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CONTENTS

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Review Article

PHARMACEUTICALS QUALITY ASSURANCE

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INTRODUCTION

Safe and effective medicines of high quality are required for treatment of diseases. Due to unfamiliar processes, unknown additives, adulteration and substitution without scientific proof, many tragic deaths have happened. Due to thalidomide case in Germany many birth defects and abnormalities have occurred. Due to diethylene glycol poisoning of sulfanilamide elixir, many children died. Similarly in India poisoning of gripe water with toxic preservative has caused many deaths. Hence prior proof of medicine is established by clinical trials. Quality control department plays important role for assuring safety and purity of Pharmaceutical products. Quality may be defined according to ISO as the totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs. Quality is the desire of the customer. Loss of quality means the loss of customer satisfaction, loss of public health and loss of the organization's resources. This is a prime business parameter and from time to time the concept and process of quality have changed depending on the prevailing market environment. Quality is an outcome of a quality culture in a business organization it cannot be achieved only by technical application. Quality culture means prevention and elimination of errors, waste, reworks etc.

Quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. With regard to pharmaceuticals, quality assurance can be divided into four major areas: quality control, production, distribution and inspections.

Production

Good manufacturing practice (GMP) is 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. GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production, which may broadly be categorized in two groups: cross contamination/mix-ups and false labeling. Above all, manufacturers must not place patients at risk due to inadequate safety, quality or efficacy; for this reason, risk assessment has come to play an important role in WHO quality assurance guidelines.

Distribution

Any comprehensive system of quality assurance must be founded on a reliable system of controlling the quality, safety and efficacy of a finished product delivered to a market. It is important that all manufacturing operations are carried out in conformity with the accepted norms of GMP.

The distribution channel and supply chain need to follow quality assurance as well in order that patients are getting quality medicines. WHO has issued a number of international standards assisting Member States and those involved in the supply chain.

Inspection

It is the art of applying tests, preferably the aid of measuring appliances to observe as to whether a given item is within the specified limits of variability.

Inspections are part of the overall drug quality assurance system. The objective of inspecting pharmaceutical manufacturing facilities is either to enforce Good Manufacturing Practice (GMP) compliance or to provide authorization for the manufacture of specific pharmaceutical products, usually in relation to an application for marketing authorization. A further aspect of pharmaceutical inspection is monitoring the quality of pharmaceutical products in distribution channels, from the point of manufacture to delivery to the recipient, as a means of eliminating the hazard posed by the infiltration of counterfeit drugs.

Inspection Methods

1. Trial run inspection prior to production.
2. First piece inspection.
3. Pilot piece inspection.
4. Working inspection at different intervals with limits of tolerances.
5. Key operation inspection: Prior inspection to avoid substandard goods and critical inspection to check accuracy of work.
6. Sampling operation by statistical methods.
7. Percentage inspection.
8. Pre-assembly inspection.
9. Functional inspection to check accuracy of assembly.
10. Efficiency or performance inspection.
11. Endurance inspection.
12. Instructive inspection: Resistance or effectiveness of objectives.
13. Piecework inspection.
14. Product inspection.
15. Industrial inspection.

Inspection Standards

1. Physical conditions.
2. Dimensions and form of product.
3. Degree of finish.
4. Functional performance or product.

Inspection Devices

Many instruments and gauges are available for inspections:

1. Fixed size gauges.
2. Micrometers.
3. Comparators.

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4. Combination gauges to check dimensions.
5. Automatic gauges.
6. Air gauge.
7. Optical comparators.
8. Electronic Inspection devices to match colours, record pressure, temperature, humidity, velocity of air, acidity or alkalinity, automatic electronic sorters for rejecting defective over size and under size product, electron tube to inspect article which is inside the chamber which is not visible to naked eye.
9. Closed circuit industrial television to see around corners and to monitor critical operations.
10. Industrial radiography.
11. Ultra-sonics to measure thickness, porosity, surface characters and to find volume of fluids in closed tanks.
12. Magnetic particle inspection devices.
13. Industrial detectors, scanners, Readers, Sensors, Indicators.

Objectives of Inspections

1. To compile and collect factual information regarding the performance of the product with specifications.
2. To segregate defective goods.
3. To locate flaws in raw materials or in process material which may cause troubles at subsequent operations. It is designed to anticipate and prevent manufacturing difficulties.

It is scientifically planned by

(a) Control of raw materials and purchase cost.
(b) Locate inspection strategically.
(c) Plan inspection operations: relative importance and acceptable quality level.
(d) Inspect for defects promptly.
(e) Relate the amount of inspection to the degree of quality.
(f) Control inspection output and accuracy by standard rate of inspection.
(g) Setup a procedure to handling borderline materials.
(h) Make use of inspection records.

