INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

PILOT PLANT SCALE-UP STUDIES FOR PARENTERAL - A REVIEW

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Article Received on: 30/07/21 Approved for publication: 08/09/21

DOI: 10.7897/2230-8407.1208158

ABSTRACT

The dosage form of parenteral is sterile and gives a quick beginning of activity and gives an immediate action to accomplishing the medication impact inside the body. The route of parenteral administration is the most well-known and productive route for the conveyance of dynamic medication substances with poor bioavailability and medications with a tight therapeutic index. The principal objective of the technique was to endeavour to talk about the different procedures needed for the pilot plant production considers. The pilot plant is the term that is normally more modest than large-scale production plants yet it is the underlying scope of sizes. It is planned for learning, and making the definitions on a limited scale to accomplish the relationship with the enormous scope production, and they are normally more adaptable perhaps to the detriment of the economy. Most of the pilot plants are implicit in the maker's own research centres of the manufacturer utilizing stock lab hardware. These pilot plant studies are performed by using a technology transfer (TT) documentation report which is made by the research and development department for product development. Hence, this process would meet product quality, safety, and efficacy and further this production techniques will transfer to large-scale production for parenteral preparation.

Key Words: Pilot plant studies, TT Documentation, Parenteral dosage form.

INTRODUCTION

The pilot plant is a hybrid developmental facility for pre-commercialized production and a small-scale manufacturing unit, which is used for the integrated early development activities of various dosage forms. It includes the clinical supply manufacture, technology evaluation, scale-up, and transfer to production sites. Major technical aspects of pilot plant studies include determining the critical components, critical process parameters, operation ranges for the equipment, and formulation variables during manufacturing. It gives the brief outline of requirements, training, reporting responsibilities of personnel for the successful product scale up. These studies contain practice of current good manufacturing practices (cGMP) environment and close monitoring of the dosage formula to determine its consistency over the various batch scales and process modification in the pharmaceutical industry[1]. The pilot plant technique performs the process according to the technology transfer documentation which is a drug product development report given by the research and development phase. Parenteral dosage forms are sterile dosage forms that are administered directly to the bloodstream by injection via one or more layers of skin or mucous membranes to provide rapid onset of action. The present article attempts to discuss the overall scale-up techniques for the parenteral dosage forms in detail.

DESIGN AND LAYOUT FOR PILOT PLANT PARENTERAL PRODUCTION

The design and layout for pilot plant parenteral production illustrated in Fig. No. 1. The stockroom/warehouse, compounding area, aseptic area, clean up area, sterilization area, isolation area, and storage area are lined up in layout[2, 3]. During the pilot plant production; each area should have adequate requirements and facilities for parenteral production.

Stock Room

Stockrooms are the optimized storage area for all the raw materials for the parenteral, to be manufactured are kept in that area. The raw materials include the active pharmaceutical ingredients (API), excipients like suspending and buffering agents, solvents, isotonic preparation substances of stabilizers, blood and or microbial additives. Stockroom is well equipped with a controlled humidity conditioned environment in order to ensure the product stability of the raw materials. A chemical unit contains lithium and silica gel is satisfactory for relative humidity levels below 20%. This room must be treated with disinfectants to avoid the contamination of the products.

Clean Up Area

The area should be carried out to clean bottles, vials or ampoules and other glass things for parenteral preparations from the stockroom. During the cleaning process, ensure the area has required temperature and relative humidity. The temperature shall be 19-23°C are considered as acceptable, relative humidity ranges from 45-55% and normal humidity levels achieved with the air conditioning system. Choose an approved cleaning agent to clean the bottles, vials or ampoules and other glass things before going to the sterilization area. HVAC systems should be provided in this area to prevent accumulation of dust particles. The filtration rate should be 95%[4].

Filling Area

The product and sterilized segments are presented to the room climate. Thusly, these regions are extraordinarily built, separated,

and kept up with to forestall ecological tainting. Cleanroom should meet a few prerequisites: The room ought to go through 15-20 air changes each hour. HEPA filters are to tidy up the air going into the room. HEPA filters eliminate all airborne particles of size 0.3 or bigger with effectiveness of 99.97%. Keeping up with higher pneumatic stress (+ve pressure) inside the basic region to limit invasion of airborne pollutants from outside. Adjoining rooms of various grades ought to have a pressing factor differential of 10 - 15 Pascals. Care ought to be taken to guarantee that wind streams don't circulate particles from a molecule creating individual, activity, or gear to a zone of higher item hazard. An admonition framework ought to be given to show failure noticeable all-around supply. Counters in the perfect room ought to be made of hardened steel or other nonporous, handily cleaned material. Dividers and floors ought to be liberated from breaks or fissures and have adjusted corners. In the event that the dividers or floors are to be painted, epoxy paint is utilized. The wind stream should move with uniform speed along equal lines. The speed of the wind stream is 90 20 ft/m^3. Giving temp. and mugginess controls fitting to the item being produced[5].

