant company from getting this certification.

The study will inform the manufacturers the imperativeness of preventing cross-contamination to guarantee product safety, efficacy and quality.

1.8. Scope of the study

The scope of this study did not extend to prove whether unacceptable level of cross-contamination exist in either of the 2 factories involved, rather the cross-contamination practices in these companies was weighed against the GMP requirements. Evaluating the effectiveness of the equipment cleaning procedures of the companies was done analytically without suggesting whether unacceptable carryover exists or not. Also, this study's sole target was production areas.

1.9. Conceptual framework of the Study

The main purpose of this study was to make a detailed analysis on cross-contamination prevention practices in two pharmaceutical manufacturing companies. Based on the aforementioned review of guidelines and concepts on sources of cross-contamination the conceptual frame work for this study has been developed. (See Fig. 1.1)

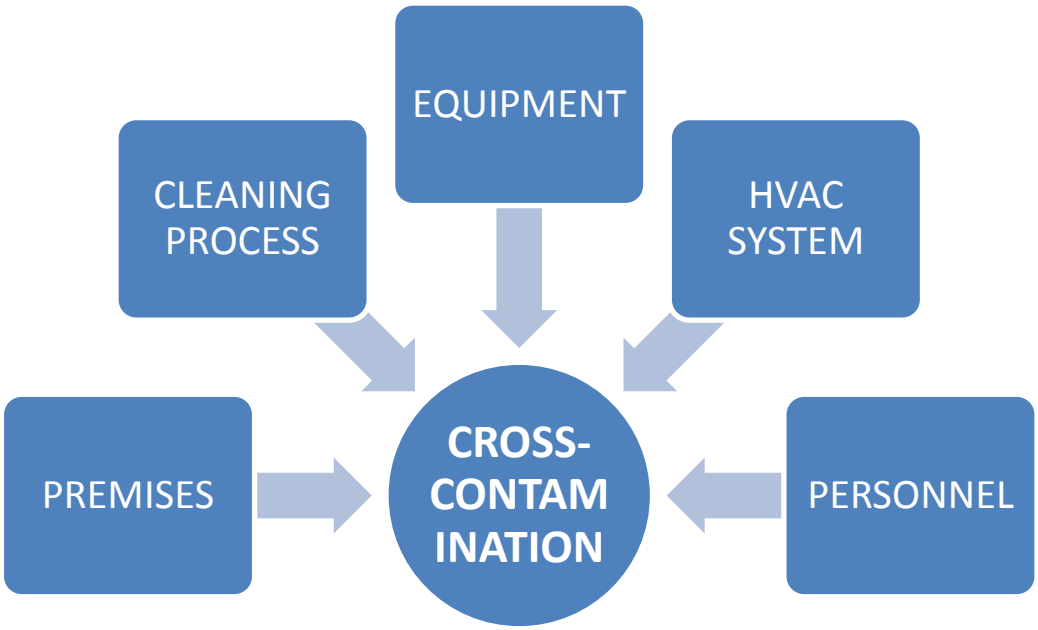

Figure 1.1: Conceptual framework of the study

In studying cross-contamination, while regulatory recommendations differ from country to country, the broad trend has been to segregate the manufacturing of specific types of products including sensitizing ones *(David, 2014).* According to *WHO(2007*) In order to minimize the

risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins). Also according to *EFMHACA (2014)* the layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination.

Considering HVAC system, cross-contamination risk can be prevented along with others by controlling airborne contaminants through effective ventilation and filtration, putting sufficient magnitude pressure differentials to ensure containment and prevention of flow reversal without creating turbulence *(David, 2014).* Also it is a requirement to separate air handling systems for non-penicillin products from those used for Penicillins (*WHO, 2007*). In addition EFMHACA *(2014)* require that air containing dust from highly toxic processes shall never be re-circulated to the HVAC system (*EFMHACA, 2014*).

Having inappropriate or ineffective cleaning procedures could invariably cause cross-contamination between products. While manufacturing different products without dedication, cross-contamination can be controlled through production campaigning, following appropriately qualified cleaning processes and performing checks during product changeover to minimize the amount of product carryovers *(David,2014).* In addition, according to *WHO (2007)* non-dedicated equipment should be cleaned according to validated cleaning procedures between being used for production of different pharmaceutical products to prevent cross-contamination.

The suitability of the equipment for its intended purpose taking into consideration requirements such as smooth finishes, right quality of construction materials assuring that surfaces with product contact are cleanable, maintenance which have little impact on clean room production processes do have tremendous impact on activities of controlling cross-contamination *(David,2014 & WHO(2007).*

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. Moreover, dedication as needed and conducting adequate qualification works at every stage from design to performance is also necessary.

Training is key in imparting good practices in personnel, that is, knowing that each and every person has a responsibility to consumer health. Prior to and during employment, all personnel working in production area should undergo the relevant GMP training, and be periodically assessed for competency *(WHO, 2007).*

2. Objectives

2.1. General objective

To assess, evaluate and compare how cross-contamination prevention guidelines are implemented and practiced in production areas of two local pharmaceutical manufacturing companies one of which is GMP certified from PIC/S and the other working towards acquiring PIC/S certification.

2.2. Specific objectives

- To assess how premises, HVAC systems and production area equipment are designed, constructed and adopted to prevent risk of cross-contamination in two local pharmaceutical manufacturing companies one of which is GMP certified from PIC/S and the other working towards acquiring PIC/S certification.
- To evaluate personnel capacity in preventing risk of cross-contamination in the two local pharmaceutical manufacturing companies.
- To evaluate how the cleaning process is developed and implemented in preventing risk of cross-contamination and to analyze the extent of active residues carryover after equipment cleaning in the two local pharmaceutical manufacturing companies.

3. Methodology

3.1. Study design

The study has been conducted with comparative case study approach by comprehending of data from 3 different sources i.e. self-administered questionnaire, field observation checklist and laboratory test results. The rationale behind selecting case study design to conduct the study is due to the complexity and multi dimensionality of the subject of the study. Cross-contamination is associated with multiple factors and demand a holistic and in-depth analysis.

The definition and relevance of case study have been provided by different scholars and in numerous works. Yin, 2003 has defined it as an empirical inquiry that contextually and realistically examine contemporary phenomenon. In the same book, Yin has also mentioned the relevance of case study research in circumstances where triangulation of data from multiple source is converged and as another result. Hancook and Algozine also described case study research as a means of identifying a topic that lends itself to in-depth analysis in a natural context and that use multiple sources of information. (Hancook and Algozine,2006)

Triangulation of data was practiced in this study to have in-depth analysis of the cases. Two major approaches have been followed in this study. On the first approach, assessment survey has been conducted by collecting data from the companies' key personnel through self-administered questionnaire and field observation by PI with semi structured observation checklist. While the second approach involves laboratory based test. On the laboratory based test, residual analysis of active pharmaceutical ingredient (API) was conducted on cleaned equipment using swab sampling technique and validated analytical method.

Comparative case study is a distinct form of multiple case study approach which enables the researcher to draw independent conclusions from different cases. Moreover, in circumstances where researcher predicts contrasting result for predictable reason which is also known as theoretical replication such kind of multiple case study is appropriate. *(Yin, 2003)*Hence, to evaluate the cross-contamination prevention practices in a context of GMP certification comparative case study method was preferred.

3.2. Study area and setting

The cases to be studied were selected to be two local pharmaceutical manufacturing plants of Ethiopia licensed to manufacture and sell medicines in different dosage forms by the national

regulatory authority (EFMHACA).The first case i.e. Company A, did have GMP certification from a foreign organization named pharmaceutical inspection co-operation scheme (PIC/S).While the second case (Company B) was working towards GMP certification but did not have one. Selection of cases was intentionally done so as: a) to be able to contrast the extent of cross-contamination prevention practices between GMP certified company and not certified one b) to weigh in the background idea "GMP certification from authorized regulatory organization can obviously indicate better extent of cross-contamination prevention requirements".

This study was conducted in June and July 2016. At the time of the study, there were nine pharmaceutical manufacturing companies in Ethiopia producing human and veterinary medicines. Since the country GMP Roadmap was made official in 2013, the factories have been working towards implementing GMP elements by 2018. At the time of study 3 of the 9 manufacturing plants were able to get PIC/S Certification.

3.3. Study population

Two pharmaceutical manufacturing companies that were licensed to manufacture and sell medicines in different dosage forms by the national regulatory authority (EFMHACA) were involved in the Study. Key technical and management staff members working in selected pharmaceutical manufacturing companies that were directly or indirectly involved in the implementation of product QA system within their respective companies were included in the study**.**

3.4. Sampling and sample size

According to Yin (2003), following replication logic is more applicable for multiple case study research than sampling logic. Hence exactly the same logic is followed in conducting this study in the selected 2 companies. Key respondents were selected on the basis of responsibilities they have and the role they play in the subject matter of this study. Hence, plant managers, production managers, quality assurance and quality control managers, maintenance and engineering department managers and division heads and other senior professionals working in these key departments in both companies were included in the study. Following the same replication logic, personnel with similar positions and responsibilities were selected in both companies

3.5. Inclusion and exclusion criteria

- **Inclusion criteria (For the manufacturing companies)**
  - ✓ Pharmaceutical manufacturing companies that were producing generic medicines for human use
- **Exclusion criteria (For the manufacturing companies)**
  - ✓ Pharmaceutical manufacturing companies that were not producing generic medicines for human use
- **Inclusion criteria (For key respondents')**
  - ✓ Staff members that are directly or indirectly involved in the implementation of product QA system in the pharmaceutical manufacturing companies.
- **Exclusion criteria (For key respondents')**
  - ✓ Staff members with less than one month work experience within the company and not involved in implementation of QA system.

