QUALITY ASSURANCE OF TABLETS IN WIMITS PHARMACEUTICALS

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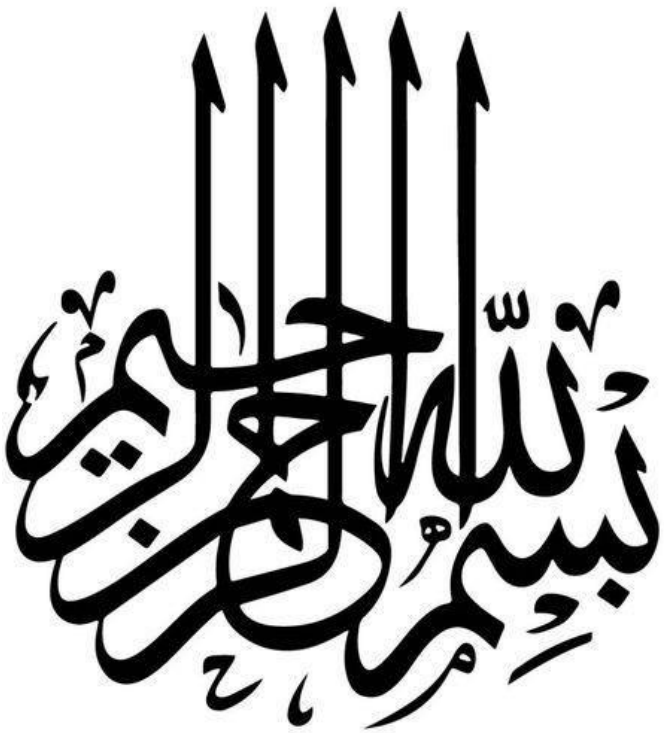

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DECLARATION

I, **Ali Hassan** S/O **Masood ul Hasan** ID: **15008067015** Session **2015-2021** hereby declare that the matter printed in the internship titled **"QUALITY ASSURANCE OF TABLETS IN WIMITS PHARMACEUTICALS"** is my own work and has not been printed, published and submitted as research work, internship or publication in any form in any University, Research institution etc. in Pakistan or Abroad.

_____ _____

Date **Ali Hassan**

DEDICATION

To my loving and caring parents whose heartily prayers, understandings and support has helped me throughout my hard times and brought every success in my life.

ACKNOWLEDGEMENT

First, I am thankful to **Allah Almighty**, who bless me good health strength and gives courage me to complete my task in a successful way and without help of Allah I was not able to do my work completely and respects for the **HOLY PROPHET MOHAMMAD (PEACE BE UPON HIM)**, who guide us to the straight path for our success in life.

I would like to thank **Prof. Dr. Arshad Majid Mirza,** (Dean, School of Science, UMT Lahore) and **Dr. Sohail Nadeem,** (Associate Professor, and Chairperson, Department of Chemistry, UMT Lahore) for their valuable guidance throughout my studies. They provided me with the tools that I needed to choose the right direction and successfully complete my degree.

Now I would like to thank my respected supervisor **Shah Muhammad Haroon,** (Assistant Professor, University of Management and Technology Lahore) whose expertise was invaluable in formulating the research questions and methodology. The insightful feedback pushed me to sharpen my thinking and brought my work to a higher level.

Ali Hassan

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List of Abbreviations

APIs	Active Pharmaceutical Ingredients
BPCS	Basic Process Control System
CAPA	Corrective and Preventive Actions
$CGMP_S$	Current Good Manufacturing Practices
DQ	Design Qualification
FIFO	First in First Out.
FEFO	First Expiry First Out
HPLC	High-Pressure Liquid Chromatography
IQ	Installation Qualification
IC	Integrated Circuit
IPC	In Process Control
LAL	Limulus Amebocyte Lysate
Ov	Oven
pH	Potential of Hydrogen
PVC	Polyvinyl Chloride
PVDC	Polyvinylidene Chloride
PO	Purchase Order
QMS	Quality Management system
QC	Quality Compliance
QA	Quality Assurance
SRMS	Standard Reference Materials
TMC	Tetramethylcyclam
URS	User Requirements Specifications
UV	Ultraviolet