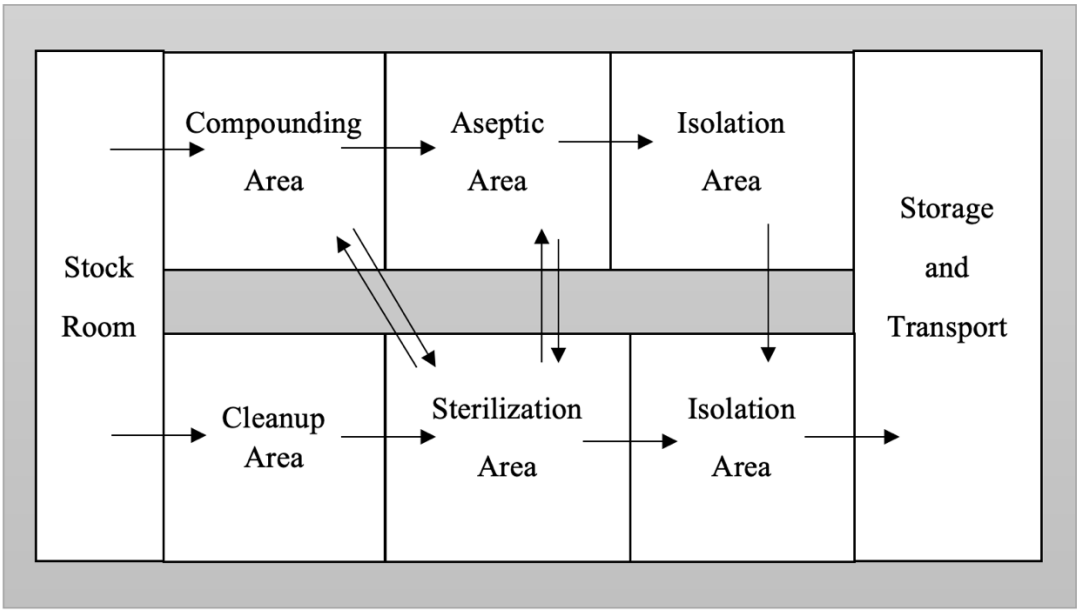

Fig. 1. Layout for Pilot Plant Parenteral Production

Compounding Area

The area contains cabinets and counters which are made up of stainless steel and are involved in the compounding process. This area removes dust from raw materials during compounding and weighing and it should be adopted to control the dust and other contaminants caused by dusting agents.

Aseptic Area

The compounded preparations are transferred to the aseptic area through a pipeline where the filling operations are carried out. The aseptic process done to avoid the contamination during transferring the preparations and especially the stainless-steel cabinets and counters do not allow the dirty particles to accumulate inside the preparations. The risk of contamination occurred by mechanically or manually removed microorganism of drugs, containers, closures, and other components hence caution control is required during handling.

Sterilization Area

Sterilization is the process of killing all forms of viable microorganisms. This process is usually done to produce the sterile state in the dosage form, to avoid contamination in the product. Microorganisms displays a differing protection from sterilization methodology. The level of obstruction of microorganisms differs with the particular creature, so every one of the boundaries required for a sterilization cycle should be arranged, from which microorganisms typically experienced, and to keep away from the extra treatment intended to give an edge of security against a sterilization failure. This process may be used for both pharmaceutical ingredients and packaging components. Most common method of sterilization of parenterals is the terminal sterilization.

Terminal Sterilization

The different types of (LVP & SVP) parenteral are sterilized after the packing of the eventual outcomes are known as terminal cleansing/sterilization. For the most part, the parenteral arrangements are cleaned terminally in bunches after they are fabricated. These parenteral arrangements are sterilized by filtration during assembling. It diminishes the danger of the non-sterile unit inside the product it should be sterile [6]. The hold time frame of the parenteral ought to be checked before the terminal sterilization measure begins. It is important to keep up with the product nature of parenteral on the grounds that microbial development might happen during the capacity before the terminal sterilization that can hurt the product quality. The terminal cleansing/sterilization cycle is generally done by three strategies; Autoclave, Irradiation, Ethylene oxide.

