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Quality Control and Quality Assurance in Pharmaceutical Industry

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ABSTRACT
Quality assurance can be defined as "the part of quality management aimed at ensuring confidence that quality must be performed". The trust provided by quality assurance is dual internal to management and external to clients, government agencies, regulators, certification bodies and third parties. An alternative definition is "the complete performance of targeted and organized activities within the framework of a quality method that can be documented to provide assurance that the commodity or service will meet the required quality. Quality assurance is comprehensive and does not have to do with the specific necessity of the product being developed. Quality Assurance (QA), Quality Control (QC), and Good Manufacturing Practice (GMP) are major considerations in the manufacturing, distribution, and marketing of pharmaceutical products to ensure their identification, potency, purity, pharmacological safety, and efficacy and effectiveness. (8) The terms Quality Assurance, Quality Control and Good Manufacturing Practices are defined in most international regulatory documents including WHO, USFDA, MHRA,TGA, MCC, etc. The quality of a pharmaceutical manufacturer's products depends on the fact that up to what satisfactory level of QA, QC and GMP system has been adopted in the process of production, distribution and marketing of products during their total shelf life. The main objective of this article is to demonstrate the fundamental difference between quality assurance, quality control and good manufacturing practice (GMP) and to emphasize their necessity for a pharmaceutical product. (8) This overview describes quality by design and identifies some of its elements. Process parameters and quality attributes are identified for every unit operation. The advantages, opportunities and steps involved in Quality by Design for pharmaceutical products are described. It is based on ICH guidelines Q8 for pharmaceutical development, Q9 for quality risk management and Q10 for pharmaceutical quality systems. It also provides the application of Quality by Design in pharmaceutical drug development and manufacturing.

1- INTRODUCTION

Quality Control

QC is the part of GMP convey with sampling, specifications, testing, organization , documentations and release
procedures which make sure that the necessary and relevant tests are carried out and that the materials are neither
released for use nor products released for sale or supply until their quality has been satisfactory QC is not limited to laboratory operations but must be involved in all regarding to the quality of the product (11)

A. Scope of Quality Control

Supply Quality Assurance: Supplier quality assurance (SQA) is a agreement with the provider of raw
materials and components. Under this contract, the manufacturer make sure that incoming materials and parts
will be of uniform and reliable quality.
In-process control: Random samples of the product are taken and their quality is measured against predetermined standards of quality during the stage of processing materials. Such tests may tell certain faults in
the production process. Primordial steps are taken to make sure that right quality products are manufactured. Post- mortem inspection: It is taken after the products are manufactured or completed. It is a technique of classifying the units into acceptable and reject-able class and assessing the quality of a product. Inspection
controls are frequently called quality assurance.

1.2 Quality Assurance

Quality Assurance (QA) is a management method defined as "all those planned and systematic activities required to provide reasonable confidence that a product, service or result will meet given quality requirements and be fit for use".

2-HISTORY OF DRUG REGULATIONS

In the field of drug products, it is the United States of America that has always been at the forefront of developing the necessary regulatory guidelines, and the trend continues to this day. Much of the history of drug regulations therefore cover events in the US. In the olden days, medicines were prepared mainly in the form of elixirs, ointments and pills, and sold

by the person making them. These medicine containers were labeled with nothing much beyond the name of the product they contained, and the troubles they promised to cure. Later, as science and technology advanced, some small family businesses began manufacturing other products like vaccines and anti-toxins too, but there was almost no control over these operations. In 1902, a mishap occurred to focus attention on the dangers of such manufacturing. Twelve children died after being administered an antitoxin for diphtheria and it was found that the product had been contaminated with live tetanus bacilli. In response to strong protests from the public, the United States Congress passed the Biologics Control Act. Under this Act, the manufacturers and sellers of such biological products had to test their products for strength and purity; they also had to undergo regular inspections by the health authorities.

In 1906, the US Congress passed the Pure Food and Drug Act. This made it illegal for people to sell adulterated/contaminated food or meat. Medicines were now required to have labels that stated the true facts about their contents, without any false information or promising magical cures. Out of this Act was born one of the world's first government regulatory bodies, which we now known as the United States Food and Drug Administration (USFDA).

This body was conferred the authority to seize illegal drugs and foods. Any dangerous ingredients in medicines now had to be labeled, and the labeling had to be true and accurate.

In 1935, 107 people, a majority of them children, died after consuming oral sulphanilamide elixir. An investigation showed that this product had been made using a solvent called diethylene glycol which is a poisonous solvent! The public was incensed and demanded stricter laws.

In response, the US Congress passed the Federal Food, Drug and Cosmetic Act of 1938. For the first time in the history of drug manufacturing, it became necessary for companies to prove that the products made by them were safe, before allowing them into the market. This Act also made factory inspections mandatory, set down standards for food products, and made penalties and criminal proceedings more stringent.

In 1941, yet another tragedy occurred in which close to 300 people died. The cause was Sulfathiazole tablets had got contaminated with a sedative Phenobarbital. This led to significant changes in the regulations controlling manufacturing and quality control requirements for drugs. The Public Health Services (PHS) Act that was passed in 1944 further expanded the scope of regulations to biological products.