VRA	Validation Risk Assessment
XLD	Xylose Lysine Deoxycholate

CHAPTER 1:

INTRODUCTION

1.1. Introduction

WIMITS Pharmaceutical was incorporated in March 1984 as a Private Pakistan Based Limited Company that is situated in Lahore: which is a historical and culturally enriched city of Punjab. Though it was initiated as private company but in 1995 with its excellent work it got the status of a public company. After getting the status of a public institution, company shares were listed from the start and its alliance has been made with reputable research houses around the globe. As a results of its alliance with world' reputable institutions, WIMITs has been ranked among the top twenty pharmaceutical industries, Pakistan Stick Exchange. Currently, this company is also working on various portfolios and projects for upgrading the status of its opportunities and facilities.

Varieties of new equipments are being implanted in this company. Therapists of WIMITs are focusing on the betterment of various departments such as gastroenterology, cardiology, as well as diabetics and respiratory. These departments are being considered very reliable by general public as they have been equipped with modern technologies and facilities. This company appreciates the initiatives and creative ideas provided by its employees and have a very excellent department for implementing these innovations. All the officials of that company work and coordinate like a family and it is a very positive point to raise the standards and repute of that institution. It is indeed one of the leading industries in Pakistan.

1.2. Role of Chemist in Pharmaceutical Industry

This part talked about the part of science inside the pharmaceutical business. In spite of the fact that the concentration will be upon the business inside the United States, a significant part of the discourse is similarly applicable to pharmaceutical organizations situated in other first world countries. David stated that a chemist has to play the role in quality control, sampling and sample management, process control, approval of material and product, analytical method validation, process validation, equipment qualification, stability studies, water analysis, pest control, documentation, and complaint recover. The real target of the pharmaceutical business is the disclosure, advancement, and promoting of strong and safe medications for the

treatment of human sickness. Hence, there exists a problem between the double objectives of upgrading the quality and span of human life and that of expanding investor value.

1.3. Prominent Feature of WIMITS

WIMITS is famous for its toll manufacturing for many multinational Companies like Abbot, Almirall, Biogenic etc.

1.4. Departments

There are 2 main departments in WIMITS namely:

1.4.1 Quality Operations

1.4.2 Production

Main departments of quality operations and production have several sub departments which perform variety of unique functions. Detail of sub departments working under the umbrella of quality operations and production is as follows:

1.4.1. Quality Operations

Under quality operations six sub departments are operating, name of these departments are as follows:

i. Validation and Audit
ii. Raw Material
iii. Packaging
iv. Finished Product
v. Product Monitoring
vi. Microbiology

1.4.2. Production

Second main department of WIMITS is production and under this department, further six departments are operating. Name of these departments are as follows:

i. Dispensing

ii. Oral Liquid Manufacturing

iii. Packaging Hall

iv. Solid Dosage Form

v. Semi Solid Dosage Form

vi. Product Development

CHAPTER 2:

EXPERIMENTAL WORK

During my internship, it was worked in the department of quality operation. It was informed by my coworkers about the tasks that are accomplished in the department of quality operations. Information which was gained during my internship through my coworkers and observations is as follows:

2.1. Quality Operations

Employees working in the department of quality operations reviewed all the factors and carried out the tests that are necessary for any formulation/production. They also gave the decision for acceptance or denial of every formulation/production. Their roles and responsibilities were divided into following sections:

i. Validation and Audit
ii. Raw material
iii. Packaging
iv. Finished Product
v. Product Monitoring
vi. Microbiology

2.1.1. Validation and Audit

This department supervised various functions for the validation and audit of a formulation/production. Detailed description of these functions is as follows:

2.1.1.1. Calibration

Before starting the process of validation, comparison of equipment was made with standard equipment, this process was named calibration. My seniors clarified me that some equipment is calibrated daily while others are calibrated on monthly basis, weekly basis, after 6 months, and annually. Calibration of equipment's was depended upon the frequency of equipment used. Calibration was performed by internal source and external source. During this function, I learned to calibrate the equipment.

2.1.1.2. Validation

After calibration, validation was carried out for processes and procedures. Validation was of many types.

