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Review

CURRENT TRENDS IN MANUFACTURING FOR LARGE VOLUME PARENTERAL IN THE PHARMACEUTICAL INDUSTRY AND FUTURE SCOPES

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ABSTRACT

The current features of manufacturing of Large Volume Parenteral from receiving the API and excipient to the final dispatch of product addressed many features including, sampling errors, manufacturing errors other controls, and individuals involved in various phases. The pharmaceutical industry nowadays places a greater focus on production-related issues like handling manpower and quality-related problems and implementing systems like Good Manufacturing Practises, and other systems. To reduce reliance on humans and raise the quality of products, future trends and possibilities in automation in various areas like production, quality assurance, and quality controls were discussed in this paper. For the production of an enormous quantity of parentals, the roles and responsibilities of both the manufacturing team and the quality assurance team are crucial. Future manufacturing initiatives can reduce labour expenses while enhancing product quality, nevertheless, they will also encourage more automation research and development.

KEYWORDS: Large Volume Parenteral, Quality Assurance, Production, Automation, Pharmaceutical industry.

List of abbreviations and symbols

USP	United States Pharmacopeia
API	Active Pharmaceutical Ingredient
SOP	Standard Operating Procedure
BMR	Batch Manufacturing Record
HEPA	High Efficiency Particulate Air
QC	Quality Control
CIP	Clean in Place
SIP	Sterilization in Place
LED	Light Emitting Diode
%v/v	Volume by Volume
BMR	Batch Manufacturing Record
LHS	Left hand side
RHS	Right hand side

1. Introduction

Parenteral items are defined as "those preparations intended for injection through the skin or other external boundary tissue, rather than through alimentary canal so that the active substances can be administered directly into a blood vessel, organ, tissue, or lesion" by the USP 24/NF19. Intravenous (IV), subcutaneous (SC), and intramuscular (IM) are common ways to deliver medication directly into the body, and they all fall under the category of parenteral administration. Besides these methods, there are also less common options. For example, intrathecal delivery injects medication into the area around the spinal cord, while intra-arterial delivery puts drugs directly into an artery. Another method is

convection-enhanced drug delivery, which helps push medication through brain tissue. Additionally, implants can be used to release medication slowly over time. Each method is chosen based on the specific needs of the treatment. However, the word "parenteral" is used in the pharmaceutical industry to refer to medications that are injected. For individuals who cannot take drugs orally, the parenteral mode of administration offers advantages such as a quicker onset of action [1].

The pharmaceutical industry Active Pharmaceutical Ingredients (API) and other necessary excipients are included in parenteral formulations, which can either be delivered as solid, liquid solutions, emulsions, or suspensions. Additionally, parenteral administration is used to provide innovative dosage forms such as biodegradable implants, and colloidal drug carriers including polymeric nanoparticles, polymeric micelles, liposomes, and intramuscular depot injections for the sustained, targeted, and controlled delivery of drugs. Parenteral distribution of biologicals is increasingly in demand as biomolecules, peptides, and proteins cannot be easily supplied by any other route due to bioavailability and stability concerns [1,2].

Parenteral product development presents a number of difficulties, including those related to drug solubility, product stability (important for biopharmaceuticals), drug delivery, and manufacturability. The significant advances in technology and science have increased the pressure on the established regulatory paradigms. Pharmaceutical development aims to create a product that is resilient, repeatable, and consistently provides the product for the intended purpose while maintaining an acceptable level of quality [3]. Compared to other dosage forms, the parenteral dosage form is superior. Even handling, evaluating, and storing of parenteral dosage forms are critical. A brief description of current trends and future automation scopes are described below.

2. Current Trends in Manufacturing for Large Volume Parenteral in the Pharmaceutical Industry

Once active pharmaceutical ingredients and excipients arrive at the storage facility, either from the company's own manufacturing unit for APIs or from a certified vendor, the pharmaceutical company begins producing a parenteral product. After the material arrives at the facility, the Certificate of Analysis is evaluated by Quality Control, cross-checked, and validated by Quality Assurance. Pending material approval, it is kept in storage areas known as "slagging rooms." The product remains under testing until it is approved or rejected by the pharmaceutical company according to proper labeling. Once the item is certified, the appropriate entries are made. Computerized systems verify the substance's moisture content, batch number, expiration date, and other relevant information. After completing the appropriate records, the substance is stored at the temperature designated on the label in compliance with the company's numbering system.

