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DEVELOPMENT AND MANUFACTURING OF INJECTABLE (PARENTERAL) DRUG PRODUCTS

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ABSTRACT

The present study will outline development, manufacturing and the evaluation methods of injectable dosage form. The drug that we need should be most convenient and in proper form then only it reaches to the desired site of action. This is greatly influenced by which the type of dosage form of the drug. Since, injections include much variety of therapeutic agents. Injections are sterile, pyrogens limited, that is, bacterial endotoxin units' limit, preparations intended to be administered parenterally. It is well recognized that the advantages of parenteral injections are immediate systemic drug availability and rapid onset of action.

KEYWORDS: Injectable, Parenteral, Preformulation and formulation, Lyophilization.

INTRODUCTION

1. Pharmaceutical product development overview

After development of a new pharmaceutical product, several technical aspects need to be evaluated and numerous validation activities need to be performed prior to start routine production and commercialization. Technology transfer involves transfer of product and process knowledge to achieve product realization and includes all the activities required for successful progress from pharmaceutical development (R&D) to production. Additionally, technology transfer is also applicable for marketed products and involves transfer of processes from one manufacturing site to another. The aim of pharmaceutical development is to develop a product suitable for its intended use, using a defined manufacturing process, which should be robust and reproducible in order to deliver consistently a product with the

desired quality. The data obtained and the knowledge gained from the pharmaceutical development studies and manufacturing experience during the R&D phase, provides evidence to support the establishment of the design space, specifications and manufacturing controls / critical process inputs. The intention is to build quality into the pharmaceutical product while it is still in the research and development phase, to make sure that the final product is going to meet the requirements prior to entering the production phase. Critical process inputs, i.e., critical material attributes (CMAs) and critical process parameters (CPPs), should be identified through a risk-based approach since they represent sources of variation that affect the product quality. Once these parameters are identified, they should be controlled commensurate with the risk they represent to the product quality by implementing the proper control strategies.

1.2. Injectable Pharmaceutical Products

According to USP Chapter, ―Parenteral articles are preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion‖. Parenteral or injectable pharmaceutical products are prepared by methods designed to ensure that they meet Pharmacopoeial requirements for sterility, pyrogens, particulate matter and other contaminants. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration.[1]

1.2.1. Nomenclature and definitions

The preparations intended for parenteral administration are available either as liquid (solutions, emulsions or suspensions) or solid products.[2] According to USP Chapter, the following nomenclature can be used to classify these types of preparations.

[DRUG] Injection – Liquid preparations that are drug substances or solutions thereof.

[DRUG] for Injection – Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.

[DRUG] Injectable Emulsion – Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

[DRUG] Injectable Suspension – Liquid preparations of solids suspended in a suitable liquid medium.

[DRUG] for Injectable Suspension – Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

1.2.2. Raw materials[3]

Preparations intended for parenteral administration contain one or more drug substances, also known as active pharmaceutical ingredients (API). Additionally, these preparations may contain appropriate excipients (vehicles and/or other substances).

Aqueous Vehicles – Water for Injection (WFI) is the most common vehicle used for aqueous parenteral preparations. WFI is water purified by distillation or other purification process equivalent or superior to distillation in the removal of chemicals and microorganisms. It contains no added substances and bacterial endotoxin content less than 0.25 USP Endotoxin Unit/mL. It is intended for use in the preparation of parenteral solutions and not for direct parenteral administration.

Non Aqueous Vehicles – Oils used as vehicles for non-aqueous injections are of vegetable origin, are odorless or almost odorless and have no odor suggesting rancidity. Synthetic mono- or diglycerides of fatty acids and other non-aqueous vehicles may be used as vehicles, provided they are safe and do not interfere with the therapeutic efficacy of the preparation or with its response to the specified assays and tests.

1.2.3. Added Substances

Suitable substances may be added to preparations intended for injection, provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy or with the responses to the specified assays and tests. For instance, sufficient amounts of Sodium Chloride may be added in order to obtain an isotonic solution. Some substances, such as coloring agents, may be avoided and should not be added only for the purpose of coloring the finished preparation. Special attention may be given when using added substances for preparations that are administered in a volume higher than 5 mL. Preparations intended for injection that are packaged in single-dose containers do not require the use of antimicrobial agents. On the other hand, a suitable substance or mixture of substances to prevent the growth of microorganisms must be added to preparations intended for injection that are packaged in multiple-dose containers, unless when the substance contains a radionuclide with a physical half-life of less than 24 hours or when the active ingredients have themselves antimicrobial activity.

ADVANTAGES OF PARENTERAL PRODUCTS

- ✓ These are useful in
- Unconscious patients.
- Uncooperative and unreliable patients.
- ✓ Onset of action of drugs is faster; hence it is
- ✓ suitable for emergency.
- ✓ Patients with vomiting and diarrhea.
- ✓ These are suitable for irritant drugs and drugs with
- ✓ High first pass metabolism.
- ✓ Drugs are not absorbed orally.
- ✓ Drugs destroyed by digestive juices.