The process of certification of batches by the FDA began during the time of World War II. Manufacturers of insulin, penicillin and other antibiotics would submit samples to the FDA from each lot they made and get permission for the release of these products.

In 1955, days after a mass polio vaccination drive began using the newly developed Salk polio vaccine, it had to be abandoned. The reason was children who received the vaccine (from batches made by Cutter Laboratories) were found to have developed the disease. An investigation showed that there had been a failure in the process of inactivating the live polio virus, and this had gone undetected! This incident was widely discussed internationally
and brought home the need for even more control over the safety standards of vaccines. The worst was yet to come, though.

In 1957, a pharmaceutical company in Germany called Chemie Grunenthal GmbH developed the world's first non-barbiturate anti-convulsant drug called as Thalidomide. It was found to also have a sedative effect and doctors began prescribing it as a tranquilizer. Thalidomide was sold over-the-counter based only on the claims of its manufacturer. Laboratory studies on animals showed it was practically impossible to reach a LD50 dose. (LD50 is the lethal dose which causes death in 50% of the animals tested.) So the company advertised it as totally safe even for mother-and-child. This "wonder drug" became hugely popular and was marketed to 46 countries across the world. Around 1960, an Australian obstetrician McBride noticed that the drug also helped to reduce the morning sickness associated with pregnancy. He began recommending it to his pregnant patients, and through word-of-mouth reports in the medical fraternity, this practice, too spread across the world. Only in the USA, the drug had not been approved for use by the FDA's drug examiner named Frances Kelsey. (Years later, she was conferred with awards for the service she had rendered to the American public through this act.)

However, by 1961, McBride began noticing a severe birth defect called phocomelia in babies delivered by his patients who had taken Thalidomide. Phocomelia is the condition where a baby has no limbs, or shortened or flipper-like limbs. A newspaper in Germany reported that close to 161 babies had been thus adversely affected by the drug, and the distribution of Thalidomide in Germany was stopped, with other countries following suit. By 1962, after at least 10,000 cases of deformed infants had been born, Thalidomide was finally completely banned.

This shocking tragedy was the catalyst for putting in place a more rigorous drug approval and quality monitoring system developed by the USFDA. Companies were now required to test both efficacy and safety of their drugs. Drugs had to be tested on animals before they could be tried on humans. Clinical trial regulations became more stringent and the drug investigators were made responsible for supervising the drugs being studied. In other words,

companies now had to obtain consent from the regulatory authorities before testing a drug and had to prove the drug's safety and efficacy before manufacturing it and taking it to the market.

2.1 QUALITY ASSURANCE

Getting FDA approval is however only the start of yet another equally tough journey. The drug formulation has to transit from the laboratory to the manufacturing floor, which has its own challenges. As obvious from the history of how cGMP came into being, there are many things that can go wrong and it is vital to have sufficient control over all the factors that can influence the quality of the final drug product.

For several years, pharmaceutical companies relied a lot on Quality Control (QC) for adequate testing of the quality of their products. With time, however, as processing operations grew more complex, the realization grew that testing often misses detecting problems because tests are run on randomly selected samples. One cannot hope to "test quality into" products that do not have the quality inherent in them.

This realization led to the development of the concept of Quality Assurance (QA) which seeks to build quality into the products from the very beginning of the process of drug manufacture. By careful planning, training and monitoring QA is a means to control processes right from choosing the right vendor for the starting and packing materials, to the manner in which distribution of finished product takes place. The aim is to cover all the aspects that individually and collectively impact the quality of products. The World Health Organization (WHO) defines QA as, "The totality of arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use."

Differences between QA and QC

Attribute	QA	QC
Goal	Preventing defects.	Identifying defects.
Focus	Building quality into product from design stage itself.	Testing if quality exists in product after its manufacture.
Work flow	Establish quality management system, continuous monitoring of processes.	Find source of problems in quality.
Type of tool	Managerial.	Corrective.

RESPONSIBILITIES OF QC UNITS

Every pharmaceutical manufacturing unit should have a quality control unit. There must be written procedures to describe the functioning and responsibilities of this unit, and these procedures must be followed.

The QC unit has the responsibility of testing all raw materials, drug products, containers, closures, in-process materials, labeling and packaging material. It also has the authority to accordingly approve the materials that meet quality, safety and efficacy specifications and reject the ones that do not meet them.

The QC unit also has the authority to review the records generated during production of every batch to ensure that errors have not occurred at any stage or that any errors that occurred have been completely investigated. In case a company A gets products manufactured under contract by another company B, the QC unit of A has the authority to approve or reject those products manufactured, packed, processed or held by B for A.

The QC unit must have access to necessary laboratory space and facilities to test and approve all raw materials, drug products, containers, closures, in-process materials, labeling and packaging material.

Any procedures or specifications that are likely to impact the strength, identity, purity and quality of the drug product must be approved by the QC unit.