Brief and detailed description of validation types is as follows:

i. Process Validation

ii. Analytical Validation

iii. Equipment Validation

iv. Cleaning Validation

v. System or utilities Validation

i. Process Validation

This kind of validation has been divided into three major stages, which were as follows

First stage has been denoted as process design and in this stage defines the process of commercial manufacturing. Besides it, this stage includes knowledge that is obtained from scale up activities and development process.

Second stage has been termed as process qualification and the major function that is performed during that stage is to ensure the quality of process design (i.e to ensure that either recommended design is suitable for producing commercial products or not).

Third stage which is known as verification of continued process aimed at ensuring the correctness of whole process and ensured that all activities are under control.

ii. Analytical Validation

This kind includes preparation and use of samples, reagents, and apparatus etc.

iii. Equipment Validation

It was done to validate the equipment's used and results are documented on the validation plan. Validation Risk Assessment (VRA) was done to assure that the process done is accurate.

Design qualification that is also termed as DQ demonstrated information related to design and ensured that proposed design fulfill the desired requirements that have been described in URS (user requirements specifications).

Installation qualification which is also termed as IQ demonstrated the equipments and products that meet all the specifications provided by chemists, is correctly installed, and ensured that all required components have been installed at right places.

Operational Qualification: It demonstrated that all processes were working accurately.

iv. Validation for Cleaning

Cleaning validation is used for the removal of active pharmaceutical ingredient residues in a piece of equipment during product manufacturing. It utilized various microbial attributes and cleaning aids during the cleaning process.

v. System Validation

System validation demonstrated the whole process and equipment performed as intended in consistent manner overtime. Information related to this function enabled me to go through the whole process of validating equipment's.

2.1.1 Raw Material

Raw Material that was received by the store officer was placed in quarantine until QC (Quality Compliance) performed tests on it and declared the results.

- Process Flow PO (Purchase Order) receipts from Inspection to stock raw material

It goes as the raw material list is received by the QC analyst. After that entry was done in log book of raw material. From that sampling was done and verification of supplier was done. Then analytical format was generated and testing was carried out as SRMS (Standard Reference Materials). After that the result was compiled. I was informed that if the result will not be according to requirement than QC manager will intimate for re-sampling and testing and report will be generated accordingly. The intimation was done in BPCS (Basic Process Control System) system for releasing or rejecting material. Finally, label was affixed and was duly signed by personnel.

Materials having re-evaluation\re-test date-used for five years from date of manufacturing after re-testing every year for APIs (Active Pharmaceutical Ingredients) & Non-API's and for two years in case of flavors and essence.

2.1.2.1. Observation

After briefing about main processes of calibration, validation and raw material analysis, I was involved in formal observation. During my first formal observation I make analysis of following objects and selected these items for further experimentation:

i. Analysis of tres orix forte syrup

ii. Analysis of Serc tabs

iii. Analysis of Colofac Tabs

2.1.3. Packaging

After the process of analysis my staff briefed me about packaging. They told me that samples are packed in polythene bags and labeled accordingly. I was also informed about major types of packaging that were as follows:

i. Primary Packaging: It included caps, vials, foils, bottles etc.

ii. Secondary Packaging: It included cartons, labels, inserts and spoons.

iii. Tertiary Packaging: It included shippers, gums etc.

I was also informed about various tests that are performed in packaging section:

- Shrinkage test for PVC(Polyvinyl Chloride)\PVDC(Polyvinylidene Chloride).
- Grammage test for cartons, labels and aluminum foils.
- Anticorrosive resistance test
- Moisture content determination and physical examination

And it was clarified that following defects have been identified in packaging as a result of above-mentioned tests:

2.1.3.1. Major Defects:

- Off printing

- Bad cutting
- Bad creasing
- Color Variation
- Bad Printing
- Bad Pasting
- Torn
- Un-Varnished Area

2.1.4. Finished Products

2.1.4.1. Performed Tests

I performed following tests for my selected samples:

2.1.4.1.1. For Tablets:

Weight Variation, Thickness, Friability, Disintegration, Dissolution, Leakage test, Hardness, HPLC (High-Pressure Liquid Chromatography), UV(Ultraviolet), and Content Uniformity.

2.1.4.1.2. For Syrups:

Viscosity test, pH (Potential of Hydrogen) test, Clarity test, Refractive Index, Density, Microbiological test.