3.6. Methods Followed

3.6.1. Direct Observation

3.6.1.1. Data Collection instrument

Cross-contamination prevention guidelines implementation status assessment was made with field observation using structured checklist adopted from national and international GMP requirements (*WHO, 2007 and EFMHACA, 2014*). Since WHO cGMP guideline and EFMHACA cGMP guideline were similar in context at the time of study WHO GMP guideline was preferred (see Annex 3).

3.6.1.2. Data collection and Interpretation

After the observation checklist was coded, direct observation as per the tool was conducted by the PI. During the course of conducting the observation, each and every cross-contamination prevention practices followed in the companies were weighed against the GMP requirements in the checklist and rated for compliance. With regard to rating, two tools adopted from two sources (*Ethiopian GMP Roadmap, 2013 & Kenya GMP Roadmap, 2014)* were used to make the evaluation more complete and comprehensive. Rating of the implementation status was done following the steps below:

Step 1: Assessment made as per developed checklist

Step 2: Implementation Status of each observation is categorized as FI, PI, & NA. In this step, after having made careful observations; implementation status were identified and categorized as defined below.

- Fully Implemented (FI): All cGMP requirements preventing cross-contamination mentioned in WHO and EFMHACA cGMP guidelines are in place and as required.
- Partially implemented (PI): Partial execution of cGMP requirements preventing cross-contamination mentioned in WHO and EFMHACA cGMP guidelines.
- Not implemented (NI): Non-execution of cGMP requirements to prevent cross-contamination mentioned in WHO and EFMHACA cGMP guidelines.
- Not applicable (NA): Those elements of cGMP included in the observation checklist in WHO and EFMHACA cGMP guidelines not required to be implemented due to the companies' peculiar nature.

Step 3: Based on the implementation status of each requirement, numerical rating was made. Here evaluated cGMP elements were numerically rated to show the degree of compliance of each GMP element in the selected pharmaceutical manufacturing companies as:

- Fully Implemented (FI): 3,Partially Implemented(PI): 2 & Not Implemented(NI): 1

Finally, the total rating is computed with Eqn. 3.1 as the summation of all elements multiplied by the degree of compliance (*Ethiopian GMP Roadmap, 2013*)

(Total GMP Rating = {∑ (GMP elements assessed X rating)/maximum score possible]*100%	**Eqn. 3.1**

Step 4: Based on compliance risk, observed deficiencies categorized rated as critical/major/minor and based on the criticality of the deficiencies the evaluated GMP element is categorized as Acceptable/ Improve/Inadequate (*Kenya GMP Roadmap, 2014*)

Here, once the implementation status is evaluated as FI, PI and NI the compliance risk of observed deficiencies were categorized as critical, major and minor as defined below.

- Minor deficiency (low compliance risk): An observation describing a situation that is a departure from cGMP but has no significant impact on the product quality.
- Major deficiency (medium compliance risk): An observation describing a situation that may have an impact on the product but is not as significant as a critical observation.

- Critical deficiency: An observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk.

Then, the observations related to a specific key quality element were rated as a whole reflecting the compliance of the respective key quality element with GMP requirements as defined below:

- Acceptable: Compliance of a key quality element with WHO GMP was rated "Acceptable" if no or only "other" (i.e. "minor") deficiencies were observed on areas related to this specific key quality element.
- Improve: Compliance of a key quality element with WHO GMP was rated "Requires improvement" (short: "improve") if only few "major" deficiencies (< 5) were observed on areas related to this specific key quality element.
- Inadequate: Compliance of a key quality element with WHO GMP was rated "Inadequate" if at least one "critical" and/or a considerable number (> 5) of "major" deficiencies were observed.

3.6.2. Key Respondent Survey

Data collection from the companies' key personnel have been made through self-administered semi structured questionnaire (Annex 2*)*.The questionnaire contain both close-ended and open-ended questions which were prepared and pre-tested with 5 technical staff members working in a pharmaceutical manufacturing company that were not included in the actual study. The pre-tested self-administered questionnaire was distributed to carefully select key personnel in the two companies. Then the collected data is statistically evaluated in Minitab Version 14 which is a United States registered software of Minitab Inc.

3.6.3. Laboratory Based Tests

3.6.3.1. Equipment and materials

UV-Visible Spectrophotometer CE-21 (Cecil Instruments Ltd., UK), UV-Visible spectrophotometer 1700 (Shimadzu Corporation, Japan), Elmasonic Sonicator S15 and Ultrasonic Sonicator S60H (Nabertherm GmbH, Germany), Precision balance CPA 1245 (Sartorious Lab Instruments, Germany), Precision Balance XP-1203S,(Mettler Toledo, Switzerland),Ciprofloxacilin HCl (Zhejiong Guobong Pharma,China) ,Ashless Whatmann

filter paper number 42(GE Healthcare, UK) and Texwipe 714A large alpha swab (Jignesh Agency,I,ndia),Distilled Water(From respective companies)

3.6.3.2. Production area selected for analytical verification

Tablet manufacturing lines in each company were taken as a sample for the study to compare the extent of active residues carryover after equipment cleaning during product changeover. The selection is made for a reason that it involves higher number of unit operations and demand multiple equipment compared to other dosage forms.

3.6.3.3. Equipment selected for analytical Verification

Three kinds of equipment were selected from tablet manufacturing sections in the two companies. One equipment cleaned by semi-automated cleaning procedure, i.e., High Speed Granulator, two cleaned manually, i.e., Fluidized Bed Dryer and Tablet Press machines were selected (Annex 4 shows model, manufacturer and country of origin for these machines). Three difficult to clean locations in each equipment were selected to take swab samples.

3.6.3.4. Product selected for analytical verification

For the sake of convenience and put the plants in the study in similar positions, a product manufactured in both companies was taken for the study. With this essence; Ciprofloxacillin was selected for the study.

3.6.3.5. Sampling method

Two swabs at each sampling location were used to sample cleaned equipment with a method adapted from swabbing guide assessed online from texwipe official website.*(www.texwipe.com assessed on January, 2016).* The swabbing and analyzing was made as outlined in Fig. 3.3.

3.6.3.6. Analytical method validation

Analytical method adapted from another study (*Shah P .etal., 2014*) was used to detect and quantify active residues by swab sampling technique. The. Swab recovery, linearity, accuracy, precision and other parameters were validated as per ICH QR2

I. Preparation of standard solution

Reference standard of Ciprofloxacilin HCl equivalent to 100 mg of Ciprofloxacilin weighed and transferred into 100 ml volumetric flask dissolved into sufficient amount of purified water

by sonication for 10 min followed by dilution to the mark.10 ml of this stock solution was further diluted in 100 ml volumetric flask to give a final concentration of 100 µg/ml.