SANITATION

All areas inside the building must be cleaned regularly and cleaning records must be maintained. Drains must be sized correctly and be designed to prevent back-flow of contents. They must be closed as far as possible; if open channels are unavoidable, they must be kept shallow to allow easy cleaning and disinfection.

Wastes from manufacturing area must be disposed in keeping with regulations of Environment Pollution Control Board. Waste materials that have to be disposed must be stored in a safe manner. Any wastes that are inflammable, hazardous or toxic must be stored in a segregated area while awaiting disposal. Bio-medical waste must be disposed as per regulations of Bio-Medical Waste (Management and Handling) Rules, 1996. Rejected drugs must be stored separately and destroyed in keeping with regulations.

Restrooms, toilets and refreshment area must be located far from manufacturing areas. They must not be in direct communication with areas where materials are manufactured, tested or stored. Animal testing laboratories too must be isolated from these areas, with separate entrance and dedicated air-handling systems.

Sanitation of Sterile Areas

Sterile areas must be cleaned and sanitized often in keeping with an approved cleaning protocol. More than one type of disinfectants must be used to ensure effective bactericidal action. Regular monitoring of clean rooms must be performed to detect presence of contaminating microorganisms. Cleaning procedures must be validated to verify that disinfectant residues are detected and removed during cleaning. Detergents and disinfectants used in sterile areas must be sterile before use. For spaces that are inaccessible inside the sterile room, fumigation may be used to reduce microbial contamination. Occasional cleaning with a sporicidal agent must be part of the cleaning routine since spores are resistant to the common disinfectants.

ENVIRONMENTAL CONTROL

The temperature and relative humidity of the premises must be controlled in order to ensure the area complies with material and product requirements, as well as regulatory requirements. Attention must also be given to operator comfort wherever possible. Airlocks must be built to separate low-humidity areas from higher humidity areas; this prevents the migration of moisture that would otherwise overload the Heating Ventilation and Air Conditioning (HVAC) system.

The systems used for humidity control must be designed to avoid introducing any contaminants.

Dust and vapours must be extracted at source and not allowed to travel elsewhere. The dust extraction system must have adequate transfer velocity in order to make sure that the dust is truly carried away and does not merely settle into the ducting of the system. General direction of airflow in a room must be designed to remove vapours and dust generated in the area. It must also consider the location of the operator to make sure he/she does not contribute to contamination. It is often preferred to introduce air into the room using ceiling diffusers, and extract the room air through vents at low heights on the wall to provide a flushing effect as the air moves out of the room. In case of processes that generate a vapor that is lighter than air, the extraction grilles will need to be positioned at higher level.

CONTAMINATION

World Health Organization (WHO) defines contamination as, “The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.”

The most common sources of contamination are dust, skin, hair, microorganisms, grease, chemicals and particulate matter. Such contamination can be controlled by controlling the environmental conditions as well as personnel factors.

Environment control is exerted by having a well-designed HVAC system that efficiently removes the contaminants that may get introduced. Regular cleaning and controlled entry and exit of materials and personnel into the clean areas can also help avoid contamination.

Personnel hygiene is a must and they must be trained to follow the prescribed dress code, procedures for entry and exit into clean rooms and gowning procedures.

CROSS CONTAMINATION

WHO defines cross-contamination as, “Contamination of a starting material, intermediate product or a finished product with another starting material or material during production.” Manufacturing areas must be designed to prevent both contamination of drug product and cross contamination between products. Contamination may be avoided by controlling the quality of air in a room and by ensuring hygiene and clothing change of workers entering into the manufacturing area. Cross-contamination is a little more difficult to control.

Risk of cross-contamination is greater when dry material processing takes place because dust is generated and spreads rapidly. The most common sources of cross-contamination include dust, vapors, gases, particles, sprays, residues on equipment surfaces, operators clothing or skin.

The most dangerous contaminants include sensitizing materials, hormones, living organisms, cytotoxic materials and highly active compounds.

Documentation

All the major equipments should have a unique identification code or number, and this must be recorded in the batch manufacturing record (BMR). Separate cleaning and maintenance logs must be maintained for each of the major equipment, and any cleaning or maintenance activity must be recorded in these. Standard operating procedures must exist for operating all equipment, and they must be placed close to the equipment for use by the personnel handling them.

The major equipment being used in manufacturing a given batch must be labeled with details of product name and batch number at all times to indicate the contents within.

Approval/Rejection of Materials

All materials that meet the manufacturer’s quality requirements of identity, quality, purity and strength and other tests are to be approved for use. Materials not meeting these requirements must be rejected.

Labeling

Labels must carry the name of the product, the company’s unique reference code, manufacturer’s name and address, and their assigned batch number. It must also state the status of the contents (For example – “Sampled”, “Quarantined”, “Approved” and “Rejected”), manufacturing and expiry dates and re-test date. When attaching such labels, care must be taken that original information on the supplier’s label is not lost.

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Approved materials must be so marked while rejected materials must be conspicuously labelled and stored in a separate area to avoid chances of mix-ups or misuse.