2.1.5. Product Monitoring

My coworkers and senior colleagues also informed me about the process of product monitoring which includes stability study and also about the major function that are being performed by microbiology department. The information which I gained related to stability study and functions of microbiology department are as follows:

2.1.5.1. Stability study

Stability study was conducted for single trial batch of new formulation and some dosage forms that were packed in proposed\intended commercial packaging.

The process of stability study which I observed was carried out for first three commercial batches of the formulation, and those batches where troubleshooting was found were handled separately

Raw material source change batches including active and inactive\change of primary packaging were also subjected to stability studies.

I was instructed that stability study should be conducted on finished dosage forms packed in containers. Studies on the products outside can be very valuable as for stress testing they can play an important role. In product monitoring following parameters were checked:

- Dissolution profile
- Assay
- Impurities
- Potency
- Degradation of products
- Appearance of physical attributes
- Functionality test
- pH

2.1.6. Microbiology

At final stage, nearly all finished products required a microbiological assessment, and this assessment was carried out by performing following tests:

- Pyrogen testing
- Sterility testing
- Swab testing
- Staining of bacteria
- Microbiological testing of water
- Microbiological testing of finished products
- Disposal of culture media

All types of testing were performed into 3 rooms according to the nature of finished product, brief and detailed description of these rooms is as follows:

- Incubation Room
- Sterilization Room
- TMC (Tetramethylcyclam) Room

2.2. Incubation Room

Before entering lab buffer zone was present to prevent cross contamination in incubation room, and this room contained three types of major instruments.

Figure 2.1. Incubator in Pharmaceutical QA (Quality Assurance) Lab

2.2.1. Hot Incubators

These were used for checking bacterial growth, and specification of these incubators is as follows:

- Temp 35-37^{o} C
- IC (Integrated Circuit) 01- For TMC testing (Broth testing)

- IC04-For TMC testing (Broth testing)
- IC02-For Pathogen testing

2.2.2. Cold Incubators

These were used for checking fungal growth, and specification of these incubators is as follows:

- Temp 32.5^{o} C
- IC05- for TMC testing

2.2.3. Oven

It was used for heating:

- Ov-01 phase (It is suitable for the separation of drugs, alkaloids, phenols and steroids)

Figure 2.2. Oven in Pharmaceutical QA Lab

2.3. Sterilization Room

Microbiological equipment's were sterilized in this room and sterilization was done by following equipment's:

2.3.1. Dry heat sterilization

Specifications of this sterilization were as follows:

- OV-05: A necessary laboratory instrument is hot air oven, it is used for sterilizing equipments and other material of laboratory by dry heating.
- At 160^{o} C for 2 hrs.

2.3.2. Moist heat sterilization

Specifications of this sterilization were as follows:

- AV01-Autoclave (HIRAYAMA)
- At 121^{o} C for 15min at 15 pounds' pressure.
- One is fully automatic and one is semi-automatic.

2.4. TMC (Tetramethylcyclam)Room

It was also called LA-01 Laminar flow cabinet. Following methods were performed in this room:

i. Method of pour plate

ii. Method of spread plate

iii. Method of membrane filtration

2.4.1. Frequency of Testing

Specification of testing for various kinds of materials and dosages were as follows:

- For Raw Materials every batch
- For Solid dosage form every 5th batch
- For Duphalac 1st batch of every campaign

- Other liquid dosage form –every batch
- Up to 0.1g balance is present in TMC room

2.4.2. List of Refrigerated Items

List of various refrigerated items that were available in this room is as follows:

- E. Coli
- Bacillus subtilizes
- Candida albicans
- LAL (Limulus Amebocyte Lysate) single test vial
- Mineral oil
- Malachite Green Oxidase
- List of Medias:
- Trypton Soya Agar
- Trypton Soya Broth
- Sabouraud Dextrose Agar
- Peptone
- Lactose Broth
- XLD (Xylose Lysine Deoxycholate) agar
- Bismuth sulfite agar
- Cetrimide agar

2.5. Observations

I observed the whole process of Medias Preparation in these rooms and learned a lot about the usability of various instruments/equipments.