Quality Control

The term quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical. Such procedures may range from the performance of simple chemical experiments, which determine the identity and screening for the presence of particular pharmaceutical substance (thin layer chromatography, infrared spectroscopy, etc.), to more complicated requirements of pharmacopoeial monographs. Activities extend to the area of quality control laboratories (good laboratory management practices, models, e.g. for certificate of analysis and lists of laboratory equipment and an external assessment scheme.

Objectives of Quality Control

1. To establish standards of quality which are acceptable to customers.
2. To enable machine settings, adjustments and resetting of processes and machinery.
3. To keep up quality of product during manufacture by taking corrective steps.
4. To locate and identify the process faults and defects of products and to control scrap and wastes.
5. It is a preventive function for corrective defects.

Advantages of quality control

1. It helps in reduction of rework and adjustments.
2. It helps in continuous production and better utilization of labour and material.
3. Improved technical knowledge for product development and manufacturing design is achieved.
4. It provides us lower cost for the design of the product and processes.
5. It enables the feed back of inspection information to the designers, specification writers and operators.

With the help of the inspection records defects are sorted out and corrective actions are taken by following methods:

(a) Processes are studied in detail and improved.
(b) A change over to better type of machinery or more capable operator may be resorted.
(c) Specifications may be revised.
(d) Defective products may be sorted out.

Responsibilities of quality control

1. To prepare a plant quality control programme for management.
2. To advise production department regarding uniformity of materials, quality aspects and specifications.
3. To advise manufacturing department about machinery, instruments and process control.
4. To assist purchasing department in the evaluation of suppliers and defects of incoming materials.
5. To advise and assist in inspection and selection of sampling plants.
6. To assist sales in making use of quality and guarantees.
7. To find losses and their causes.
8. To train quality control personnel in means of preventing defects.
9. To study and experiment special processes for eliminating the defects.
10. To assist the management in making the people quality minded.

To analyze customers complaint report and to development a system for applying quality of product.

Quality Control Graph and Charts

Quality control chart are used to measure variation due to chance and variation due to assignable factors. For pharmaceuticals and operations by physicochemical and biological parameters of products can be used for making charts. Control charts are of following of following types depending upon type of defects.

1. X and R chart.
2. P Chart
3. C Chart

Sampling Plans

A. Single Sampling Plan

When the acceptability decision is based on the sample it is known as single sampling plan. This type of sampling is applied in situations when a multiple number of units is presented for inspection in static form and when the method of inspection and when the method of inspection is attribute's type (go or no go) measuring device:

1. Inspect a sample of n pieces from the lot 'N'.

2. If number of defects found in sample does not exceed 'C' the lot be accepted.
3. If numbers of defects found in sample exceed the value 'C' all the pieces in the reminder of lot be inspected.
4. All the defective pieces so found should either be corrected or replaced.

N - Number of articles in lot.
n - Number of articles drawn from lot.
C - Acceptance number.
P - Fraction defective.

B. Double sampling Plan

1. Inspect a first sample of 'n' pieces (n sample size).
2. If number of defects in first sample does not exceed C_1, accept the lot (C_1 is acceptance number).
3. If number of defects found in first sample exceeds C_2 all pieces in reminder of lot must be inspected.
4. If number of defects in first sample exceeds, 'C_1' but does not exceed 'C_2' a second sample n^2 pieces should be inspected.
5. If the total number of defects found in the first and second samples combined does not exceed 'C_2' the lot be accepted.
6. If the total number of defects found in the 1st and 2nd samples combined exceed 'C_2' the piece of in the reminder of lot be inspected.
7. All the defective pieces should either be replaced or rectified.

Multiple Sampling

Here one, two, three or more samples may be taken from a sample in order to decide to accept or reject a lot.

Various Records For Evaluation By Control Department

Records must provide check points at every stage of pharmaceutical manufacture, Records give complete history of operation and feed back for problems. It helps to inspect and pin point problem. These records include material receipt records, material stock records, materials release or approval including analytical report, materials requisition record, manufacturing and batch record, packaging records, complaint file and distribution records.

Organization And Set Up of Quality Control Laboratories For Pharmaceutical Units

Various departments of quality control division are chemical lab, microbiology lab, pharmacology lab, animal house, instruments room and library.