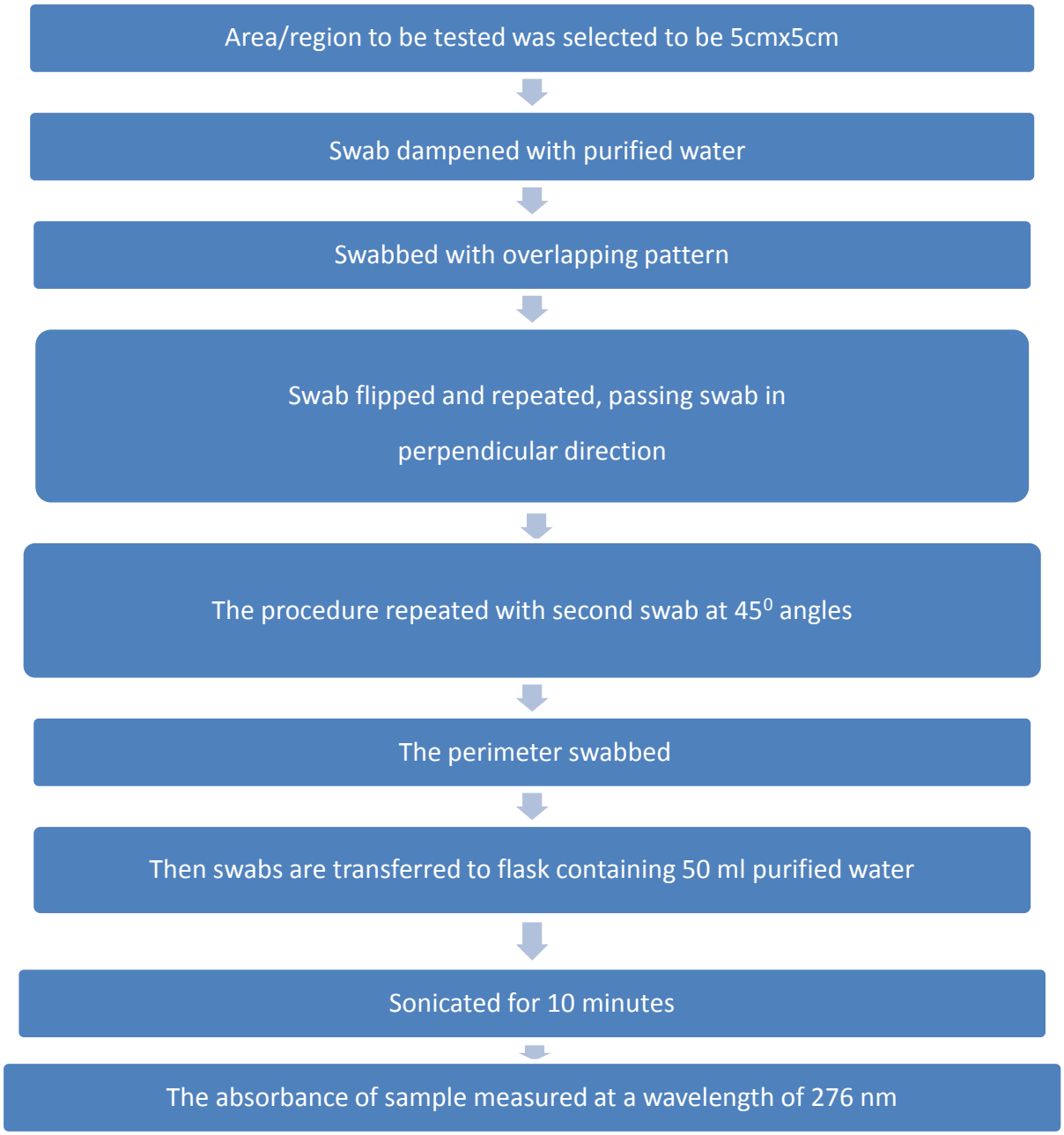

Fig 3. 1: Sampling and Analytical Procedure

II. Calibration curve

The standard solution of Ciprofloxacilin HCl was subsequently diluted to prepare final concentration in the range of 0.1 - 5.0 µg/ml. Absorbances of the prepared solutions were measured in a UV/Visible Spectrophotometer at a wavelength of 276 nm. Regression analysis was performed by plotting Absorbance versus concentration.

III. Linearity and Sensitivity

The linearity of the method was checked by different concentrations of the standard solution from 0.1 µg/ml to 5 µg/ml. Regression line was drawn and equation was determined for the graph with Minitab (version 14).

IV. Limit of detection and Limit of quantitation

The LOD and LOQ of the analytical method were calculated from the calibration curve taking the standard deviation of the response (intercept) and the slope of the calibration curve using equations:

$$LOD = 3.3 \times \sigma/S$$

$$LOQ = 10 \times \sigma/S$$

Where σ = standard deviation of the response (intercept)

S = the slope of the calibration curve

The standard deviation of the response was calculated using "LINEST" function on Microsoft excel 2013

V. Accuracy and Recovery

The accuracy of the method was determined by spiking sample solution with known standard. The accuracy was checked at 80, 100 and 120% with three replicates. Accuracy is expressed as percentage recovered.

VI. Precision Repeatability

Precision repeatability of the method was determined by making multiple (n=6) determinations at one Concentration i.e., 5 µg/ml.

VII. Precision Intermediate

Inter day precision was determined by analyzing six replicates in two different days. Inter instrumental variation was also determined by analyzing 6 measurements of 5µg/ml standard solution prepared in different laboratory and at different time measured with different instrument.

VIII. Swab Recovery from the stainless steel surface

1 ml of 100 µg/ml solution was spiked on 25 cm^2 stainless steel surface and allowed to dry in oven at 70 ^{0}C then swabbed with the same fashion as production equipment were swabbed. This test is repeated 6 times and the average calculated.

3.6.3.7. Residual analysis of cleaned Equipment

Finally, the effectiveness of equipment cleaning in the 2 companies was measured by the method was adapted from another study (*Shah P .etal., 2014*).5cm x 5cm swab areas from 9 sampling locations of which 3 sampling points from each equipment were swabbed and analyzed with UV/Visible spectrophotometer at a wave length of 276 nm.

3.7. Data analysis and Presentation

Data collected through all methods was comprehended and organized in a way it can show all themes developed build in the conceptual framework section. Based on this, status of the premise, HVAC, equipment, cleaning process and personnel is analyzed separately for each of the companies studied and then thematic analysis of cross-contamination prevention practices across the cases was presented. In addition data was summarized and presented using tabular and graphic presentations for the interpretation of findings.

3.8. Ethical considerations

Prior to the commencement of the study, the requisite ethical clearance was obtained from the School of Pharmacy, College of Health Sciences, and Addis Ababa University (Annex 5). Permission from each pharmaceutical manufacturing company was also obtained before going into the study. Prepared informed consent was also signed by the study participants (Annex 1). The companies involved in the study and key respondents were guaranteed about the confidentiality of the information gathered in the study and piece of information that may provide clue to the identity of the companies will not be reported in the study.

4. Results

4.1. Profile of selected manufacturing companies

The two companies selected for this study were manufacturing firms that do have marketing authorization from EFMHACA to formulate, develop and manufacture medicines in different dosage forms. Both the GMP compliant company and the company working towards GMP certification have been manufacturing and marketing different medicines in Ethiopia. To go in accordance with the ethical principles this study is based, the name of the companies involved in the study will remain anonymous and specific code will be assigned. Codes A and B are assigned to the GMP compliant company and the company working towards GMP certification respectively. Company B manufactures larger variety of products with more diversified dosage forms and pharmacological activity when compared with company A.

Table 4. 1: Profile of Studied companies, June 2016

Indicators	**Company A**	**Company B**
Total number of products	26	Above 50
Products by pharmacological category	Analgesics,Antibacterial,Anticonvulsant,antifungals,Antihypertensives,GI agents	Analgesics, Antibacterial, CNS medicines, Dermatological, antitussives, antidiabetics, GI agents antifungals, Antihypertensives,
Products by dosage form	Tablets, Capsules and one other dosage form*	Tablets, Capsules, Oral Liquids, Topical ointments, LVP and one other dosage form*
GMP Certification	From PIC/S	Not yet certified

* Not mentioned intentionally to avoid possibility of tracing the companies.

4.2. Within case analysis

4.2.1. Case study of Company A

4.2.1.1. Socio-demographic characteristics of respondents

Eleven selected key respondents (technical staffs) filled-out and returned the self-administered questionnaire which is 100% response rate. The socio-demographic characteristics of key respondents are summarized in Table 4.2.The mean and standard deviation of respondents' age was 35.4 and 8.9 respectively. Majority of respondents were males making up 63.6%. Respondents having MSc in Pharmacy related fields were found to be 27.3% and as it can be seen in Table 4.2, majority of the respondents (45.4%) were found to have a total work experience between 5 to 10 years. With regard to the position respondents held: 54.5% of them were managers who are leading different departments including production, QA, QC and Engineering. All respondents have received trainings on basic WHO GMP modules and supplementary WHO GMP modules.

4.2.1.2. Status of Cross Contamination Prevention Practices

4.2.1.2.1. Premise, HVAC and Production Equipment suitability

I. Respondents' perception on suitability of Premise, HVAC and Production Equipment

The key respondents' responses on suitability of Premise, HVAC and Production Equipment is presented in Table 4.3. 100% of respondents completely agree with the idea that the design and construction of the premise and the production area equipment is adequate to prevent cross-contamination.

II. Status of the Premise, HVAC and Production Equipment in avoiding cross-contamination

According to the observations made concerning the premise design and construction: Company A is fully and partially GMP compliant for 50% and 12.5% of the GMP elements respectively. The HVAC system in the company was evaluated and the result shows the company is fully GMP compliant for 45.4% of evaluated GMP elements on HVAC aspect.

Table 4. 2: Socio-demographic characteristics of respondents in Company A, June 2016

Variable	Category	Count	Percent
Age	20-29 years	5	45.4
	30-39years	2	18.2
	40-49 years	3	27.3
	Above 49 Years	1	9.1
	Total	11	100.0
	Mean ± SD	35.4±8.9	
Sex	Female	4	36.4
	Male	7	63.6
Respondents highest level of education	BSc in Chemistry	4	36.4
	Bachelor of Pharmacy	4	36.4
	MSc in Pharmacy disciplines	3	27.2
Total experience of respondents	>10 years	2	18.2
	1-5 years	4	36.4
	5-10 years	5	45.4
Experience of respondents in the company	>10 years	1	9.1
	1-5 years	4	36.4
	5-10 years	6	54.5
Position of respondents in the company	Manager	6	54.5
	Division Head	2	18.2
	Senior Pharmacist	3	27.3
GMP training Experience of Respondents	Basic WHO GMP Modules	11	100.0
	WHO supplementary GMP Modules	11	100.0

Table 4. 3: Key respondents response on suitability of Premise, HVAC and Production Equipment in Company A, June 2016

S/N	Questions	Response	Company A	
1.	Design and construction of the production area premise, HVAC systems and production area equipment are adequate to avoid risk of cross-contamination	Completely agree	11	100.00
		Partially agree	0	0.00
2.	The reason to not completely agree (If your answer for the question above is different from completely agree)	Highly sensitizing and potent medicines are not adequately segregated	NA	NA
		There is no HVAC system or not qualified	NA	NA
		Recirculated air is not treated with HEPA or other adequate grade filter	NA	NA
		Equipment design and construction is not as per GMP	NA	NA
		Others (Risk assessment not conducted on the facility)	NA	NA
3.	Does the company have recent plan to rectify any design and construction deficiencies?	Yes	0	0.00
		No	11	100.0
		I don't know	0	0.00
	What is the company's plan?	Building new facility	NA	NA