2.6. Quality Compliance (QC)

This department was divided into four branches:

i. Dispensing

ii. IPC (In Process Control)

iii. Batch release

iv. QMS (Quality Management system)

I observed this functions of thee branch and detail of task/functions that were performed in these branches is as follows:

2.6.1. Dispensing of Raw Material

After receiving raw material for manufacturing by production pharmacist it was checked by QC officer. QC officer awarded line clearance as per check list. He checked various information written on products such as MFG (Manufacturing) date, Batch No, Lot No, Exp (Expiration) date etc.

2.6.2. IPC

I observed that before startup of any formulation an officer from IPC comes and gives line clearance. Afterwards work on formulation was being started. Diverse criteria were used for clearance of diverse items such as:

2.6.2.1. For Liquid

Following check indicators were carried out:

- pH of liquids used in manufacturing
- Verification of Volume per BMR.
- Use of manufacturing vessel per BMR

2.6.2.2. For Solid

Following check indicators were carried out:

- Cleaning of equipment's
- Mixing time
- Moisture contents
- Thickness

- Hardness
- Weight variation
- Verification of line loss

2.6.2.3. In Packaging Hall

Following check indicators were carried out:

- Check proper blistering
- Record readings after proper time
- OA officer performs leakage test.
- During Batch release QC officer checks the quantity of shippers packed, Batch No, Expiry date. Mfg. price etc.

Figure 2.3. Medicine Packaging Hall

2.6.3. Quality Management System (QMS)

QMS dealt with all the complaints of products. While a committee known as CAPA (Corrective and Preventive Actions) dealt with all the complaints that were received from QMS.

2.6.4. Sampling

During the packing of dosage forms QC officer took certain amount of packs as reference packs for future correspondence.

2.6.5. Market Complaint Handling

IPC members were also responsible to deal with the market complaints that were related to following categories.

- Equipment's and Apparatus
- Viscometer
- Disintegration Apparatus
- pH meter
- Weighing Balance
- Hardness Tester
- Thickness Tester
- Fribiliator
- Dissolution Apparatus

2.6.6. Inventory Management System

In this system, there were three sub systems and brief description of these subsystems is as follows:

2.6.6.1. FIFO System

This means First in First Out. This means that the material that was received first shall be dispensed first.

2.6.6.2. FEFO System

This means First Expiry First Out. This means that the material whose expiry is coming nearer should be dispensed first.

2.6.6.3. BPCS System

WIMITS Pharmaceuticals Industry follows BPCS system. This stands for BUSINSESS PLANNING AND CONTROL SYSTEM. This is an online system and all the documentation is done on this system.

CHAPTER 3:

PRODUCT DEVELOPMENT

3.1. Product Development

This department was responsible for the new formulation of the product. By keeping in mind the competitor's product various experiments are conducted here. There could be the change in excipients or compressional weight to yield the new product. After experimentation the sample was moved towards QC department for further analysis. I was informed that if QC department will be satisfied by the results than 3 badges will be formed under the supervision of PD department. Afterwards the batch was marketed. The formulation of Batch Manufacturing Record (BMR) was the responsibility of Product Development Department also.

3.1.1. Functions of PD Department

Major functions that I observed in this department were as follows:

- Formulations
- Trials
- Stability
- Troubleshooting
- Documentation
- Medical Bioequivalence and clinical trials
- HR trainings
- Finance costing
- Effective storage of sensitive materials

3.1.2. Observations

- Compression of Hi-Statin Tab

3.2. Work Experience

On the basis of my experience, I suggest that kindly increase the days for internship program. Besides it, kindly let the internees work practically in supervision of professionals so that they might learn something more precisely with their hands.

It’s quite necessary if you increase the duration of working in Q.A. dept. because that's the core area to learn the expertise. Accommodation of students in a single place was also an issue. IPC area is so congested. Therefore, it is suggested that students may be placed for internship at diverse companies so that they can get ample opportunities of learning. I had a privilege in working in this industry. During my internship I learned a lot. My skills are further enhanced by working in this industry. The Atmosphere was quite comfortable and the people worked in collaboration with each other. It is indeed one of the leading pharmaceutical industries in Pakistan. I wish to work again with WIMITS Pharmaceuticals Industry in near future. INSHALLAH

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