Using Approved Materials

Approved materials must be stored properly and issued for use in a way such that earliest approved stock is used first before more recently approved stock. Many companies use a FEFO (First Expire First Out) system for stock rotation. Another deciding factor is that the drug product's shelf life must not exceed the shelf life of the APIs.

If materials have been stored for very long period without usage, or if they have been exposed to any condition that may have an adverse effect on their quality or safety, they must be re-tested for the same parameters as the initial test. Results of the re-test must be used to determine if the materials are approved or rejected.

3-QUALITY CONTROL

SAMPLING

QC personnel must be authorized to enter the stores and production areas for sampling of materials, intermediates and final products. The samples must be drawn in keeping with approved written procedures in a way to be truly representative of the materials. Care must be taken during sampling to avoid contamination of the containers, and also the mix-up of materials sampled. This is achieved by using clean and sterilized (if necessary) sampling equipment.

The containers from which samples have been drawn must be resealed correctly after sampling. Such containers must be labelled with details of name of material, batch or lot number, sampling date, and signature of the sampler.

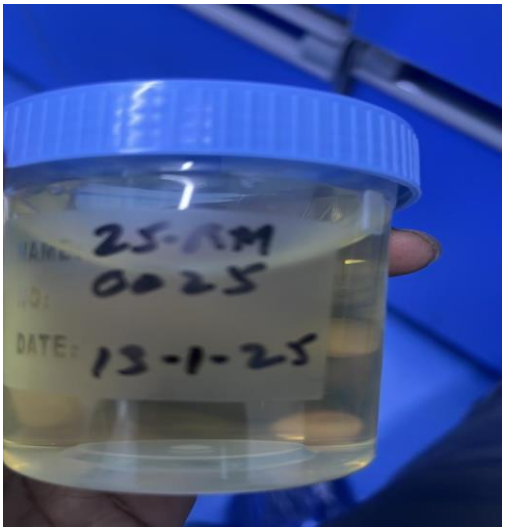

Fig: Sampling of Raw material in sampling sterile Container

TESTING AND ANALYSIS

Analysis must be performed on the samples drawn, and results informed to the stores and production heads. Containers must duly be affixed with "Approved" or "Rejected" labels as the case may be; rejected material must be removed to a separate area with entry restricted to authorized persons only.

PRODUCT ASSESSMENT

All batch processing records must be reviewed for conditions under which production was done and results of testing of starting material, in-process and finished products must be studied. Compliance of final product to specifications and presence of complete documentation must be confirmed. After verifying all these, the assessment records are signed by the Production Head and the QC Head and only then is the product released for distribution and sale.

Documentation of OOS result investigation:

Information to be documented for every OOS result investigation:

- Reason for investigation.
- Details of the OOS result.
- Phase I Laboratory investigation details and findings.

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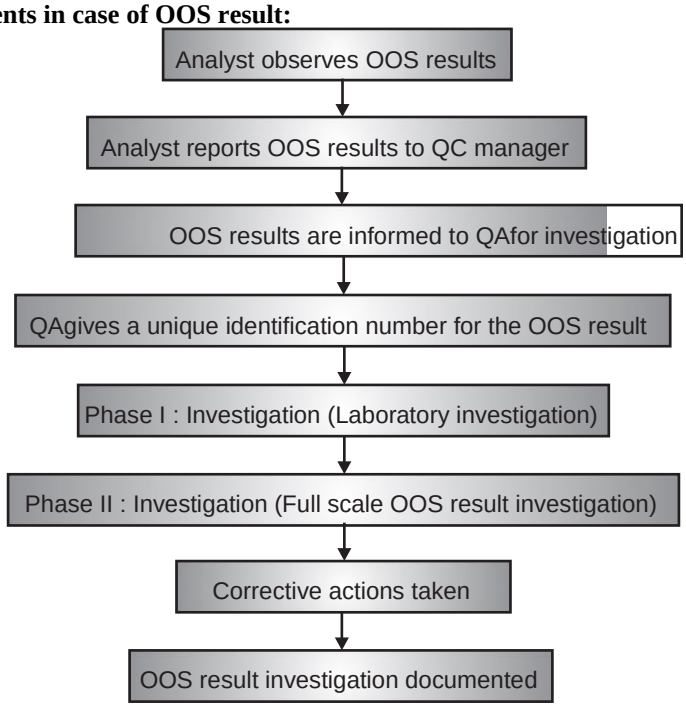
- Summary of Phase II analysis performed.
- Root cause identified as actual/probable cause of the OOS result.
- Description of corrective actions taken following the OOS result.
- Result from document review of previous batches to check if similar problem has occurred before.

Flow of events in case of OOS result:



4-GOOD LABORATORY PRACTICES FOR NON-CLINICAL LABORATORIES

Introduction

In 1976, the United States Food and Drug Adminsitration (USFDA) received information from a whistleblower about some problems in data submitted by a company called Syntex. Erroneously, an FDA official picked up a file on a contract laboratory called IBT (Industrial BioTest Laboratories) which was under contract to Syntex.

