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Review Article

A Methodical Review on Industrial Manufacturing and In-process Quality Control of Injectables

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ABSTRACT

The foremost aim of pharmaceutical Industry is quality control which is an indispensable section that mention to a procedure of endeavoring to manufacture formulations with stringent measures demanding a systematized effort by single individual of the industry to ensure and reduce the errors in the manufacturing processes. As quality is prime importance part of pharmaceuticals, quality control plays the vital role in achieving it. Quality control includes sampling, testing, validation, documentation and release of procedure which ensure that all tests are actually carried out prior to release of material for sale. Injectable are essentially manufactured in the sterile and aseptic zone where no microbial growth is possible. These are tested under the Quality Control and assured by the Quality Assurance. In-processes quality control assures sterility, freedom from particulate matter, and leakage. stringent procedure are followed for the preparation as well as the quality control test of the injectable to achieve the quality and safety of the product for use .So we became interested about current study to provide the careful orientation of the in process quality control of injectable.

Keywords: Validation, Record, Sampling, Quality control, Quality Assurance and GLP (Good Laboratory Practice).

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1. INTRODUCTION

In Process Quality Control means the quality check of pharmaceuticals in the time of manufacturing before packaging. It observers all the types of the manufactured goods which affects the quality and constrains liabilities

during manufacturing. This is not only helping in maintaining quality in finished products but also in the raw materials. It involves a series of testing which may be mechanical, physical, chemical and biological. It is apprehensive with providing accurate certain & final explanations of the measures to be starting with raw materials to the finished formulations [1].

Approaches towards Quality control

Features such as panels, job management, clear and well succeeded processes, performance and integrity criteria, and identification of records. Ability such as skills, experience, knowledge and qualifications. Some Soft fundamentals like for example personnel, integrity, confidence, organizational culture, motivation, team work and quality relationships. The real advantages of quality control are increased productivity, reduced cost of repairs, and increased loyal customer base and better profit [2].

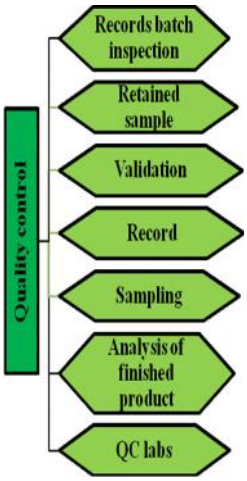

Fig 1: Various components of Quality control

2. TYPES OF QUALITY CONTROL

RM (Raw material)

QC is also responsible to sample and analyse the raw material batches used to produce a batch of finished product, including packaging materials [3].

Raw material are tested by –TOC (Total Organic Carbon), GC (Gas chromatography)

Stability

QC has to perform expire date of the product. Products are stored in stability chamber; s are called as walk in humidity chambers. There are four types of walk in humidity chamber. These stability chambers are used to test and store a wide range of products in specific temperature and in specific relative humidity conditions [3].

GLP

GLP represent Good Laboratory Practices, it correctly referencing the quality arrangement of organized control for inquire about research facilities and organizations to guarantee the stability, dependability, reproducibility, consistency quality and synthetic substances containing pharmaceuticals non-clinical security tests; from physio-concoction properties through intense to constant poisonous quality tests [4].

Microbiology

Microbiology are the department in Q.C which gives knowledge &thoughtful with respects to the implication of the occurrence of microorganisms in different stages of pharmaceutical product. It ensures safety and efficiency of pharmaceuticals. The tests performed in microbiology lab are mainly Microbial Limit Test; BET test, Antibiotic Assay, Sterility Testing etc [5].

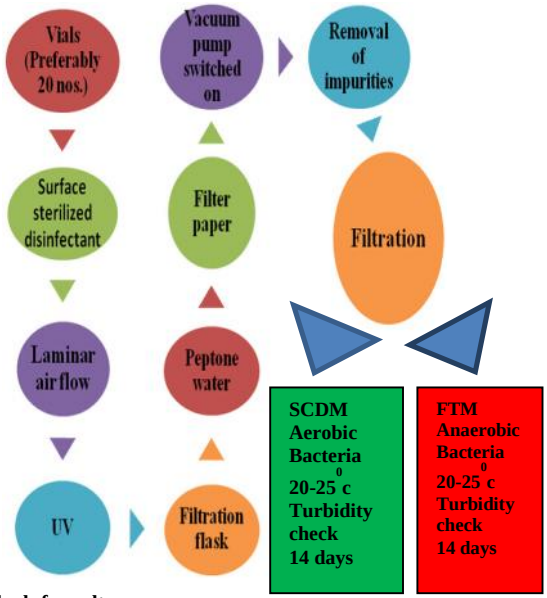

Fig 2: Methods for culture

***SCDM (Soybean casein digest medium) *FTM (Fluid thioglycolate medium)**

Finish products–

It is a division in Q.C in where a medicinal product that takes undergone all phases of production, containing packaging in its final container and labelling. The requirements of the finished material production may be differ from those of the medicinal product at expiry.