Source: own survey, 2016(Data collected with self-administered questionnaire)

Table 4. 4: The implementation status of premise, HVAC system and production equipment in avoiding cross-contamination in Company A, June 2016

Observation element	Implementation status			Risk classification			Rating	
		Count	Percent				Qualitative	Quantitative
Premise	FI	8	50.0	Critical	0	0.0	Improve	93.3%
	PI	2	12.5	Major	2	100.0		
	NI	0	0.0	Minor	0	0.0		
	NA	6	37.5	Sub Total	2	100.0		
	Sub Total	16	100.0					
HVAC	FI	5	45.4	Critical	0	0.0	Improve	81.8%
	PI	6	54.6	Major	2	33.3		
	NI	0	0.0	Minor	4	66.7		
	NA	0	0.0	Sub Total	6	100.0		
	Sub Total	11	100.0					
Equipment	FI	8	60.0	Critical	0	0.0	Acceptable	93.3%
	PI	2	20.0	Major	0	100.0		
	NI	0	20.0	Minor	2	100.0		
	NA	0	0.0	Sub Total	2	100.0		
	Sub Total	10	100.0					

Source: own survey, 2016(Obtained through checklist based observation by the PI)

With regard to risk based classification of deficiencies on premises and HVAC, major deficiencies were observed with the extent of 100% and 33% on the premise and HVAC system respectively. These makes the ultimate rating of these GMP elements in Company A to be "needs improvement". On the other hand the production equipment only showing minor deficiencies its implementation status was rated "acceptable". On the other hand no critical deficiency was found in all the Premise, HVAC system and Equipment. (Table 4.4)

4.2.1.2.2. Cleaning Process suitability

I. Respondents' perception on suitability of the cleaning process

With regard to the cleaning process suitability, 100% of the respondents say "yes" for the question about presence of cleaning process as well as conducting cleaning validation. Looking into the response how complete cleaning validation achieved all responds claimed the presence of strong management commitment.(Table 4.5)

Table 4. 5: Key respondents response on suitability of cleaning process in Company A, June 2016

S/N	Questions	Response		
1.	Do production areas and equipment have standard cleaning procedure?	Yes	11	100.0
		No	0	0.0
		I don't know	0	0.0
2.	Do production areas and equipment cleaning procedures validated	Yes	11	100.0
		No	0	0.0
		I don't know	0	0.0
3.	What are the challenges and barriers that have prevented the company from conducting cleaning validation (If your answer is yes for conducting cleaning validation)	Inadequate trained skilled man power	NA	NA
		Lesser commitment from the top management	NA	NA
		Other(Lack of access to suitable detergents and samplers)	NA	NA
4.	What helped the company to validate the cleaning procedure(If your answer is no for conducting cleaning validation)	Strong management commitment	11	100.0
		Technical and financial Support from stake holders	3	27.3
		other	0	0.0

Source: own survey, 2016(Data collected with self-administered questionnaire)

II. Status of the cleaning process

Of 11 elements evaluated on how cleaning process is developed and maintained in Company A, 72.7% of them were fully implemented and the rest 27.3% were partially implemented. When weighed based on the risk observed deficiencies pose 100% of them were rated minor making the overall rating of cleaning process "acceptable". (Table 4.6)

Table 4. 6: The practice of cleaning process in avoiding cross-contamination in Company A, June 2016

Observation element	Implementation status			Risk classification			Rating	
Cleaning Process		**Count**	**Percent**		**Count**	**Percent**	**Qualitative**	**Quantitative**
	FI	8	72.7	Critical	0	0.0	Acceptable	81.8%
	PI	3	27.3	Major	0	0.0		
	NI	0	0.0	Minor	3	100.0		
	NA	0	0.0	Sub Total	3	100.0		
	Sub Total	11	100.0					

Source: own survey, 2016(Data collected with self-administered questionnaire)

III. Residual Analysis of Cleaned Equipment

The effectiveness of equipment cleaning procedures evaluated, with measurement of the extent of API carryover on cleaned equipment. The result is depicted in Table 4.7.The residual analysis result in company A didn't show any quantifiable carryover of Ciprofloxacilin in the cleaned equipment. (The Analytical method validation result is found as Annex 6)

Table 4. 7: Residual Analysis on sampled production equipment in Company A.

Equipment	Sampled Locations	Residue carryover (µg)
High Speed Granulator	Beneath the Chopper	Below LOQ
	Top surface of the impeller	Below LOQ
	Discharge Chute	Below LOQ
Fluid Bed Dryer	1 Side of the loading Pan	Below LOQ
	Top surface of the sieve	Below LOQ
	1 Side of the FBD	Below LOQ
Tablet Press Machine	1 Feed Frame	Below LOQ
	Turret	Below LOQ
	Hopper	Below LOQ

Source: own chemical analysis result, 2016

4.2.1.2.3. Personnel Suitability

I. Respondents' perception on suitability of the cleaning process

While considering the personnel suitability unlike the other cases 18.2% of respondents respond "no" for the statement "Personnel involved in product manufacturing, cleaning and approval of cleaning process receive adequate relevant training". Lesser support from academia and absence of academic curriculums tailored with the manufacturing companies demand are mentioned as a possible reason for backing their response of only partially agree with the idea

II. Status of personnel

With regard to personnel suitability 77.8% were fully implemented.1 element was not evaluated as there were no highly potent and hypersensitive product that demand dedicated personnel. On the other hand one minor deficiency was observed due to inadequate training program. The overall rating of the personnel became "acceptable".

Table 4. 8: Key respondents response on suitability of personnel in Company A, June 2016

S/N	Questions	Response	Company A	
1.	Personnel involved in product manufacturing, cleaning and approval of cleaning process receive adequate relevant training	Yes	9	81.8
		No	2	18.2
2.	If your answer for question 1 is yes what kind of training did they receive?	Basic GMP principles	9	100.0
		Cleaning procedures implemented in the company	9	100.0
		Other	0	0.0
3.	If you think that there is no adequate training, what do you think is the possible reason?	The company's focus on training is less	0	0.0
		The academic institutions support is less	2	100.0
		Other	0	0.0
4.	In your opinion what should be done to improve trainings to personnel	More company Management commitment	3	27.3
		Sound company-academic relationship	11	100.0
		Other (Tailoring curriculums based on the demands in pharmaceutical manufacturing factories)	3	27.3

Source: own survey, 2016(Data collected with self-administered questionnaire)

Table 4. 9: The status of personnel in avoiding cross contamination in Company A, June 2016

Observation element	Implementation status			Risk classification			Rating	
Personnel		Count	Percent		Count	Percent	Qualitative	Quantitative
	FI	7	77.8	Critical	0	0.0	Acceptable	95.8%
	PI	1	11.1	Major	0	0.0		
	NI	0	0.0	Minor	1	100.0		
	NA	1	11.1	Sub Total	1	100.0		

4.2.2. Case study of Company B

4.2.2.1. Socio-demographic characteristics of respondents

The socio-demographic characteristics of key respondents in Company B are summarized in Table 4.10.The mean and standard deviation of age was 39.9 and 8.5 respectively. Majority of respondents were males making up 90.9%.With regard to educational background of respondents, no respondent did have MSc at the time of the study. Also more than half of the respondents (54.6%) in company B were found to have greater than 10 years of total experience. Considering the position respondents held: 54.6% of them were managers. All respondents in the company have received trainings on basic WHO GMP modules and supplementary WHO GMP modules.

Table 4. 10: Socio-demographic characteristics of respondents, June 2016

Variable	Category	Count	Percent
	20-29 years	1	9.1
	30-39years	5	45.4
	40-49 years	4	36.4
	Above 49 Years	1	9.1
	Total	11	100.0
	Mean ± SD	39.9±8.5	
Sex	Female	1	9.1
	Male	10	90.9
Respondents highest level of education	BSc in Chemistry	4	36.4
	Bachelor of Pharmacy	7	63.6
	MSc in Pharmacy disciplines	0	0.00
Total experience of respondents	>10 years	6	54.6
	1-5 years	1	9.1
	5-10 years	4	36.4
Experience of respondents in the company	>10 years	6	54.6
	1-5 years	1	9.1
	5-10 years	4	36.4
Position of respondents in the company	Manager	6	54.6
	Division Head	5	45.4
	Senior Pharmacist	0	0.0
GMP training Experience of Respondents	Basic WHO GMP Modules	11	11.0
	WHO supplementary GMP Modules	11	100.0

4.2.2.2. Status of cross-contamination prevention practices

4.2.2.2.1. Premise, HVAC and Production Equipment suitability

I. Respondents' perception on suitability of Premise, HVAC and Production Equipment

27.3% of respondents in Company B only partially agree on the adequacy of design and construction of premise, HVAC and equipment. Out of the respondents who do not completely agree in Company B, all claimed segregation of potent medicines is not adequate and 2 respondents claimed inadequate HVAC and not conducting risk assessment on the Facility. However, all respondents say the company is building new facility to overcome this deficiencies. (Table 4.11)

II. Status of the Premise, HVAC and Production Equipment in avoiding cross-contamination

According to 16 observations made concerning the premise design and construction, the premise of company B is partially and fully GMP deficient for 31.3% and 25% of evaluated GMP elements respectively. With regard to risk based classification of deficiencies. 45.5% in the premises and 12.5% in the HVAC were critical deficiencies. Similarly major deficiencies were also observed.22.2%, 62.5% and 40% of deficiencies were rated major in the premises, HVAC and Equipment respectively. The presence of critical deficiencies have made the overall rating of premise and HVAC to be "inadequate". While the equipment was rated "improve". (Table 4.12)