On reviewing the data submitted by IBT, serious defects in the study were found, and the FDA performed an inspection of the IBT facility where even more shocking critical deficiencies in scientific procedures were unearthed. It was found that data was being fabricated, adverse health effect results were being removed from reports, dead study animals were being replaced with healthy ones, histopathology data was being fudged and report conclusions were being modified to make the drug appear favourable.

A little later, similar malpractices were found in the long-term toxicology studies being conducted in laboratories of the company called G.D. Searle and Company.

Suspecting that similar situations existed in most research facilities throughout the pharmaceutical sector, the FDA decided to institute a monitoring program to ensure sound and scientific laboratory practices were followed.

In august 1976, draft proposal for Good Laboratory Practice (GLP) regulations was published in the Federal Register on 19th November 1976. These regulations laid down a uniform approach to ensure the integrity of data produced during non-clinical laboratory studies. By creating a system of Quality Assurance (QA) unit in testing laboratories, it was sought to ensure that the facility complied with regulatory requirements. On 4th September, 1987, the Good Laboratory Practice Regulations, The Final Rule, were published.

DEFINITION OF GLP

FDA defines GLP as, “A set of principles intended to assure the quality and integrity of non-clinical laboratory studies that are intended to support research or marketing permits for products regulated by government agencies.”

The term non-clinical laboratory study refers to the *in-vitro* or *in-vivo* experiments where item being tested is studied in systems under laboratory conditions to evaluate how safe it will be.

Thus, GLP ensures that testing facilities comply with the minimum requirements the FDA expects with respect to the planning, conducting and reporting of safety studies related to non-clinical testing. By providing a framework for a well-controlled study, GLP assure an overall accountability.

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SCOPE OF GLP

The term GLP applies to the non-clinical testing required for approval of new drug products for human and animal use. Its scope also extends to cover non-pharmaceutical compounds like food additives, colour additives, food packaging, food contamination limits, biological products, electronic products and medical devices.

If a firm hires the services of a contract laboratory or a consultant laboratory service for the testing, that laboratory must also abide by GLP.

The testing laboratory must permit an inspection of their facility and records of the studies being conducted by a duly authorized employee of the FDA.

GLP ***does not cover*** human clinical studies, discovery-related toxicology studies, nonclinical pharmacology studies to study efficacy and drug action and bioanalysis of samples drawn from clinical trials.

IMPORTANCE OF DOCUMENTATION IN PHARMACEUTICAL INDUSTRY

Proper documentation is the backbone of current Good Manufacturing Practices (cGMP) and in the regulatory world, it is commonly held that "If it isn't documented, it wasn't done!"

Documentation is the most essential part of a quality management and quality assurance system for the following reasons:

- Documents are evidence of all manufacturing and testing activities and provide traceability to verify if certain actions were performed or not.
- Written procedures provide clarity and ensure there are no errors that may arise during spoken communication.
- Records, documents and reports give a clear picture of what has been done and is ongoing work, and it also helps to plan better for the future.
- A comprehensive review of the documents maintained in a pharmaceutical facility is often the key used by regulatory bodies to assess the quality function of the facility.
- Accurate and clear records allow the critical reviewing of processes, which can help to improve quality and create cost-saving measures too.

5-RESULTS

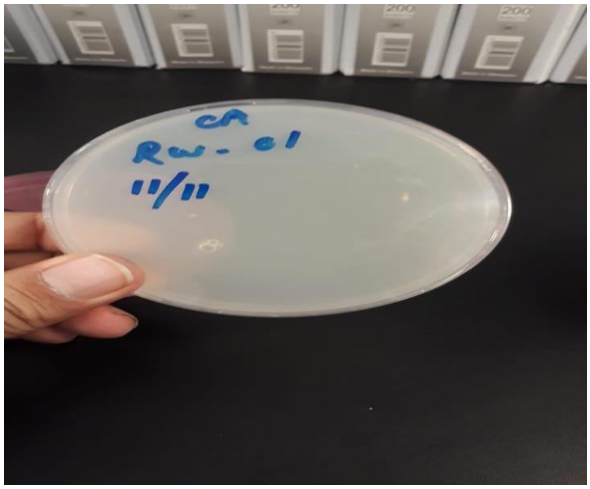

Fig: Underground water shows no growth

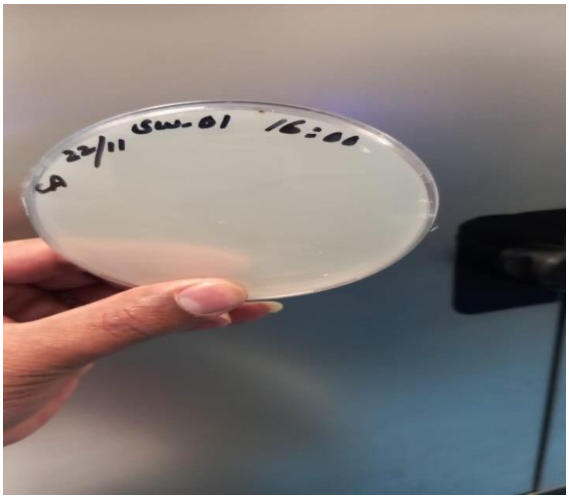

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Fig: softner water shows no growth