Packaging material

Pharmaceutical packaging is the meant to provide protection, performance, identification, information and convenience to encourage compliance with a course of therapy. The commonly used packaging materials in pharmaceuticals are containers closures, cartons, shippers, etc.

Types of packaging and defects

Primary packaging which is in direct contact to the product. The next one is 2^0 packaging which is outdoor the primary, possibly cast-off to cluster primary packaging Tertiary packaging it is used to bulk handling and shipping. E.g.- barrels, shippers etc. and the defects in packaging materials are critical defects, major defects and minor defects [6].

Raw material inspection

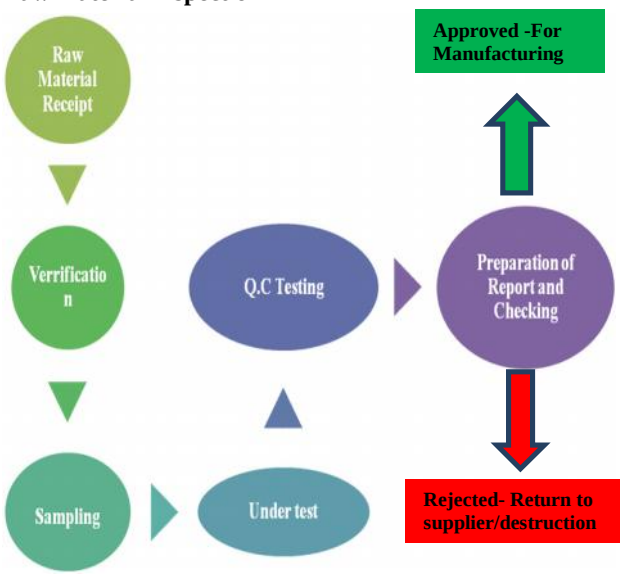

Fig 3: Raw material inspection

Finished product inspection

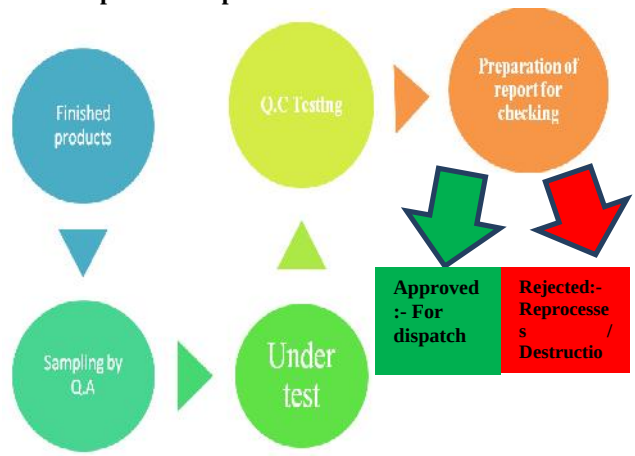

Fig 4: Finished product inspection

Quality assurance

Quality Assurance is a systemic arrangement for evaluating the product and made through the object of confirming that product will be safe for the intended use. Quality assurance is the organized watching & assessment of different stages in manufacturing process to minimize the manual as well as the instrumental errors. Q.A department assists in the planned direction and enlargement of quality systems, standard operating procedure and document control program, to ensure with the company policies and regulatory requirements [7].

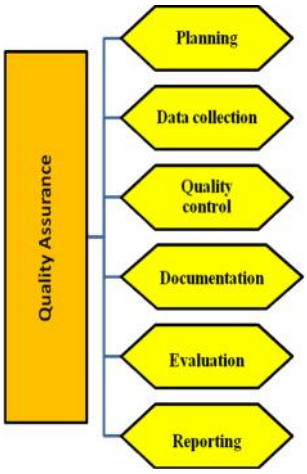

Fig 5: Components of Quality assurance

IP Q.A in development stage are during research and development, inspection of the condition of raw materials, sellers, methods, validation of processes ,maintaining documents, calibrations and working procedures and maintain records, and formulations of active ingredients and other products.

Documentation Q.A include study and approval of BMR and method of analysis data before any intermediate , Raw materials or finished product is released, as fine as episodic trending of the facts , reviewing and checking whether the BMR and BPR are properly filled or not and checking for data integrity [8].

3. INJECTION

Manufacturing of injectable where sterile environment needs to be established [9]. Injection is placing a liquid specially a drug into a human systemic circulation by using a syringe & needle. T Injection is a method for supplying drugs by parenteral administration i.eby passing fast pass metabolism in liver [10].