Table 4. 11: Key respondents response on suitability of premise, HVAC and production equipment in Company B, June 2016

S/N	Questions	Response	Count	Percent
1.	Design and construction of the production area premise, HVAC systems and production area equipment are adequate to avoid risk of cross-contamination	Completely agree	8	72.7
		Partially agree	3	27.3
2.	The reason to not completely agree (If your answer for the question above is different from completely agree)	Highly sensitizing and potent medicines are not adequately segregated	3	100.0
		There is no HVAC system or not qualified	2	66.7
		Recirculated air is not treated with HEPA or other adequate grade filter	0	0.00
		Equipment design and construction is not as per GMP	0	0.00
		Others (Risk assessment not conducted on the facility)	2	66.7
3.	Does the company have recent plan to rectify any design and construction deficiencies?	Yes	11	100.0
		No	0	0.00
		I don't know	0	0.00
4.	What is the company's plan?	Building new facility	11	100.0

Table 4. 12: The implementation status of premise, HVAC system and production equipment in avoiding cross-contamination in Company B, June 2016

Observation element	Implementation status			Risk classification			Rating	
		Count	Percent				Qualitative	Quantitative
Premise	FI	7	43.7	Critical	4	44.5	Inadequate	72.9%
	PI	5	31.3	Major	2	22.2		
	NI	4	25.0	Minor	3	33.3		
	NA	0	0.0					
	Sub Total	16	100.0	Sub Total	9	100.0		
HVAC	FI	3	27.3	Critical	1	12.5	Inadequate	60.6%
	PI	3	27.3	Major	5	62.5		
	NI	5	45.5	Minor	2	25.0		
	NA	0	0.0					
	Sub Total	11	100.0	Sub Total	8	100.0		
Equipment	FI	5	50.0	Critical	0	0.0	Improve	83.3%
	PI	5	50.0	Major	2	40.0		
	NI	0	0.0	Minor	3	60.0		
	NA	0	0.0					
	Sub Total	10	100.0	Sub Total	5	100.0		

Source: own survey, 2016(Obtained through checklist based observation by the PI)

4.2.2.2.2. Cleaning Process suitability

I. Respondents' perception on suitability of the cleaning process

With regard to the cleaning process suitability, 100% of the respondents say "yes" for the question about presence of cleaning process. However the response on conducting cleaning validation is 100% no. Lack of adequate skilled man power, lesser top management commitments and lack of access to suitable detergents and samplers are mentioned by the respondents to be reasons that impede cleaning validation works in the case of Company B.

Table 4. 13: Key respondents response on suitability of cleaning process

S/N	Questions	Response	Count	Percent
1	Do production areas and equipment have standard cleaning procedure?	Yes	11	100.0
		No	0	0.0
		I don't know	0	0.0
2	Do production areas and equipment cleaning procedures validated	Yes	0	0.0
		No	11	100.0
		I don't know	0	0.0
3	What are the challenges and barriers that have prevented the company from conducting cleaning validation (If your answer is yes for conducting cleaning validation)	Inadequate trained skilled man power	11	100.0
		Lesser commitment from the top management	4	36.4
		Other(Lack of access to suitable detergents and samplers)	5	45.4
4	What helped the company to validate the cleaning procedure(If your answer is no for conducting cleaning validation)	Strong management commitment	NA	NA
		Technical and financial Support from stake holders	NA	NA
		other	NA	NA

II. Status of the cleaning process

Of 11 elements evaluated on how cleaning process is developed and maintained in Company B, 63.6% of them were fully implemented and the rest 36.4% were partially implemented and not implemented 18.2% each. When weighed based on the risk observed deficiencies pose 50% of them were rated major making the overall rating of cleaning process "improve". (Table 4.14)

Table 4. 14: The practice of cleaning process in avoiding cross-contamination in Company B, June 2016

Observation element	Implementation status			Risk classification			Rating	
		Count	Percent		Count	Percent	Qualitative	Quantitative
Cleaning Process	FI	7	63.6	Critical	0	0.0	Improve	89.1%
	PI	2	18.2	Major	2	50.0		
	NI	2	18.2	Minor	2	50.0		
	NA	0	0.0	Sub Total	4	100.0		
	Sub Total	11	100.0					

Source: own survey, 2016(Data collected with self-administered questionnaire)

III. Residual Analysis of Cleaned Equipment

As depicted in Table 4.15, quantifiable carryover of Ciprofloxacilin residues have been observed in cleaned equipment particularly on the Fluid Bed Dryer and High Speed Granulator. Tablet press machine didn't show quantifiable carryover.

Table 4. 15: Residual Analysis on sampled production equipment in Company B

Equipment	Sampled Locations	Residue carryover (µg)
High Speed Granulator	Beneath the Chopper	17.4
	Top surface of the impeller	Below LOQ
	Discharge Chute	18.9
Fluid Bed Dryer	1 Side of the loading Pan	33.8
	Top surface of the sieve	Below LOQ
	1 Side of the FBD	Below LOQ
Tablet Press Machine	1 Feed Frame	Below LOQ
	Turret	Below LOQ

4.2.2.2.3. Personnel Suitability

I. Respondents' perception on suitability of the personnel

72.7% of respondents in the Company respond yes for the state of "Personnel involved in product manufacturing, cleaning and approval of cleaning process receive adequate relevant training". Less focus from the company's management, lesser company academia relationship were the reasons for backing inadequate training as it is found from respondents who responded "No" for the presence of adequate training for the staffs (Table:.4.16)

Table 4. 16: Key respondents response on suitability of cleaning process

Questions	Response	Count	Percent
Personnel involved in product manufacturing, cleaning and approval of cleaning process receive adequate relevant training	Yes	8	72.7
	No	3	27.3
If your answer for question 1, Part IV is yes what kind of training did they receive?	Basic GMP principles	8	100.0
	Cleaning procedures implemented in the company	5	62.5
	Other	0	0.0
If you think that there is no adequate training, what do you think is the possible reason?	The company's focus on training is less	3	100.0
	The academic institutions support is less	3	100.0
	Other	0	0.0
In your opinion what should be done to improve trainings to personnel	More company Management commitment	11	100.0
	Sound company-academic relationship	11	100.0
	Other (Tailoring curriculums based on the demands in pharmaceutical manufacturing factories)	2	18.2

II. Status of personnel

With regard to personnel suitability 77.8% were fully implemented. While 22.2% of the elements were partially implemented. Likewise the observed deficiencies were rated minor. Hence the overall rating of the personnel became "acceptable". (Table 4.17)

Table 4. 17: Suitability of Personnel in avoiding cross-contamination in Company B, June 2016

Observation element	Implementation status			Risk classification			Rating	
		Count	Percent		Count	Percent	Qualitative	Quantitative
Personnel	FI	7	77.8	Critical	0	0.0	Acceptable	92.6%
	PI	2	22.2	Major	0	0.0		
	NI	0	0.0	Minor	2	22.2		
	NA	0	0.0	Sub Total	2	100.0		
	Sub Total	9						

Source: own survey, 2016(Data collected with self-administered questionnaire

4.3. Cross case analysis

4.3.1. Overall assessment of cross-contamination prevention guidelines

4.3.1.1. Overall implementation status of the quality elements

A total of 57 observations were made in the 2 companies. Field observation by the PI has revealed that 24.6% of evaluated GMP elements in company A were partially implemented and no GMP element was not implemented. While in company B: 29.8% and 19.3% were partially implemented and not implemented respectively. 15.8% of assessed GMP elements were not applicable in company A (Figure 4.1).

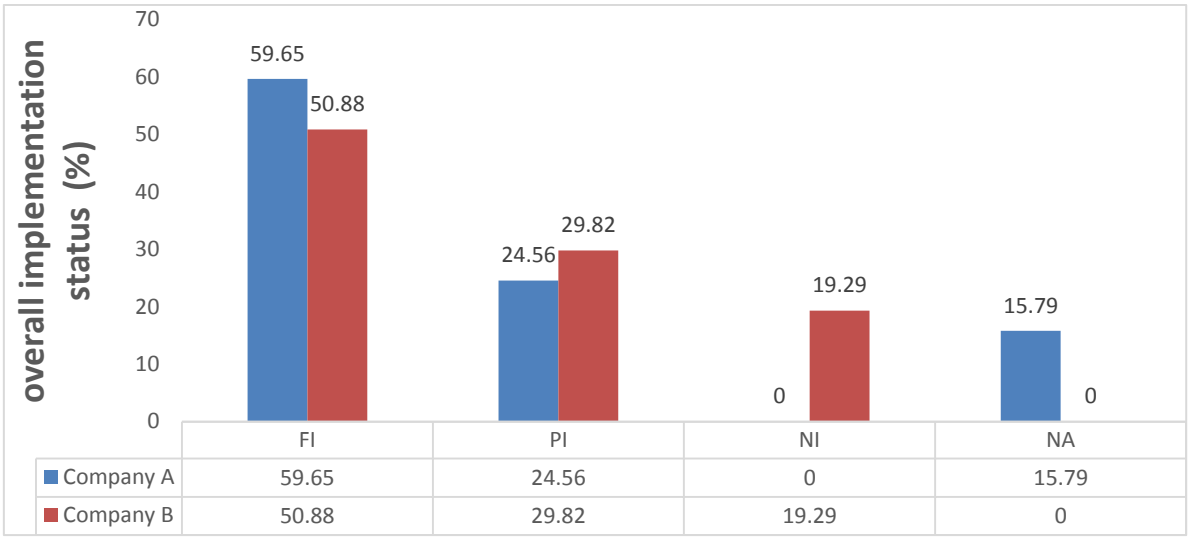

Fig. 4. 1: Overall implementation status of cross-contamination prevention guidelines in the two companies, 2016

4.3.1.2. Overall Risk Based Classification of Deficiencies observed

With regard to overall risk based classification of deficiencies, the majority in both companies were rated minor accounting 70.6% and 42.3% of deficiencies in company A and company B respectively. However, the major deficiencies in company B were higher, i.e., 38.5% vs. 29.4% in company A. In addition, critical deficiencies were also seen in company B (See Figure 4.2).