Isolation Area

Give an isolate region to the disengagement of returned, broken, reviewed and in any case removed product forthcoming a choice on removal or re-loading by the certified individual or office. Materials inside isolated regions should be obviously related to their status. Finished products, intermediates, packaging materials are stored physically at the isolation/quarantine area to find out any contaminations happening in stored products[7]. In the pharmaceutical industry quarantine is a quality operation for manufactured products. The isolate program comprises of four

fundamental stages: warning, record planning, isolation, and attitude. When fostering an isolate program, start by recognizing hierarchical assumptions. In the event that this undertaking is another program, workers might go through an expectation to absorb information and experience a few difficulties. Perhaps the most basic components of the isolate program are correspondence. It is significant that there is open correspondence between the isolate division and the association[8].

Storage or Transport

Explicit bearings are expressed in certain monographs concerning capacity conditions (e.g., the temperature or stickiness) at which parenteral arrangements should be put away and dispatched. Such bearings apply aside from where the mark on the arrangements has distinctive capacity conditions that depend on steadiness examines. Where no particular headings or impediments are given in the planning's naming and should be shielded from dampness, freezing, and inordinate warmth, were important from light during transportation and dispersion. Medication substances are excluded from this norm[9].

Space Requirements for Parenterals[10]

Table 1. Pilot Plant Space requirements for Parenterals

Function	Area required for manufacturing	
	Square meters	Percentage
Warehousing	7,606	30.9
Production	11,094	45
QC	1,715	8.9
Handling	1,013	5.0
Organisation	1,016	4.0
Utility	1,716	4.1
Services	1,013	3.9
Safety	40	1.0

MANUFACTURING OF PARENTERAL

The assembling system incorporates the entirety of the preparing ventures from the aggregation and consolidating of the elements of the recipe to the encasing of the product in the individual holder for dissemination.

Formulations

The plan of a parenteral product includes a mix of at least one ingredient with an additive to upgrade the accommodation, agreeableness, or viability of the product. All the parenteral preparations must contain the following agents as the ingredients for the parenteral product[11, 12].

Active Pharmaceutical Ingredients (API)

It is the active chemical compound which is intended to produce the therapeutic action. It should be evaluated for the molecular weight, solubility, purity, colligative properties, chemical reactivity and adverse interaction reaction with another API or excipients substance.

Solvent Selections

A parenteral preparation is administered by solution. So, it is indeed to select the quality solvent system for the parenterals. Aqueous solvents the solution is physiologically compatible with body tissues, and the biologic response elicited is easily predictable. The high dielectric constant of water makes it dissolve ionizable electrolytes, its hydrogen bonding potential brings the solution of such organic substances as alcohols, aldehydes, ketones, and amines. Conversely, water is a poor solvent for nonpolar compounds, such as alkaloidal bases, which require non-polar solvents. Since therapeutically active compounds given by injection range in property from highly polar to non-polar, solvents having complementary properties must be employed if a solution is to be achieved.

Vehicles or Solvent System

Vehicles or solvent systems play a crucial role as it serves as the base in the preparation of the parenterals. It can be of Aqueous and Non- Aqueous Systems.

Aqueous Systems

The most suitable universal vehicle or solvent system for parenterals is sterile water. The quality water should be used according to specific monographs like IP, USP, BP. The quality can be checked by the total dissolved solid contents (TDS) by the gravimetric evaluation and conductance of the water.

Non-Aqueous Systems

The non-aqueous solvent should be liberated from aggravating, poisonous, or sharpening, and it should not apply an antagonistic impact on the elements of the definition. It ought to evaluate for actual properties, like thickness, consistency, miscibility and polarity solidness, dissolvable action, and harmfulness to guarantee the nature of the solvents.

Solutes

Solutes are added to assist the API to dissolve with the solvent systems. It should be free from the microbial and pyrogenic contaminants. Its compatibility should be checked with the physical and chemical properties of the API.

Added Agents

Substances added along with the API to enhance its stability and prevent contamination. Such substances include agents of antibacterial, antifungal, antifoaming, buffers, solubilizers, cell reinforcements, inhibition of hydrolysis and numerous other substances for specialized purposes. It should be free from toxic, adverse effects with API, and should not interfere with the therapeutic activity of the API[11, 12].

EQUIPMENT

There are different types of equipment needed for each step of the manufacturing process. Pilot plant techniques should be having the following equipment as per schedule M recommended which are follows,

Manufacturing area having adequate storage equipment for storing vials, ampoules, packaging containers and closures, material washing and drying equipment, dust remover, ingredients mixing vessels, equipment for filtrations, autoclave, hot air oven.

Aseptic filling room having filling and sealing desk, filters for remove microorganism, laminar air flow (LAF) workplace.

General room having table and benches for visual inspection, leakage test, labeling and packing, and refrigerator for cold storage[13].