There are numerous methods parenteral products are available like infusion , intradermal, S.CI.M, I.V, I.O, I.P, intraarticular, intracavernous, intrathecal ,epidural, intracardiac, and intravitreal [11].

Different types of injectable

Ampules injection, Liquid vials injection, Dry powder injection [14, 35]

Ampules injection

It is a small airtight vial that second-hand to hold and reserve a sample typically a solid or liquid. They are made of borosilicate. Currently they are mostly used to contain the pharmaceuticals product and chemicals which are protected from air and impurities.

Washing procedures of ampoules

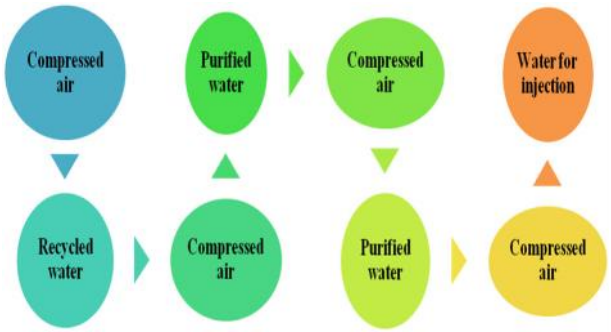

Fig 6: Washing procedures of ampoules

Preparation of ampoules

After washing of ampoules with 3 different water it goes into Depyrogenating tunnel with the help of conveyer belt under Laminar Air Flow [10, 34].

Depyrogenating tunnel divided into 3 zones

- Drying zone
- Sterilizing zone
- Cooling zone.

Filling principle

1. After sterilisation ampoules are conveyed to the filling area where nitrogen gas is filled into the ampoules before and after filling to keep the product stable and the ampoules are sealed by tip sealing process using specific heat and pressure with the help of LPG and oxygen.
2. After filling and sealing of ampoules, they are visually inspected for rejection like crack of vials sealing defects, volume defects, black and white particles, glass or fibre particles and empty vials.
3. After visual inspection the ampoules are send for autoclaving 121 ^{0}C should be maintained for 15 minutes [2].
4. Ampoules are then transferred to auto inspection machine.
5. After the process the ampoules are transferred to the packaging section.
6. Ampoules are first labelled at sticker labelling machine and product details are printed on the labels printing which are inspected by ACG inspection machine.
7. Ampoules are then transferred to RONDO packing machine.
8. After packing of ampoules in rondo trays are packed secondarily in cartoons by CP-120 HLCART packing machine then packed into sipper and dispensed from the department.

Liquid vials injection

A liquid vial injection is used for the parenteral administration (injection or infusion) that contains more than one dose of medication. Multi-dose vials are considered such as antimicrobial preservative which help to prevent from growth of the bacteria [27].

Preparation of liquid vial injection

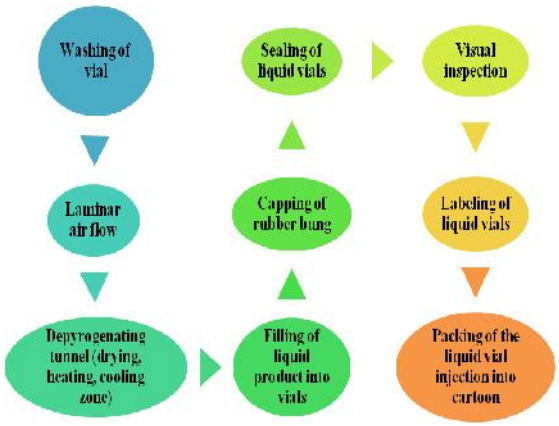

Fig 7: Preparation of liquid vial injection

Dry powder injection

Dry powder injection are manufacture and process by using high grade API aseptically and added to sterile vials in accordance with the pre-vialing medical standard.

Preparation of dry powder injection by lyophilisation

Lyophilisation is a freeze drying process in where complete removal of moisture is done from the formulation after it is freeze dried under reduced pressure, by changing vapour phase from solid phase without converting to liquids [15,31,33].