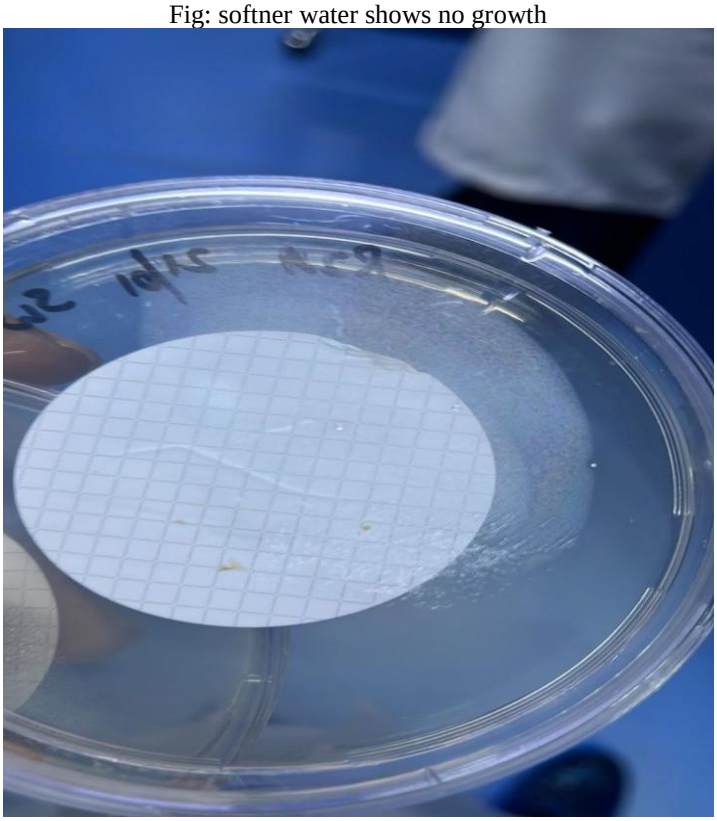

Fig: Water For Injection shows acceptable colonies

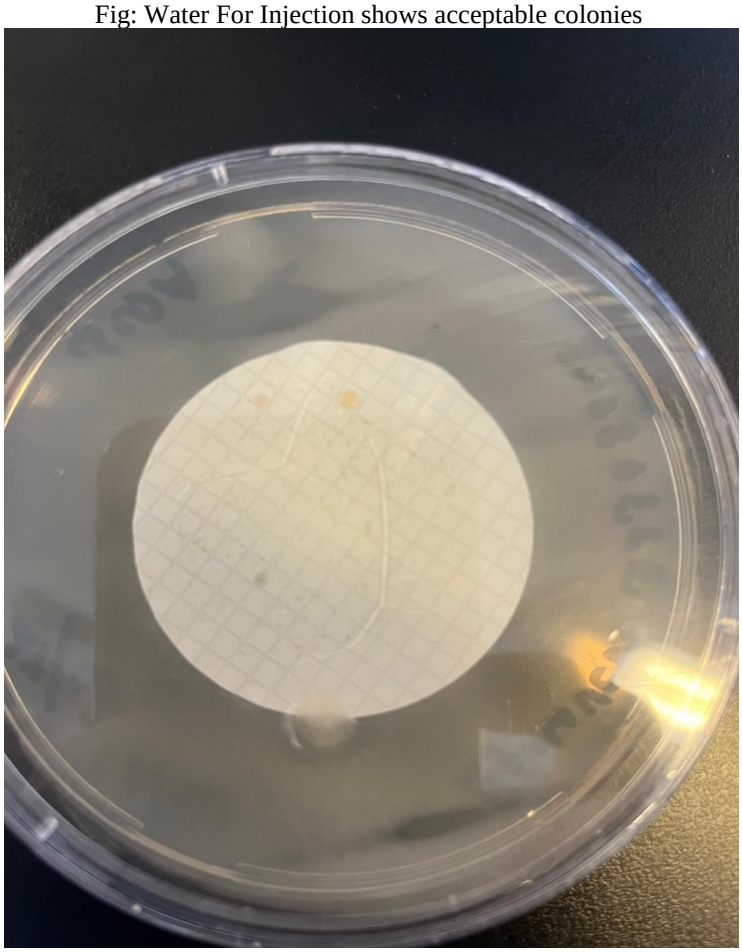

Fig: Purified Water shows acceptable bacterial colonies

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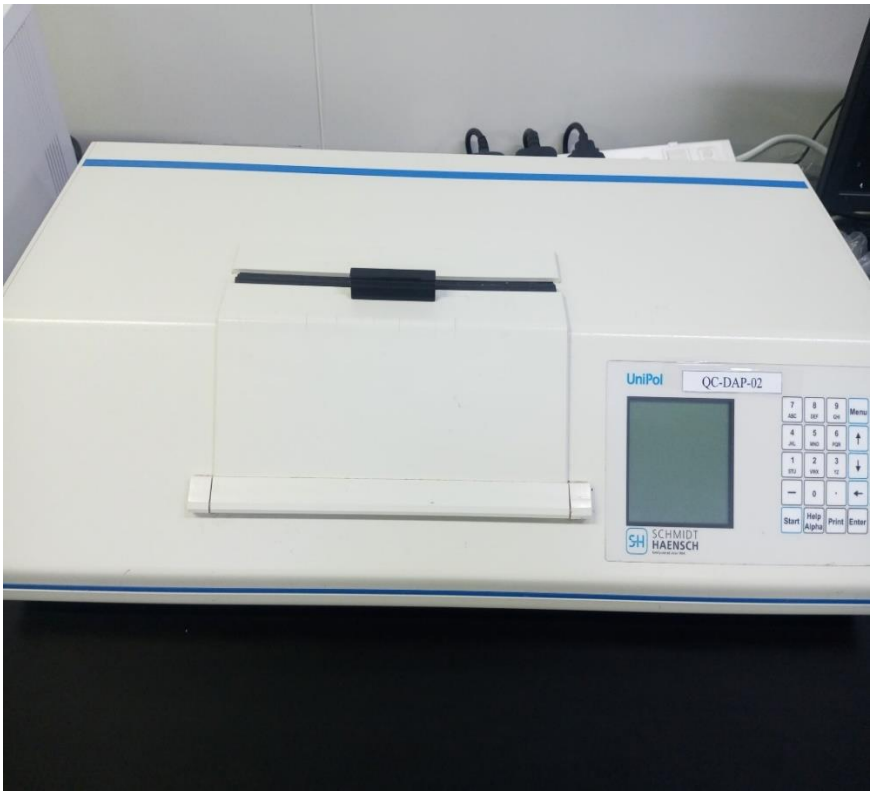