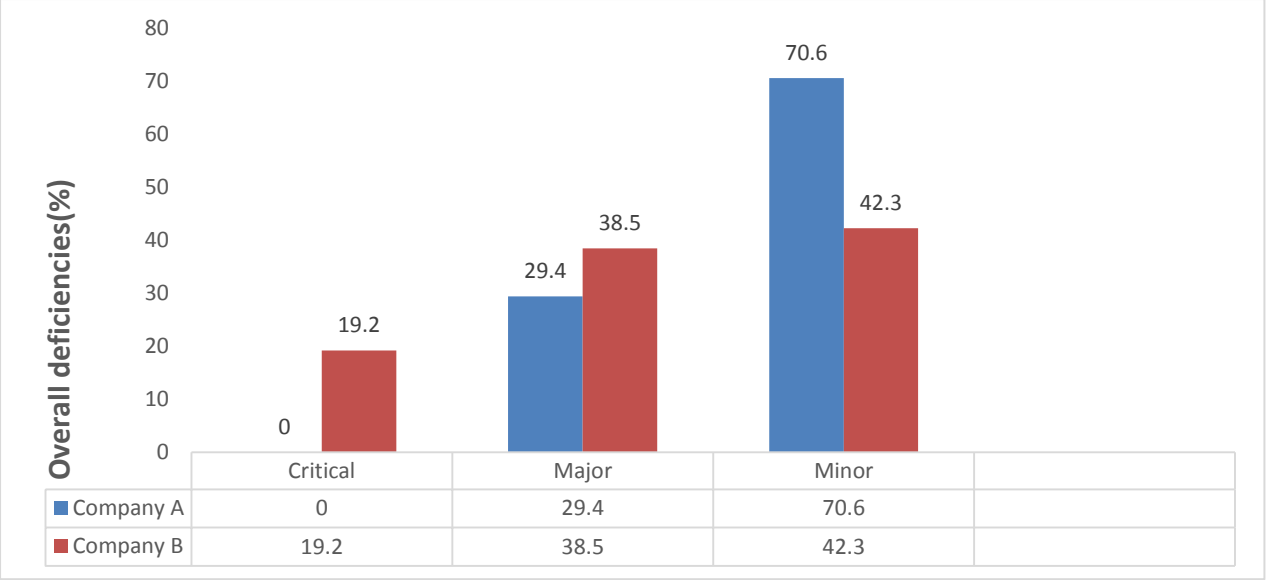

Fig. 4. 2 : Overall observations on the status of cross-contamination prevention guidelines in the two companies classified based on risk, 2016.

4.3.2. Categorizing the Companies based on their GMP compliance

The implementation of cross-contamination prevention guides in each company was computed individually according to the USP-PQM GMP rating. It is found that the overall compliance rate of cross-contamination prevention guides was found to be 90.3% in company A and 77.2% in company B (Table 4.18).

Table 4. 18: Overall compliance score in company A and company B, June 2016

	Rating Score in company A	**Rating Score in company B**
FI	102	87
PI	28	34
NI	–	11
Total score	130	132
Total score possible	144	171
Percentage rating	**90.3%**	**77.2%**

Each core element in cross-contamination prevention guides was evaluated with a tool adapted from Kenya GMP roadmap (2014). Premises and HVAC systems have been rated "improve”

in company A and “inadequate” in company B. Meanwhile the cleaning process and equipment have been rated “acceptable” for company A and "improve" for company B. On the other hand the personnel in both companies was rated “acceptable” (Table 4.19).

Table 4. 19: Overall assessment of each element in company A and company B, June 2016

	Company A	**Company B**
Premises	Improve	Inadequate
HVAC	Improve	Inadequate
Personnel	Acceptable	Acceptable
Equipment	Acceptable	Improve
Cleaning Process	Acceptable	Improve

5. Discussion

Comparative assessment and evaluation of the implementation status of different elements of cGMP guidelines with respect to avoiding risk of cross-contamination was conducted in two pharmaceutical manufacturing companies producing medicines in Ethiopia. One of the companies studied did have GMP compliance certification from PIC/S and the other working towards getting this and other GMP certifications.

The study has shown that cross-contamination avoiding guidelines were better implemented in company A than company B. Moreover, the manufacturing site of company B was not well designed and maintained potentially causing critical deficiencies. It has been also observed that qualification works were poorly implemented in this company which makes it hard to comply with GMP requirements. The presence of penicillin products that demand special considerations in company B also made it the problem more serious and needs special attention of the management.

The formal higher education level of key respondents in Company B is lesser when compared with A. On the other hand company B is larger in the type and number of products it manufactures when compared with company A. Though not extensively studied, some studies have shown the relationship between level of education of managers' and a company outcome.

Wiersema(1992) have shown direct association between top managements level of education and organizations ability to anticipate and respond to opportunities or pressures in a way that its competitiveness and viability are ensured. On the other hand literatures also indicate increases in organizational size can create progressively resistance to fundamental change in organizational strategy and actions (*Tushman and Romaneli, 1985*).The national pharmaceutical development strategy and the national GMP roadmap can be considered as an opportunity for GMP compliance. Companies must act in a way to seize this opportunities. Considering all these perspectives though not conclusive, suggestions can be made that managerial composition in Company B along with its larger size and complexity might be contributing to slower actions to move forward for GMP compliance and seize this opportunity.

With an ultimate goal of bridging the gap, this study evaluated the extent of measures taken by the companies in avoiding risk of cross-contamination and what practices are differently implemented in these two companies taking cGMP principles as a benchmark. Various

contributing factors like the way the premises, HVAC system and production equipment are designed, constructed and maintained as well as the status of the cleaning process including how it is adapted and maintained were examined. This study has also attempted to evaluate the efficiency of cleaning process implemented to clean equipment during product changeover and the extent of carryover using validated analytical method by utilizing swab sampling technique.

The study has revealed that company A has been with less compliance risk when compared to company B. The premise and HVAC system of the two companies were considerably different with critical deficiencies observed in company B.

Cleaning process, equipment and personnel were adapted relatively in better compliance in both companies, though these quality elements were also in a better implementation status in company A.

According to EFMHACA guideline on GMP for Pharmaceutical Products, in order to minimize the risk of serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials like Penicillins (*EFMHACA, 2014*). In this study, it is found that though separate air handling unit is set and dedicated and self-contained, manufacturing area is laid out for production of penicillin products. It is however, difficult to conclude zero risk of cross-contamination from this highly sensitizing product as quality control laboratories, ancillary areas including laundry and canteen are not dedicated for operations to be carried out and personnel working on Penicillins.

Unlike the case in Company B, in Company A highly potent and sensitizing materials that demand self-contained and dedicated facility don't exist; hence, this criterion is not included in the assessment of this company. On the other hand, the air flow pattern in Company A is designed in such a way that it allows powder and dust flow from the manufacturing rooms to the corridors which are contrary to the cGMP requirement that demands dust flow to be from corridors to manufacturing rooms for non-sterile powdered dosage forms manufacturing area (*WHO, 2007*). Other minor deficiencies have been observed in company A inside buildings including cracks and damages in clean room floors that pose difficulty of cleaning which in turn can cause dust accumulation and ultimately creating potential risk of cross-contamination. Hence, based on these observation that the premise of company A is rated as "needs improvement".

Looking into certain differences found on the way HVAC system is designed, constructed and adapted in these 2 companies, in company B, routine works including monitoring of pressure differential between the corridor and the manufacturing room, quantification of supply air and return air and also air sample at rest were not conducted. This again, along with complete absence of qualification works, make the HVAC system "inadequate".

Whereas the HVAC system in company A was rated "improve" with better compliance than company B as routine monitoring and initial qualification were conducted with deficiencies in implementing adequate requalification system and absence of efficient corrective and preventive maintenance.

Personnel part of the assessment has shown that it is in less compliance risk and rated "acceptable" in both companies. However, regular refreshment and gap based trainings were not implemented at the desired level in both companies. Training is an important part of GMP as it is key in sustaining good practices and personnel can also be source of cross-contamination by themselves. Hence refreshing regularly the personnel awareness of requirements needs improvement in both companies

In both companies, the equipment were either stainless steel made or stainless coated and located in a way that permits effective cleaning. The equipment qualification works are better implemented in company A. Installation qualification and operational qualification were not done for most equipment in company B and for some equipment in company A. Performance qualification is done for all equipment in company A but not in company B. In both companies, some equipment have been old and have a lot of scratches that impose difficulties in cleaning.