Objectives of lyophilisation

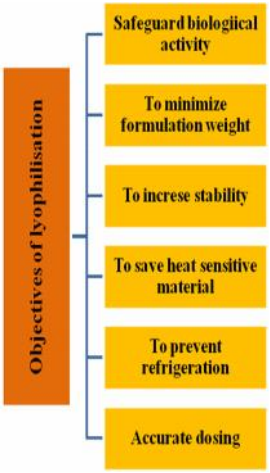

Fig 8 : Objectives of lyophilisation

Steps in lyophilisation

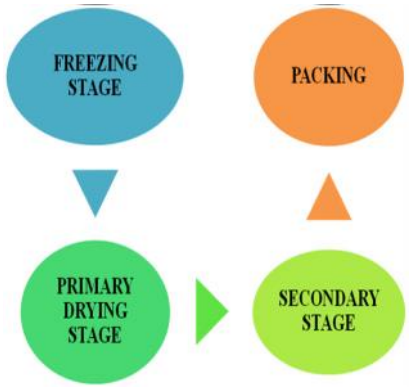

Fig 9: Steps in lyophilisation

Manufacture of dry powder injection

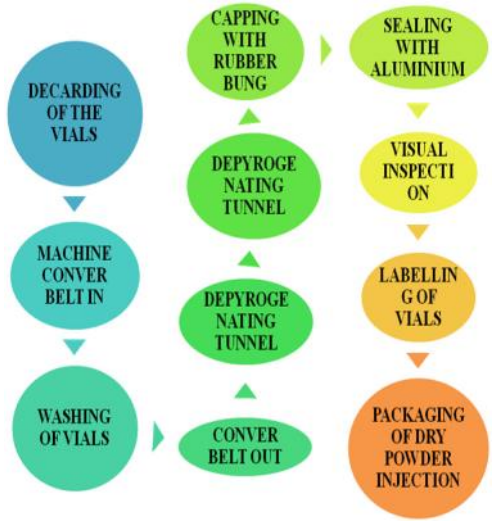

Fig 10: Manufacture of dry powder injection

Uniformity of content

Determination of uniformity of the content in injectable is done by taking 10 containers taken at random. All individual values obtained should be between 85 and 115 % at an average value. If any sample value is outside the limits 85-115% but within the limits 75-125% of the average value, the procedure is repeated by taking 20 samples [9].

Clarity test

Foreign visible or sub-visible particulate matter in injectable/ parenteral formulation is the major concern. Erythrocytes have a diameter of approximately 4.5µm so particles of more than 5µ must be the base of estimation. If the particle size more than RBC, then it must be discarded and procedure should be followed stringently to avoid such issue [14].

Coulter counter method

One of the most used methods decides the particle size. In an electrolyte solution sample is added. The sample is drawn through very small orifice. Orifice is separated by both the electrodes. When the particle permits over the orifice, it relocates its own volume of electrolyte and upsurge in electrical resistance is detected between the electrodes. The subsequent voltage beats which are relational to the particle size, are augmented and are measured and counted. Less than .2m particles can be measured in this method [9,16, 17,18].

Leakage test:

These particular tests only performed for ampoules which used to be closed by merging to guarantee that the product is totally leak proof it may be achieve by a) Vacuum Chamber Test b) Dye Bath Test. [11,19, 21,22]

Vacuum chamber test:

Ampoules are immersed in vacuum chamber containing of a dye of1% methylene blue solution. A pressure of about 27inch Hg (-ve) even more is formed up to half an hour. This causes the solution to arrive the ampoules with defective sealing. Ampoules thoroughly washed from outside and observed for the presence of dye in the ampoules. The presence of dye colour confirms leakage [11,20,25].

Clarity of solution

Free from foreign particles of parenteral product is the objective of this test. There should not be any solid undissolved, b) parenteral product should be equivalent or more clear than an equivalent capacity of diluents for water for injections. [11, 23, 24, 29]

Pyrogen test

This is an animal experimental procedure where rabbits used asthe model. Originally the dose 10 ml/kg body weight is inserted through rabbit vein at body temperature after 0 minutes of drug administration. The reading of temperature is taken in each one hour after injection for confirmation of presence of pyrogen [11, 30].

LAL test (Limulus Amebocyte Lysate Test)

Limulus Amebocyte Lysate test is done to find endo-toxins. The element is castoff for gel-clot development. The pipes are nurtured at 37±1ºC for 60 ± 2 minutes. After the pipes are upturned opposite angle creation of stable gel authorizes affirmative reaction. While development of a viscid gel that doesn't uphold its uprightness or nonappearance of a stable gel authorizes negative reaction. [12, 26]

Sterility testing

This test is done to find out the presence of viable microorganisms. Very little intensities of infection cannot be noticed on the base of random sampling. To achieve the goal the test has to be carried out in aseptic conditions. A grade A laminar airflow cabinet or an isolator is recommended for maintain aseptic area. Safeguards taken for this determination should not harmfully affect any micro-organisms, which are to be exposed in the test [13, 28, 35].

4. CONCLUSION

Commencing the above revision we are in a conclusion that except precise in as IPQC test we can curtail budget, time, measurable, recurrence of methods. Also able to know in general facts and stuffs of different dosage forms. It will help in advancement of the excellence of products and

curtail the tedious usage of instruments, so conducting of this IPQC test is a necessity. Throughout the handling of any pharmaceutical dosage forms, added examination on IPQC test of diverse dosage forms are going on to progress the quality of product. All the tests are mentioned are carried out for finished doses as well as raw materials which help in the maintaining quality, safety and efficacy of the product.

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