PROCESS

Pilot plant studies perform the manufacturing process according to the technology transfer documentation report which is a product development guide given by the research and development department. The drug product manufacturing process includes (Fig. 2), sterilization, aseptic subdivision and sealing, online testing, capping and sealing, terminal sterilization, leak testing, inspection, isolation or quarantine, finishing, labeling and packing, and warehousing. The manufacturing process is complicated, requiring organization and control to ensure the product meets the quality and the specifications. Aseptic processing requirement adds more complication but assures that all dosage forms manufactured are free from any contamination of microbial, endotoxin, and visible particulate matter. The manufacturing process initiates with the procurement of approved raw materials (drug, excipients, vehicles, etc.) and primary packaging materials (containers, closures, etc.) and ends with the sterile product sealed in its dispensing package. To ensure the product meets required quality, each manufacturing process should be validated to be sure that it is accomplishing what it is intended to do. For example, any process of sterilization should be validated with data showing it is killing various forms of microorganisms. The validation processes are an integral part of cGMP. Small scale dispensing (product batch size in hundreds) for the early phase of clinical trial. Large scale dispensing (product batch size in hundreds of thousands) for late phase of clinical trial or commercialization[13, 14].

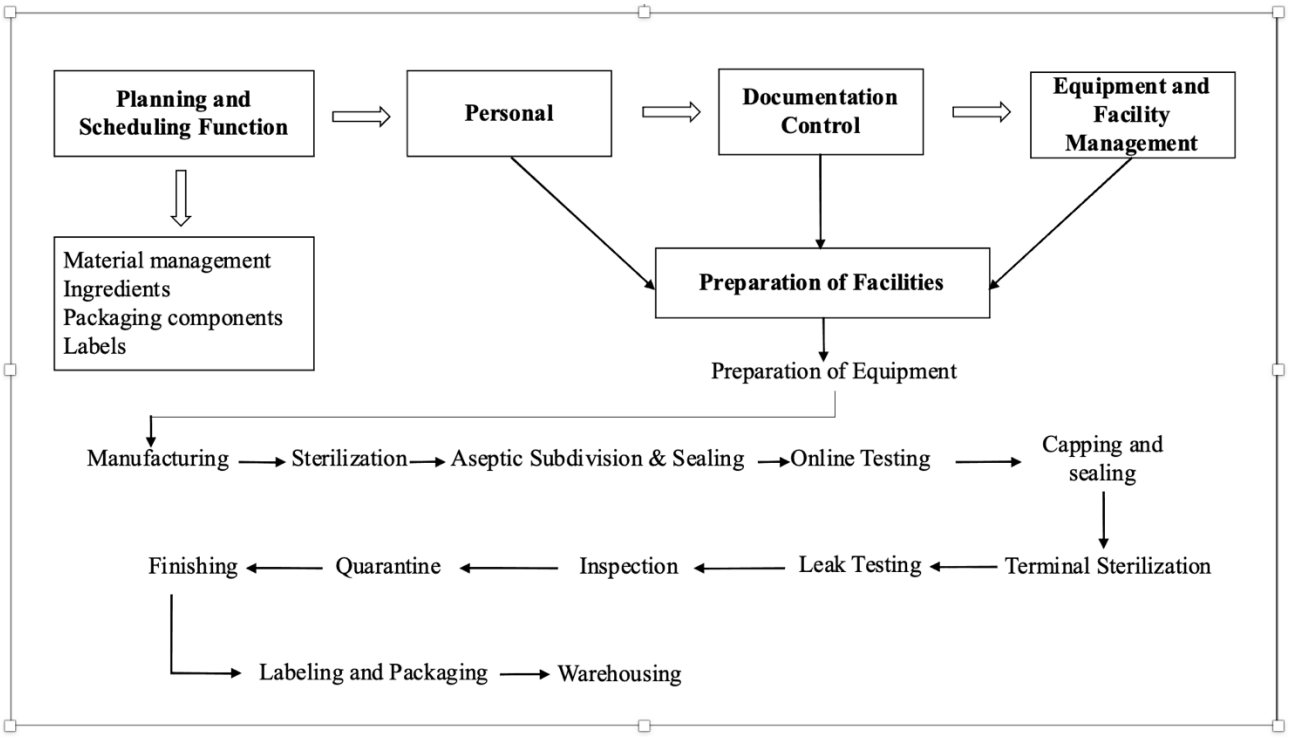

Fig. 2. Overview of Manufacturing Process for Parenteral

STABILITY

The dosage form of parenteral preparations ought to be steady under foreordained assembling, bundling, stockpiling, and use conditions. The compound and actual security ought to be kept up with all through the time span of usability of the product. Complicated compound constructions and weaknesses to natural conditions (temperature, pH, shear, light, oxygen, metal pollutions, and so forth), remedial peptides and proteins offer huge difficulties. Sterilization, aseptic subdivision and sealing, online testing, capping and sealing, terminal sterilization, leak testing, inspection, isolation or quarantine, finishing, labeling and packing, and warehousing affect the stability of the product. In that each area should maintain proper temperature and relative humidity as per cGMP standards. Numerous parenteral medications are shaky in arrangement, which challenges their lyophilization measures further. Support of sterility all through the time span of usability and utilization likewise influences the dependability of the medication. Focus on the stability of the product according to ICH guidelines which is Q1A(R2)-Q1F. The temperature and relative humidity were prescribed in these guidelines and maintained them as per our requirement for different climate zones of countries.

QUALITY CONTROL

Quality Control is the daily evaluation of all operations from the receipt of raw material to the distribution of the finished product, including analysis and testing of the finished product. Quality control generally performed by IPQC.

IPQC Test

In Process Quality control (IPQC) is a pre-planned method or set of guidelines expected to ensure that a completed process or performed administration sticks to a characterized set of value models or meets the prerequisites of the customer or client or a norm. IPQC testing involves the three major areas of testing namely

1. Incoming Stock Testing
2. Manufacturing Testing
3. Finished Product Testing (Final Product Testing)