Calculations are done on first come first serve basis material entry and exit process specified as per company policy. To allocate the quantity of API and excipients to the Production Head, Store person and Quality Assurance Head person, specific calculations are made manually or using a computer system. Calculations must incorporate the previous batch's weight and remaining raw materials to ensure efficient use in subsequent batches where specified lot number, expiry date and weight of the material are considered as critical parameters. The store staff sends the API and excipients within in the dispensing rooms. A hydrometer, different capacity weighing balances, computers for labelling and verifying material and laminar air flow units are among the equipment found in the dispensing room. Separate rooms are created for the entrance of personnel and material for the product dispensing process which starts with Personal Air lock and Material Air lock. Personal Airlock is used for personal entry, exit and wearing protective gowns and is a place from where QA person, Helping workers and Production person can enter the Dispensing area while the Material Airlock is for entry and exit of material inside the Dispensing Area. As per standard operating practices, proper gowning and sanitization are advised. The cleaning of the dispensing rooms is performed by the assistant and production staff after wearing gloves and protective gowns. Cleaning which is appropriate and in compliance with SOPs is performed. Following the cleaning of the dispensing rooms, quality personnel is contacted to inspect the premises.

Various different checkpoints include washing dispensing scoops properly, ensuring that there are no traces of previous batches, calibrating the weighting machine, working to ensure that the differential pressure logbook is appropriate, trying to check that the differential pressure in the Laminar Air Flow unit is within limits, and monitoring the temperature in the dispensing room. Production and support staff members again go through the cleaning process to check if something is discovered to be misplaced or mishandled. If everything is found to be satisfactory, a quality assurance person provides the dispensing room line clearance. The production, helpers, and quality assurance person then conduct out the rest of the dispensing operation.

When other materials are dispersed in clear bags, light-sensitive materials should be placed in bags of black colour. Each material is put inside the stainless-steel bins in batches after the appropriate weight and labels are checked and placed inside that material. At the slagging area, separate stainless-steel bins are arranged.

Slagging Area, which is basically a place to keep the material, is next to the Dispensing room. Each item that is dispensed must be utilized within 24 hours; otherwise, it is discarded. Every two hours, temperature and differential pressure data in slagging rooms should be appropriately monitored and maintained. These records are made by production and checked by a quality assurance person. The BMR (Batch Manufacturing Record) is placed above the stainless-steel bins.

The material moves from the slagging rooms to the mixing rooms. The mixing room consists of syrup vessel, mixing vessel B, filter press, hydrometer, and ranges of HEPA filters for filtration of prepared product.Clean-in-Place (CIP) is performed before starting any batches. Water for Injection (WFI) at temperatures between 70°C and 80°C continuously circulates through each vessel during the CIP process for a specified duration. Upon

completion, WFI is collected from the end of the vessel and sent for quality control (QC) analysis. The sample is tested for parameters such as pH, conductivity, and description. To check for filter leaks, a filter integrity test is conducted, including pre-integrity and post-integrity assessments.

After performing sterilization in place at 121°C for 20 minutes, a sample is taken from the bottom of each vessel and sent to quality control for examination. This sample is also analyzed for pH, conductivity, and trace analysis. Finally, a fogging test is conducted using a fogging instrument, during which an appropriate disinfectant is sprayed across the area at various angles for 10 to 15 minutes. Subsequently, floors are cleaned and disinfected using a variety of solutions, including Bacillocid Extra 2.0% v/v and Virex 0.4% v/v, applied in a zig-zag pattern with cleaning mops. All operations are performed by production staff and helpers, with verification by a Quality Assurance representative. Records of these activities are maintained in the Batch Manufacturing Record (BMR).

API and the excipients are sent to the manufacturing room after the Quality Assurance officer gave the line clearance. To begin, syrup is prepared in a syrup vessel. WFI of 70 to 80 ◦C is first collected in the mixing vessel, and then the excipients and API are added. In the vessel, more mixing is done. Following the mixing process, the syrup was transferred to Mixing Vessel A through pipes. Between them is a filter press that includes a tiny HEPA filter layer with three to eight layers or less underneath. Then, the proper amount of syrup is transferred, and the LED screen displays the pattern digitally. Following the transfer of the syrup, the proper mixing is done, and the solution is cooled using cooling jackets. A solution is transferred to mixing vessel B after it reaches the proper temperature. Holding vessel and mixing vessel B are connected.

Three separate filters are placed at the bottom of mixing vessel B and the holding vessel to filter the finished product. The product is simply transferred from mixing vessel B to three different size HEPA filters before reaching the holding vessel. Just a storage space used to move the product to the filling chamber, a holding vessel. Three different pore sizes of HEPA filters are put between the holding vessel and the filling area to guarantee that the product is free of microbes. Holding, hopper, and filling room CIP and SIP (Sterilization in Place) are completed at the same time. Once the product is in the holding area, the hopper room is given line clearance. For the appropriate batches, the Quality Assurance Officer monitors items like plastic grade, plastic manufacturer name, and plastic quantity.