Chemical Lab

In this department raw materials, packing materials and finished products are analyzed by chemical methods. Size of the lab, should be 30'X20' with cross ventilation and exhaust to remove fumes and vapors. Central table of wooden racks to keep chemicals is provided. 2' width concrete platform next to wall and covered with glazed tiles for keeping equipments is convenient. Lower rack can be used for storage of glassware's. Adequate fans, enough sinks and water taps for washing and cleaning are provided. Fuming cupboard with exhaust fan is required for carrying tests like ash content, sulphate ash and acid digestion, etc.

General tests: solubility, identifications, reaction, melting and boiling range, loss on drying ash content, limit test for arsenic, Lead, iron, chloride, sulphate, optical rotation, refractive index, alcohol content, nitrogen content, alkaloid assay and various tests of finished products as per pharmacopoeia and internal specifications.

Packing materials, which can be tested in chemical lab, are bottle, vial, ampoule, plastic container, carton, label, rubber clothes, P. P. Cap, empty gelatin capsules and strip packing materials. ISI specifications are also utilized for evaluating packing materials and coolers.

Equipments Required for Chemical Lab

Water still, pH meter, hot air oven, vacuum oven, vacuum pump, mufflefurance, water bath, hot plate, melting range apparatus, boiling range assembly, single pan balance, physical balance, polarimeter, refractometer, TLC Kit, UV Lamp, viewing cabinet, Karl Fischer moisture determination apparatus, Brook-field viscometer, Colorimeter, D. T. Machine, Hardness tester, friability taste for tablets, vernier calipers, bursting strength testing apparatus and puncture resistance tester for packing materials, spectophotometer.

For carrying out few identification tests IR spectophotometer and for element determination of organic compounds Oxygen flask, combustion equipment and atomic absorption spectrophotometer and flame photometerare required for analysis of trace elements in formulations. Fluorimeter is also used for analysis of vitamins. Gas liquid chromatograph and high-pressure liquid chromatograph are also used for stability study of few drugs accurately. Equipments for chemical lab of small scale industrial costs around 1 to 1.5 lakes rupees.

Microbiology Lab

Here bacteria are used as analytical tool. In this section antibiotics and vitamins are analyzed. Sterility testing, Microbiological limit test and sensitivity tests, microbial testing of water and other products are also done. Area of microbiological lab should be 16'X13' and 11'X8' for sterile room.

Microbial limit test for pathogenic organism like E. coli, Salmonella, Pseudomonas are carried out for raw materials and finished products if required. Effectiveness of preservative effective spectrum of antimicrobial agent are carried by sensitivity tests.

Equipments

Antibiotic zone reader, Laminar flow bench, U. V. lamp, microscope, colony counter, centrifuge, precision balance, pH meter, autoclave, incubators, refrigerator, membrane filtration unit, vacuum pump, hot air oven, colorimeter, equipments for microbiological labs costs around 1 to 1.5 lake rupees.

Pharmacology Lab

Test carried out in this lab are pyrogen test, toxicity test, histamine test and pressure activity, bio-assay of oxytocin, histamine and adrenaline, ergometrine etc.

Equipments

Precision balance, balance for weighing animals, pyrothermometer, isolated tissue bath, kymograph, oxygen cylinder, refrigerator, hot air oven, operation table, manometer, slotted angle racks, aluminum cages, polypropylene cages for animals etc., equipments of pharmacological lab cost around 1 lakh rupees.

Animal House
It should be located in quiet atmosphere, Proper hygienic conditions is maintained. Separate room should be provided for each species of animals, breading and experimental purpose. Animals purchased should be kept in acclimatization room for 2 to 3 weeks. Area of animal house: for rabbits 20'X12' (mice and rats: 16'X12') animals of fresh arrival are kept in 16'X12' room. Aluminum cages are used for rats and mice. Temperature should be 65-70^{0}F. Humidity should be 45-55% R. H. In winter heating arrangement should be provided for comfort of animal.

Feeding of Animals
Well balanced diet consisting of proper amount of protein, starch, minerals and vitamin is utilized. Dry pellezed food supplemented with milk, green vegetables or whole grain may be utilized. Veterinary Doctor should periodically inspect the health of the animals.

Toxicity tests are carried out as per IP, BP of USP using albino rats/mice.

Instrument Room
It is air-conditioned. It should be clean and dust free. Mossaic floor is preferred. Electric Supply with voltage stabilizer is preferred for instrument room. Area of instrument room should be 16'X12'.

Library
It should be equipped with various analytical reference books, standard pharmacopoeia, reference books of instrumentation and pharmaceutical sciences and important pharmaceuticals journals.

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