Considering the difference in the extent of execution of qualification works in the 2 companies, the equipment design, construction and maintenance of equipment were rated "acceptable" in company A and "improve" in company B.

Prevention of cross-contamination with active pharmaceutical ingredient residue is crucial and requires special attention. With this essence, the cleaning process in both companies was evaluated. Absence of validated cleaning procedures and cleaning procedures that heavily depend on manual cleaning techniques, along with others, have been observed as deficiencies in company B. However, the presence of standard cleaning procedures and system of

monitoring by testing residues with rinse analysis have made the rating of the cleaning process status as “improve”.

While the cleaning process in company A was rated “acceptable” as the procedures were validated and necessary systems are in place.Absence of validated cleaning process has contributed for non-uniform cleaning of equipment with considerable difference in the extent of API carryover within and between equipment. All sampled locations didn’t show the presence of quantifiable carryover in Company A. While in Company B, quantifiable carryover has been observed in high speed granulator and fluid bed dryer. The large extent of disassembly which took place in cleaning tablet press machine might have contributed to a higher degree of cleaning efficiency as compared to other machines in Company B with no quantifiable carryover.

6. Conclusion

This study has comparatively assessed equipment cleaning and cross-contamination prevention practices in two Ethiopian pharmaceutical manufacturing plants.

Company A has been found to be in a better compliance with no critical deficiency as compared to company B where critical deficiencies and high compliance risks were found. Company B manufactures large number of different products as compared with company A among these penicillin products which demand special considerations have increased a challenge for the company’s work toward GMP certification. The presence of critical deficiencies in company B demand immediate corrections by the manufacturer as it can show potential safety risk to the patient.

The issues of facility including premises and HVAC system along with poor execution of qualification works have put company B in high compliance risk than company A. Qualification and validation works are important elements that can ensure sustained quality,

deliver consistent process efficiency and increase the confidence regulatory body on the manufacturing company.

This study doesn't prove presence of cross-contamination in any of the companies. However notable gaps are observed in implementing cross-contamination preventing guides with larger extent in company B. Unless company B engage in more validation and qualification activities, totally refurbish the premise and HVAC system as per regulatory requirements, it is merely possible to ensure complete absence of medical hazard to the patient that can possibly emanate due to cross-contamination. Moreover with this status company B will not be able to get GMP certification.

Finally, though status of Premise and HVAC systems were better in company A, the study shows the existence of some major deficiencies. Hence the company management has to be cautious and need to put significant effort on this area. Otherwise having GMP certification from PIC/S neither stays forever nor guarantee GMP certification from other organizations including national regulatory authority (EFMHACA).

7. Recommendations:

Based on the findings of this study the following recommendations are made:

For the target of achieving GMP compliance certificate and protecting the safety of its customers company B has to upgrade the manufacturing site and management system in a way penicillin products are fully segregated, HVAC qualified, cleaning processes validated and manufacturing equipment qualified.

In order to ensure the safety of their customers the companies shall further go and prove unacceptable level of cross-contamination doesn't exist through risk assessment.

Company B is recommended to bench mark company A for the observed better implemented GMP elements.

Finally, further studies are recommended to evaluate GMP elements apart from cross-contamination prevention requirements.

8. Limitations of the study

As this is a case study, the findings and conclusions cannot exactly express the cases in local pharmaceutical manufacturing companies not involved in this study. The findings of this study are rather indicative than informative with regard to analytical verification of cleaning effectiveness as the scope of the study doesn't include giving remarks whether the carryover measured are acceptable or not.

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Annexes

Annex 1: Informed Consent for Data givers

Dear Respondent,

You have been randomly selected to be part of this study and we would, therefore, like to collect data from you. This study is conducted by the School of Pharmacy, College of Health Science, Addis Ababa University for partial fulfillment of graduate study for Master of Science in Pharmaceutics and will be carried out by the principal investigator of the study. This study is currently taking place in your company and one other pharmaceutical manufacturing company in Ethiopia.

The information you provide will only be used to understand production Equipment cleaning practices and the measures taken by the company in order to prevent cross-contamination between different active pharmaceutical ingredients and the company's perception towards the issue.

The self-administered questionnaire will take approximately 40 minutes to fill. I will ask you questions about:

- Some relevant personal details
- Status of training on GMP principles
- Status of cross-contamination prevention practices in the company you are working

The study principal investigator may contact you again only if it is necessary to complete needed information. Your participation is voluntary and you can withdraw from the study after having agreed to participate. You are free to refuse to answer any question that is asked. If you have any questions about this study you may contact the principal investigator:

- Eyob Assefa
- Phone Number: 0914395372
- Email: Jobacute5300@gmail.com

Signing this Consent indicates you understand what will be expected of you and are willing to participate in this study.

Read and Agreed { } Read and Refused { }

Sign Respondent:_____

Sign Interviewer: _____ Date: ____/_____/_____

Annex 2:Self-Administered Questionnaire

I. Personal Information		
1	Gender	1. Male 2. Female
2	Age in years	1. 18-25 2. 25-35 3. 35-45 4. >45
3	Current position	1. General Manager 2. Production Manager 3. Quality assurance Manager 4. R&D manager 5. Quality control Manager 6. Other[please specify]_____
4	Experience in current company	1. <1 year 2. 1-5 years 3. 5-10 years 4. >10 years
5	Total work experience	1. <1 year 2. 1-5 years 3. 5-10 years 4. >10 years
6	Level of Education	1. MSc in Pharmacy related fields 2. B pharm, BSc in Pharmacy 3. MSc in chemistry related fields 4. BSc. in Biology, chemistry 5. Other Please specify _____
7	GMP trainings you received	1. Basic GMP principles 2. Supplementary WHO GMP module 3. Advanced GMP 4. Others [please specify] _____
8	Year your company was established	
II. Facility Suitability		
1	Do you think the design and construction of the premise, production area, and equipment	1. Completely agree 2. Partially agree 3. Disagree 4. Other please specify._____

	are adequate to avoid risk of cross-contamination	
2	If your answer to question 1 Part II is different from completely agree what are your reasons (more than one answer is possible)	1. Highly sensitizing and potent medicines are not adequately segregated 2. There is no HVAC system or not qualified 3. Recirculated air is not treated with HEPA or other adequate grade filter 4. Equipment design and construction is not as per GMP 5. Others please specify _____
3	Does your company have recent plan to rectify any design and construction deficiencies?	1. Yes 2. No 3. I don't know
4	If your Answer for question3 Part II is yes. What is the company's plan?	1. Building new facility 2. Correcting the design and construction deficiency of the existing facility 3. Replacing equipments 4. Others please specify _____
5	What are the challenges and barriers your company facing in rectifying design and construction issues.	1. Financial constraint 2. Lesser government support 3. Lesser enforcement from regulatory body 4. Lesser commitment from the top management 5. Personnel qualification and skill 6. Others please specify _____
6	What do you think opportunities your company have to rectify any design and construction deficiencies?	1. Management and staff commitment 2. Adequate number of qualified and skilled personnel 3. Government committed to support local pharmaceutical manufacturers 4. Financial support from the government. 5. Others please specify _____
III. **Cleaning process suitability**		
1	Do production areas have standard cleaning procedure?	1. Yes 2. No 3. I don't know

2	If production areas have cleaning procedure, are they validated?	1. Yes 2. No 3. I don't know
3	Do production equipments have standard cleaning procedure?	1. Yes 2. No 3. I don't know
4	If production equipments have cleaning procedure, are they validated?	1. Yes 2. No 3. I don't know
5	What are the challenges and barriers local pharmaceutical manufacturers have in conducting cleaning validation?	1. Inadequate trained skilled man power 2. Weak management commitment 3. Inadequate enforcement by the regulatory body 4. There is no any barrier and challenge 5. Other please specify _____
6	In your opinion, what are the opportunities your company has in conducting cleaning validation?	1. Adequately trained skilled personnel 2. Strong management commitment 3. Technical and financial Support from stake holders 4. Other please specify _____
IV. **Personnel Suitability**		
1	Do personnel involved in product manufacturing, cleaning and approval of cleaning process receive adequate and relevant training?	1. Yes 2. No 3. I don't know
2	If your answer for question 1, Part IV is yes what kind of training did they receive?	1. Basic GMP principles 2. Supplementary WHO GMP module 3. Advanced GMP 4. Cleaning procedures implemented in the company 5. Others please specify_____
3	What kind of training programs does your company have?	1. Initial induction training 2. Regular Refreshment training 3. Continuous gap based training 4. Others please specify ……

4	Do you think the personnel is getting adequate training?	1. Completely agree 2. Partially agree 3. Disagree
5	If you think that there is no adequate training, what do you think is the possible reason?	1. The company's focus on training is less 2. The government support is less 3. The academic institutions support is less 4. Otherplease specify_____
6	In your opinion what should be done to improve trainings to personnel	1. More company Management commitment 2. Financial support from the government 3. Sound company-academic relationship 4. Other please specify _____

Thank you for your Kind Cooperation.