In hopper room temperature logbooks and Differential Pressure logbooks are placed by Production and verified by Quality Assurance at every two hours of time intervals. The manufacturing process starts as soon as the mixing vessel B is transferred to the holding room. By the use of one machine equipped with FFS technology, a bottle-forming mold is created using plastic from a hopper, which is then filled with product solution and sealed by the mold using a scrapper. Based on the machine's capacity, bottles are filled at the beginning of the batch from the LHS (Left hand side) and RHS (Right hand side). Unless the bottle weight is determined to be inadequate, the first four to ten cycles ae discarded. Engraved number displayed on the bottle should be checked by the Production team and verified by the Quality Assurance team by the start of a batch, as it contains information such as product code, date of manufacturing, and time of manufacturing as specified in BMR. From the filling line to the dispensing areas during the production process and in compliance with classes established for pharmacopoeias, robust aseptic controls such as differential pressure, temperature control, and prescribed gowning should be utilised.

A bottle storage facility is located after the filling line, andv bottles are laid up on trays there. Several factors are checked, including bottle weight, leakage test, spike test bottle thickness, bottle cap measurements, hanger cut, extra plastic, scratch marks, head tip band and other defects, such as a missing hanger, black or white particles, bottle leaks, varying bottle volumes, and weight variations. Production personnel carries out all tasks, logs them, and has them verified by a quality assurance person in compliance with the product requirements given in the BMR. Logbooks, BMRs, and other records are correctly maintained, with the appropriate entries being made at the beginning and end of the product. Bottles are placed in the baskets after being properly set on trays.

Line clearance of the Sterilization is the next stage once the batch has finished filling. A lot of things are inspected by the Quality Assurance professional, including the sterilizer's water, the requirements to confirm temperature sensors, the leakage test, steam pressure, cooling pressure, compressed air pressure, the yellow caps for the retention samples, and other factors. The trolly trays are moved into the sterilizer using hydraulics when a Quality Assurance supervisor confirms that the sterilizer complies with the compliance requirements.

In order to protect patient safety, we sterilize parenteral and injectable drug products to eliminate any possible microbial contaminants (bacteria, fungi), as well as to maintain product integrity, quality control, regulatory considerations, and the stability of thermolabile substances (gas and filtration sterilization) [16]. Any substance that undergoes significant alteration, decomposition, or destruction at temperatures of 55 degrees Celsius or higher is generally referred to as thermolabile, although biological compounds are particularly affected [15]. The most popular sterilizing technique, which is advised by several pharmacopeias, is heating under pressure while water is present to produce steam. Three procedures: heating, sterilizing, and cooling began after the sterilizer's gates were closed. Sterilization occurs at 121°C for 20 minutes at a constant temperature, while cooling entails sprinkling cooled water within the tray to cool the bottles to 50°C. Heating is the time required for the machine to reach 121°C.

After sterilization of the batch yellow caps are placed on the bottles, and those bottles are sent to QC for Analysis after Sterilization. The bottles are sent to the packaging room once the sterilisation process is finished. The batch arrives at the packing area once the sterilization procedure has finished. The packaging area consists of an assembly line that contains instruments

such as leak tester, a visual booth, labelling and capping, film rapping, cartooning, shipper placement on racks, and a printing machine.

After line clearance of the packaging line, which is examined by Production and verified by the Quality Assurance person, the material is first supplied from the store specified in the BMR. There are numerous checkpoints, namely calibrating the weighing scale, using a hydrometer to monitor temperature and humidity, checking the visual booth's light level, and monitoring the pressure on the leak tester in accordance with the product's specifications. Before starting the batch leak tester pressure, labels, printing machines, barcode codes, waste bin labels, line product status board, rejection bins, shipper code, BOPP tape colour, and other necessary things should be checked by Production person and verified by the Quality Assurance officer.

Beginning from the first leak tester machine where pressure is set by the engineering department, checked by production, and verified by Quality Assurance using the pressure gauge where a small hole is made on the tip of the bottle, a batch begins its correct sequence from leak tester to shipper placement on racks. A Quality Assurance person checks the pressure every 2 hours ± 05 minutes to ensure that the product fulfils the standards for quality.