Fig: Polarimeter for analysis of Dextrose monohydrate

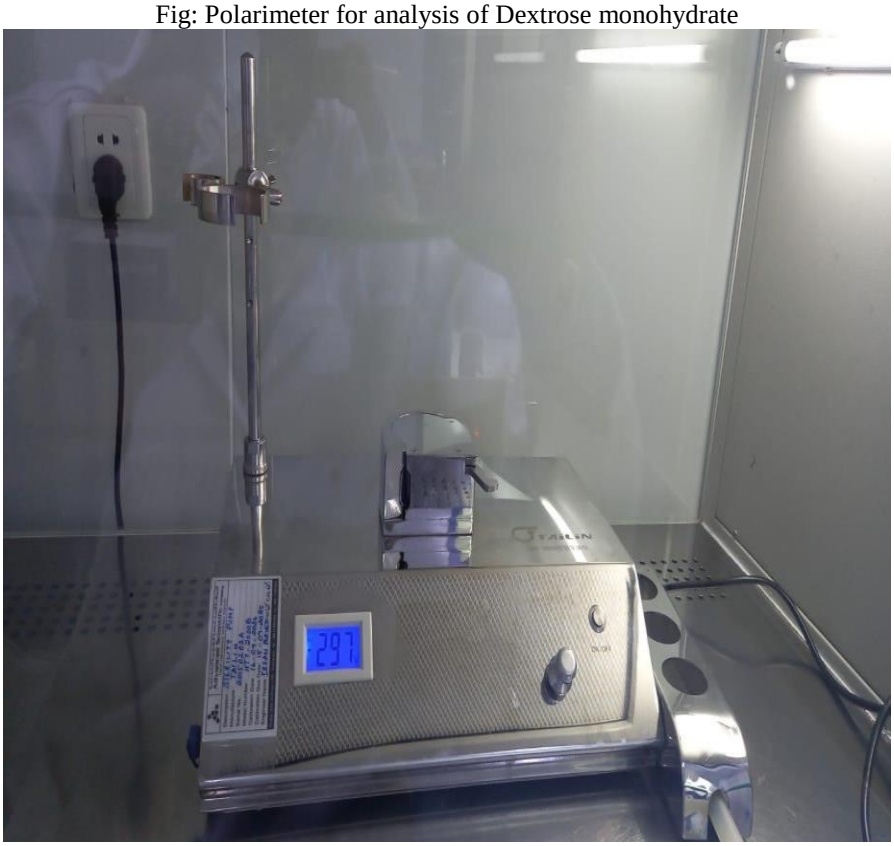

Fig: sterility Pump for Calibration

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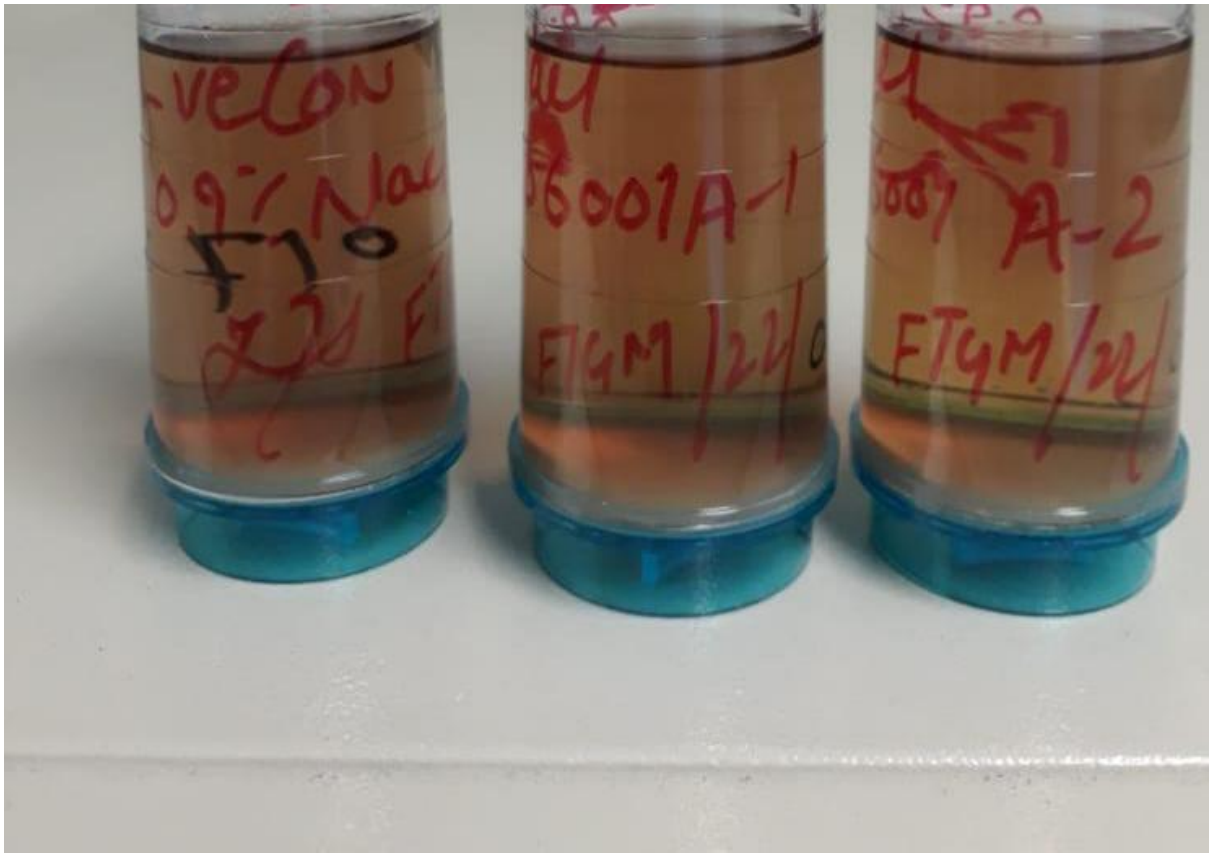

Fig: Equal splitting of 3 canisters

Fig: Handling and Distribution of samples

6-CONCLUSION

As a conclusion of the entire discussion, it clearly shows that quality assurance is somehow related to all departments in the pharmaceutical industry and in each department it plays an important role in improving the process of that department. As the name mentions that quality assurance plays a vital role and is said to be the backbone of the pharmaceutical industry. Quality assurance emphasizes customer satisfaction and also based on the guidelines that have been set by the authorities. As the thalidomide incident that happened a long time ago clearly shows the failure at the quality assurance and clinical evaluation stage that led to such major disasters that caused teratogenicity (Phocomelia). The drug was first invented for morning sickness problems in pregnant women. It has a dark history due to lack of proper analysis and quality control, which also clearly proves that quality assurance plays a very important role in drug manufacturing. Quality assurance is not only implemented or emphasized in the pharmaceutical industry, but is emphasized in every manufacturing industry that is related to every feeling. As it has been said that QA works on the basis of customer satisfaction, the customer is the main source that gives profit and revenue to any industry. If the product does not have quality, it will be a big failure for the industry. QA It has a role in every part of the industry that is interconnected, QA can create many branch departments “under their umbrella” to increase efficiency and quality standard through means and methods Ever. A QbD approach for analytical methods that has risk assessment, robustness testing and Resistance testing is much more stringent than the ICH validation requirements

(Q2 (R1)). It also includes an assessment Variability of the method compared to the specification limits, which is one of the most important methods attributes to check when deciding whether a tactic is fit for purpose. The approach described here is Indicative of this ICH Q2 (R1), while adding some value, needs to be substantially rewritten to account for risk-based QbD Approaches described in this article. This new QbD process offers the chance for much more regulation Flexibility for the future. Tactical performance criteria could potentially be registered instead the tactic itself. The tactic used can be given as an example of how to achieve the performance of the specified method Criteria. Any changes to the existing method would be covered by internal change control procedures.

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