The Incoming stock testing is usually performed to test the raw materials, vehicles, additives used in the manufacturing of parenterals. The raw materials testing includes the Conductivity test, Amount of solid content testing, Pyrogen testing, Test for dissociative and undissociated organic & inorganic substances. Some of the additive's agents like antioxidants, buffers are important to maintain the tonicity and pH of parenterals. General tests like volume check, strength, pH, turbidity, colour, sterility, pyrogenicity are to be conducted to check the efficacy rate of the product before filling. The final product testing like sterility test, pyrogen test, clarity test, leakage test, assay is to be performed for the packaged product to ensure the quality of parenterals[19].

PACKAGING OF PARENTERALS

Packaging is a container or article which contains the drug product and the container may or may not be contact with the drug product. Packaging is primarily used for product distinguishing proof and isolates a specific item from an assortment of products. The packaging must be stable[15]. It includes primary packaging, secondary packaging and tertiary packaging. Parenteral packaging should contain the container for holding the drug substance, holder, closure, cartons/ outer box.

Some of the parenteral packaging includes the vials, ampoules, i.v infusion (small volume parenterals, large volume parenterals, intrathecal injections, intramuscular injections, prefilled cartridges and syringes)[16, 17]. Packing materials for parenterals listed below.

Glass

Glass containers have been generally utilized for sterile products which are shut with elastic plugs. There are variety of glass containers used, some of them are,

1. Borosilicate glass (Type I)
2. Treated soda lime glass (Type II)
3. Standard soda lime glass (Type III)
4. NP common reason soda lime glass. (Non-Parenteral Use)
5. Coloured glass.

Plastics

The principal ingredient of the various plastic materials used for pharmaceutical containers is the thermoplastic polymer. Most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some of them contain a substantial number of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes in order to provide the stability for the container. These ingredients are not usually chemically bound in the formulation and, depends on storage and transport the drug content may contact with container.

Rubber

Rubbers are also used for the parental packaging as closures and containers. It is for the most part used to seal the kick-off of cartridges, vials, and jugs, and it gives a material delicate and versatile enough to allow section and withdrawal of needle without loss of the respectability of the fixed compartment. Rubber closure should have the elasticity, hardness and porosity nature. The closure should be completely non-reactive with the product. Natural source for rubber is tree Hevea Brasiliense's which has latex and contains the 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made in the bark. Natural rubber contains the long chain polymers of isoprene units linked together in the cis portion. Some of the examples of the rubber are Butyl rubber, Chloroprene rubber, Nitrile rubber are widely used[18].

CONCLUSION

This study reported a pilot plant scale-up techniques for parenteral preparation that was performed according to the technology transfer documentation report which was given by the research and development phase to manufacturing the product at large-scale production through the pilot plant study. This study carried out a minimum of three trial batches to perform the manufacturing process. Hence, this process would meet product quality, safety, and efficacy and further this production techniques will transfer to large-scale production for parenteral preparation and commercialization.

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Cite this article as:

V. Manikandan and R. Vinoth. Pilot plant scale-up studies for parenteral - A Review. Int. Res. J. Pharm. 2021;12(8):58-63.
http://dx.doi.org/10.7897/2230-8407.1208158

Source of support: Nil, Conflict of interest: None Declared