Next to the Leak tester, there is a visual booth where qualified visual inspectors check the bottles placing the bottles on a black and white screen and checking the defects like a surface black particle and white particle, solution particle white/ black particle, hanger cut, solution particle, high volume, less volume, head/ tip bend, deshape, broad lines, and other defects which are placed in the specified bins. Based on the bins the defective bottles that were placed inside the waste bins by the end of the batch bottles are calculated as received material subtracted by defective material. If we have extra material left then that material is carried forward to the next batch the and records are made in BMR where the reconciliation part specifies every detail of information about it. The changing frequency of Visual Inspectors is 1 hour ± 05 minutes.

Capping, labelling, BOPP film wrapping, cartoning and shipment placement on racks is a continuous process. Qualified Helpers are used in this procedure; they are highly skilled and proficient at doing these duties. Cap breakage, label errors, and carton defects in terms of colour, shape, and size are just a few of the several items that Production and the Quality Assurance persons assessed during the batch. After completion of batch, all defective bottles are counted and if material is left then it is carried forward to the next batch or returned to the store. From the beginning, the middle, and the end of the batch, retain samples were collected.

After batch completion, the Production person counts the total quantity and creates a slip, which is checked by the Quality Assurance officer. Flow chart from Material Store to Warehouse is shown in Figure 1. The batch will be stored in the warehouse and afterward transferred from the store into trucks once the BMR has been sent to the administrative departments for evaluation.

Challenges in the development and production of parenteral products:

1. Complex formulation requirements: achieving stability, solubility, and compatibility can be difficult in many parenteral formulations because they contain complex pharmacological components and excipients. To increase drug solubility and stability, solutions use innovative formulation techniques like liposomal delivery systems or nanoemulsions [4].
2. Sterility assurance: to avoid contamination and maintain product safety, sterility must be guaranteed throughout the production process. Although sophisticated sterilization methods like aseptic processing or terminal sterilisation are employed, issues with process validation and monitoring still remain [5].

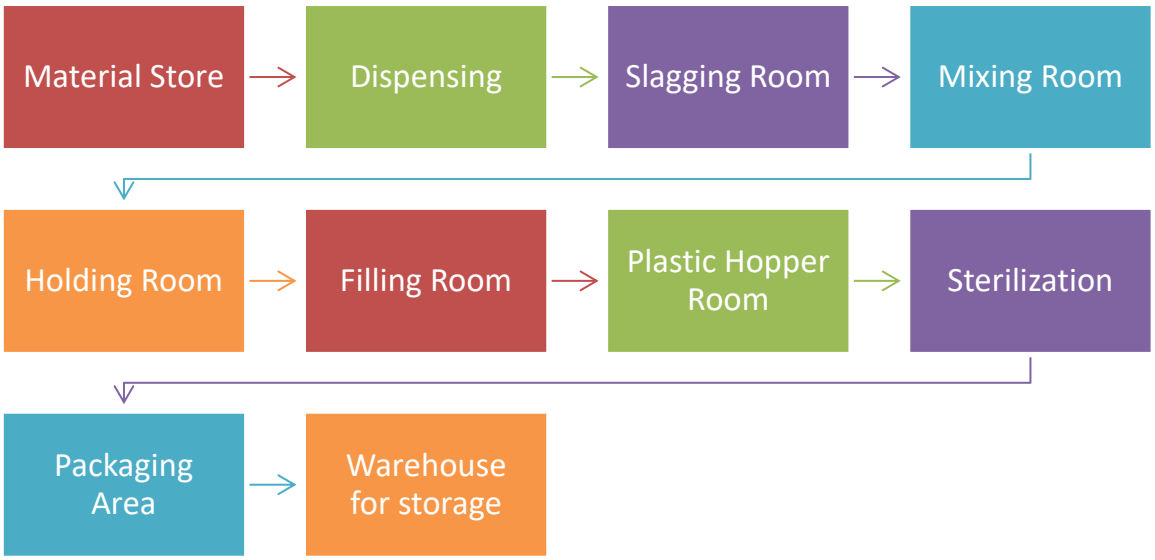

Fig 1. Steps involved for production of Large Volume Parenteral

3. Preservation of biological activity: because proteins and biopharmaceuticals are vulnerable to environmental changes, maintaining their biological activity necessitates strict control techniques. Stabilising agents and freeze-drying are two formulation techniques that assist in preserving the integrity of proteins during production and storage [6].

4. Particulate matter and pyrogens: in order to shield patients against unfavourable reactions, parenteral formulations must be carefully regulated with regard to particulate matter and pyrogens. To guarantee product purity, strict quality control procedures and cutting-edge filtration methods are used [7].

5. Container closure integrity: to avoid product contamination and microbiological infiltration, container closure integrity must be maintained. Sophisticated packing materials and exacting testing techniques including microbiological challenge tests and dye ingress have been utilised [8].