Annex 3: Checklist for observation

Code assigned to the company_____

S/N	**Premise design and construction**				
1.	Manufacturing areas are physically separate and segregated	FI	PI	NI	TD
2.	Highly Sensitizing and potent medicine adequately segregated				
3.	Dedicated staff for different segments of manufacturing areas				
4.	Dedicated laundries and cafeterias provided for highly Sensitizing medicines				
5.	IPQC Laboratory appropriately segregated				
6.	Dedicated QC laboratory for highly Sensitizing and potent medicines				
7.	Dedicated area to store change parts for highly Sensitizing products				
8.	Dedicated Ware House for highly Sensitizing products				
9.	Movement of materials, personnel or documents from dedicated areas				
10.	Premises laid out in such a way as to allow the production to take place in areas connected in a logical order				
11.	Proper air flow designed in the premise				
12.	The adequacy of the working and in-process storage space				
13.	Pipe work, light fittings, ventilation points and other avoid the creation of recesses that are difficult to clean.				
14.	Presence of appropriate air-locks and air extraction system				
15.	Cross-contamination caused by recirculation of insufficiently treated air				
16.	Construction of building from smooth and easy to Clean surface,				
	HVAC				
17.	Dedicated HVAC system				
18.	Particle count on air is monitored and operation qualified				
19.	Pressure differential monitored and operation qualified				
20.	Supply air for all diffusers quantified and operation qualified				
21.	Return air or exhaust air quantities quantified and operation qualified				
22.	Room air change rates quantified and operation qualified				
23.	The ducts do not allow cross contamination				
24.	Appropriate requalification procedure for HVAC				

25.	Adequate maintenance program for HVAC system				
26.	Adequate calibration program for HVAC system				
27.	Necessary procedures and records maintained in the HVAC system				
	Personnel				
28.	Existence of adequate number of personnel				
29.	Provision of adequate training				
30.	Direct contact of personnel and materials, products is avoided				
31.	Flow of personnel Is not negativelyimpacting on the quality of products manufactured				
32.	Existence of standard gowning procedure				
33.	The working and protective garments of staff have to be suitable for the operations to be performed and the areas of work.				
34.	Existence of standard procedure for training				
35.	Separate protective clothing shall be in place for areas in which sensitizing/hazardous products are Manufactured.				
36.	Existence of job description for each job				
	Equipment				
37.	Production equipment have qualification documents				
38.	Equipment installed in such a way as to minimize any risk of cross contamination				
39.	Equipment located to suit the operations to be carried out				
40.	Equipment designed and constructed to suit the operations to be carried out				
41.	Equipment adapted and maintained to suit the operations to be carried out				
42.	Production equipment thoroughly cleaned on a scheduled basis.				
43.	The parts of the production equipment that come into contact with the product is constructed from recommended materials				
44.	Dedicated calibration equipment for sensitizing products				
45.	Dedicated tools for maintenance for sensitizing products				
46.	Defective equipment removed from production areas				
	Cleaning Process				
47.	Availability of standard cleaning procedure for equipment				

48.	Standard cleaning procedure for equipment followed				
49.	Standard cleaning procedure for production area available				
50.	Standard cleaning procedure for production area followed				
51.	Validation of the cleaning procedure for Equipment				
52.	Validation of cleaning procedure for production area				
53.	Avoiding long campaigns during which contamination accumulates				
54.	Avoiding Heavy use of manual cleaning techniques				
55.	Availability of production equipment cleaning record				
56.	Availability of production area cleaning record				
57.	Appropriate system to avoid potential cross-contamination from personnel garments				

Annex 4: Descriptions of Equipment Selected for analytical Verification

Equipment Name	**Company A**			**Company B**		
	Manufacturer	**Model**	**Country of Origin**	**Manufacturer**	**Model**	**Country of Origin**
High Speed Mixer and Granulator	ZheJiang Xiaolun Pharmaceutical Machinery Co., Ltd.	GL25	China	Morton Machine Company Ltd	MGT 250	Germany
Fluid Bed Dryer	Changzhou Chuangke Drying Granulating Equipment Co., Ltd	GFG120	China	Niro Aeromatic	T 5	Switzerland
Tablet Press	Shanghai Tianhe Pharmaceutical Machinery Co., Ltd.	GZP-51A	China	Manesty	BB4	UK

Annex 5: Ethical Clearance of the study

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Addis Ababa University

School of Pharmacy
Ethical Review Board

ቀን Date: June 20, 2016

ቁጥር Ref. No.: ERB/SOP/81/06/2016

To: Eyob Assefa
School of Pharmacy

Subject: Ethical Clearance

It is to be recalled that you submitted a study proposal entitled, "Assessment of equipment cleaning and cross contamination prevention in production areas of Ethiopian pharmaceutical manufacturers", for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Esubalew Adugna (BPharm, MSc)
Secretary, ERB

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Annex 6: Analytical Method Validation

During the analytical method validation, all recommended parameters are validated as mentioned in the Methodology Section.

Linearity

The linearity of the method was checked with different concentrations of the standard solution ranging from 0.1 µg/ml to 5 µg/ml. Fig. 4.3 shows regression line drawn and equation determined for the calibration curve with Minitab (version 14).

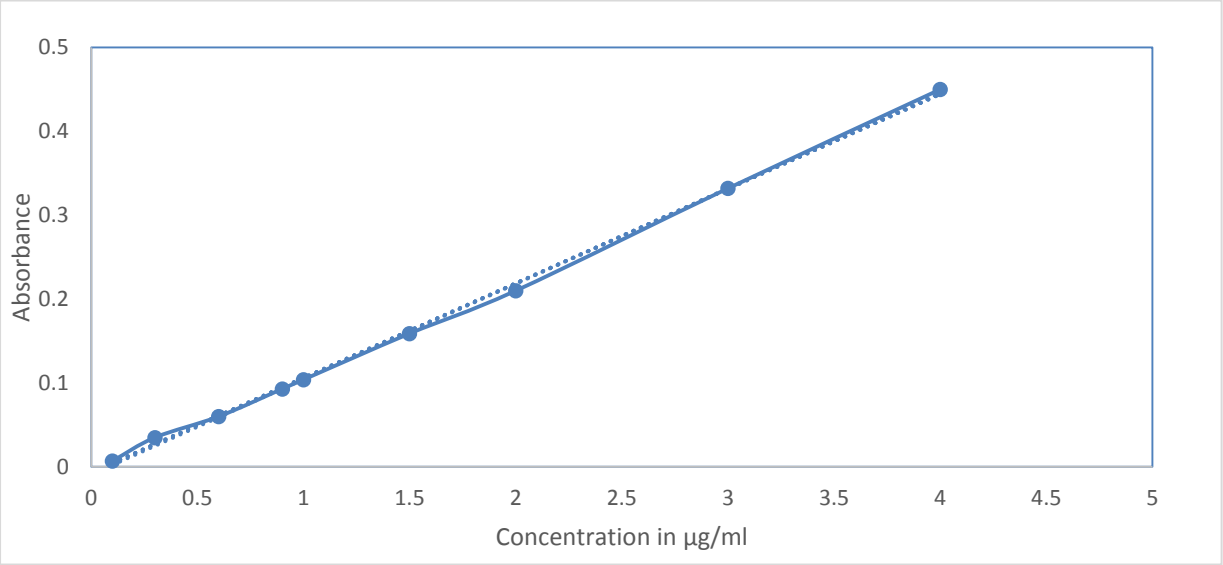

Fig. 4. 3: Calibration curve of standard Solution

The regression line drawn has a slope of 0.115 and Y-intercept of -0.00196 with r^2 of 0.999 proving linear relation of concentration and absorbance in the measured range.

Sensitivity

The Limit of Detection (LOD) and Limit of Quantitation (LOQ) of the analytical method were determined based on the standard deviation of the response (intercept) and slope of the calibration curve (Fig.4.3) according to ICH Q2 (RI) guideline. The LOD and the LOQ for Ciprofloxacillin HCL was found to be 0.092 µg/ml and 0.278 µg/ml respectively.

Accuracy and Recovery

The accuracy of the proposed method was determined by spiking sample solution with known standard. The accuracy was checked at 80, 100 and 120% with three replicates (n=3). Accuracy

is expressed as percentage of standard recovered from a sample matrix. The result of the method is depicted in table 4.8. %RSD values less than 2% shows the proposed method have good accuracy.

Table 1: Result of recovery studies for determination of accuracy of the proposed method.

Amount of Standard CPR spiked, %	Total % of CPR recovered	Mean (%)	%RSD
80	100.70	100.77	0.40
	100.40		
	101.20		
100	100.54	100.58	0.32
	100.28		
	100.91		
120	100.00	100.30	0.30
	100.28		
	100.61		

Precision

Precision repeatability and precision intermediate was determined for the method. The result of the method is depicted in table 4.9. %RSD values less than 2% shows the proposed method have good precision.

Table 2: Precision repeatability and intermediate of the proposed method

Precision study	%RSD
Intraday variation	0.59
Interday variation	0.44
Inter laboratory / inter instrumental variation	0.5357

Swab recovery from the stainless steel surface

As depicted in Table 4.10 the mean swab swab recovery result from SS plate was 84.7% with % RSD of 0.74.Reproducibility of the swabbing procedure is found good with less than 2% %RSD.

Table 3: Swab Recovery Test Result (n=6)

Measured absorbance of 100µg/ml standard solution	**Measured absorbance of recovered sample after swabbing SS plate**	**Percent Recovery**
0.2156	0.1828	84.8
0.2156	0.1824	84.6
0.2156	0.1828	84.8
0.2156	0.1800	83.5
0.2156	0.1842	85.4
0.2156	0.1828	84.8
Average & %RSD		84.7 & 0.74