6. Regulatory compliance: complying with strict regulations increases the intricacy of the product's development and production processes. It is crucial to continuously assess legal requirements and current good manufacturing practices (cGMP) compliance [9].

7. Supply chain management: coordinating with many stakeholders and guaranteeing continuous raw material availability are key components of managing the supply chain for parenteral goods. Strong supply chain management systems must be put in place, as well as backup plans [10].

8. Production cost: because parenteral products must meet strict quality control standards and undergo intricate manufacturing processes, their production prices are frequently very costly. Production costs can be reduced by implementing process optimisation techniques and utilising new technologies [11].

9. Environmental impact: the production of parenteral products may have an impact on the environment since it uses disposable materials, generates waste, and consumes energy. The environmental impact can be decreased by implementing sustainable technology and green production techniques [12].

10. Employee training and qualification: maintaining product quality and safety requires maintaining employee competency and adherence to standard operating procedures (SOPs). Staff skills and expertise are improved by ongoing training programs and qualification exams [13].

Innovations in technology, adherence to regulations, and smart alliances among pharmaceutical companies are all part of the answers to these challenges. Effectively tackling these obstacles will enable parenteral product research and manufacturing to proceed, guaranteeing patients around the world have access to safe and efficient solutions [14].

3. Future Scopes in Manufacturing for Large Volume Parenteral in the Pharmaceutical Industry

Based on artificial intelligence and machine learning, parenteral plants will be completely superfluous in the future. The automatic arms and automatic guided vehicles would conform to the items that are coded inside the software. Material is scanned through robotic arms as part of the traditional working process of receiving it first from the material store and then transporting to dispensing rooms by conveyor belts. Automation was used to clean the dispensing rooms, however, Production and Quality Assurance inspectors would check the information presented in the BMR that was displayed on the tablet screen. After the material has been verified, a digital signature is created on BMR, and the dispensing stage is then started. Afterwards the material is distributed using autonomous guided vehicles, transporting it to slagging rooms.

Production and Quality inspectors check the area where CIP and SIP are carried out to ensure compliance with the specified product before the batch starts in mixing rooms. Through the utilisation of robotic arms, the batch is able to reach the allocated syrup and holding vessels, and excipients and API are carried there using artificial intelligence arms. Where Production and Quality Assurance officers check that everything is operating according to with SOP and BMR Based on Product specifications.

Robotic arms set the filtration assembly, and a Production and Quality Assurance officer analyses the prefilter and post integrity. After a certain amount of time, samples are gathered using robotic arms and conveyer belts before being sent to the quality control department for inspection. A label with the product description, batch number, and product code is then applied to the sample collecting bottle. Once the assay is successful, the product is transferred from the mixing room to the holding room.

Afterwards, the filling and plastic hopper processes being programmed into the machine, robotic arms fill plastic into the hopper, and filled bottles are examined by automatic sensors, removing several flaws like hanger cuts and high volume/low volume in place of Helpers performing this work according to the traditional method. Robotic arms will place bottles on trays next to the filling machines according with the software-coded arrangements. Even so, automatic guided vehicles will sterilize all of the trays.

Later, the Sterilizer's LED Screen will show all the checkpoints, including temperature, pressure, and colling temperature. Automation will decrease the need for human labour and boost people's confidence in efficient technology. Automated robotic arms with hydraulics are used to move trays to the packaging area when the sterilization procedure is complete. Automatic samples are drawn from the trays as the batch makes its way to the packing area. Robotic arms in the packing section take all bottles, set them on leak testers, and then transport them to a visual booth where automated sensors identify the bottles and dump the defective ones in trash cans using conveyer belts. Later, robotic arms are utilised to cap and label bottles.

The bottle is placed in the box in accordance with the specified BMR after reaching BOPP Film Wrapping afterward. Carboard boards are organised on the racks that are designated based on the product's coding, and then it is delivered to the warehouse by automatic guided vehicles. Based on batch coding and product storage needs, products are stored in warehouses.

4. Conclusions

Parenteral injections tend to be injected directly into the blood for a fast and controlled effect or into tissues outside the blood vessels for a local or systemic effect. Parenteral products are sterile preparations that can be injected into the body through a multitude of routes. They have many upsides, including a quick onset of action and the prevention of first-pass metabolism. Crucial phases from the store to the warehouse are essential for the production of large volumes of parenteral medications. These processes eliminate sample errors, product errors, and other controls. Although the roles and responsibilities of both the manufacturing team and the quality assurance team have significance to the production of large volumes of parentals. Future manufacturing efforts are going to decrease workforce costs and boost product quality, yet they will also promote increased automation development, which could result in innovations in the field of pharmaceuticals

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