DISADVANTAGES

- ✓ Parenteral preparations should be sterile and expensive.
- ✓ They require aseptic conditions.
- ✓ Cost
- ✓ They can't easily self- administrated.
- ✓ Causes local tissue injury to nerves, vessels, etc.

Parenteral product formulation depends upon the understanding of several factors that dictate the choice of formulation and dosage form.

2. DEVELOPMENT AND MANUFACTURING OF INJECTABLE (PARENTERAL) DRUG PRODUCTS

From discovering the active ingredient to manufacturing the finished product, the production of a drug is a complex, time consuming, and expensive process. There are many factors that must be considered during the process, including.

- determining the dose.
- determining the route of administration.
- determining what to mix with the drug (excipients) to stabilize the product.
- determining how the drug is absorbed and excreted (pharmacokinetics).
- determining possible side effects.
- determining whether the drug is stable as a solution or needs to be freeze-dried (lyophilized).

- identifying the correct vial and stopper use.
- determining the manner in which the drug behaves/interacts during manufacturing.
- determining the proper filter and filtration techniques.
- determining the proper protocol for labeling, packaging, and storing the drug.
- ensuring the drug product is free of microorganisms, pyrogens, and foreign particulate matter.

The administration of drugs to humans through injection was first recorded as early as the mid-1800s; however, little was known about microorganisms at the time, so safely administering an injectable drug did not become a viable process until the early 1900s, when knowledge of microorganisms and sterilization techniques became more common. During the early year's sterilization techniques were limited to either heat sterilization or steam sterilization (autoclaving). These techniques were extremely damaging to drug products, and it was not until the advent of HEPA filters, clean rooms, and sterilizing filters that aseptic manufacturing became a more common practice for producing aseptic drugs without heating the drug product directly—all of the components were pre-sterilized then brought together in a sterile environment.

2.1. Manufacturing process

The manufacture of pharmaceutical drug products should meet the requirements of current Good Manufacturing Practices (cGMPs), which are guidelines to provide assurance of proper design, monitoring and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality and purity of drug products by requiring that its manufacturers adequately control each manufacturing operation. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations and maintaining reliable testing laboratories. It helps to prevent the occurrence of contaminations, mix-ups, deviations and failures and assures that the drug products manufactured meet their quality standards.[3][4][5]

The cGMPs are minimum requirements and are flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using appropriate design, processing methods and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality

through continual improvement. Accordingly, the "c" in cGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations.[3][4][5]

The cGMPs require testing but testing alone is not adequate to ensure quality, since it is usually done on a small sample of a batch. Therefore, it is important that drug products are manufactured under conditions and practices required by the cGMP regulations to assure that quality is built into the design and manufacturing process at every step. The safety and efficacy of drug products can be more easily achieved if their manufacture occurs at facilities that are in good condition, with equipment that is properly maintained and calibrated, by employees who are qualified and fully trained and following processes that are reliable and reproducible.[3][4][5]

The manufacture of injectable products should occur in clean areas, which should be maintained to an appropriate cleanliness standard (refer to table 1) and supplied with air which has passed through filters of an appropriate efficiency (HEPA filters). Injectable products are mandatorily sterile and sterility assurance can be achieved by validation and control of each manufacturing process step, environmental monitoring / control, maintenance of HEPA filter integrity and maintenance of a differential pressure (of 10 – 15 Pa) between areas of differing class.[3][4][6][7][8][9]

Particle size	ISO 14644-1	United States FDA Guidance and USP <1116>	European Union Annex 1
	ISO 5	**ISO 5 / Class 100**	**Grade A Grade B (at rest)**
≥ 0.5 µm	3520	3520	3520
≥ 5 µm	29	Not specified	20 (Grade A) / 29 (Grade B, at rest)
	ISO 6	**ISO 6 / Class 1000**	**N/A**
≥ 0.5 µm	35200	35200	N/A
≥ 5 µm	290	Not specified	N/A
	ISO 7	**ISO 7 / Class 10000**	**Grade B (in operation) Grade C (at rest)**
≥ 0.5 µm	352000	352000	352000
≥ 5 µm	2900	Not specified	2900
	ISO 8	**ISO 8 / Class 100000**	**Grade C (in operation) Grade D (at rest)**
≥ 0.5 µm	3520000	3520000	3520000
≥ 5 µm	29000	Not specified	29000

Figure 1: Clean area air classification (particles/m3).

An environmental monitoring program should be implemented in order to maintain the clean areas to an appropriate cleanliness level. The most commonly accepted international cleanroom standard is ISO 14644-1.[9] ISO class designations are based on the number of particles greater than a specified size (0.1 – 5 μm) per cubic meter of air sampled. ISO 14644-1 defines classes from 1 to 9 (with ISO 1 being the cleanest) but only ISO classes 5 to 8 are used in the pharmaceutical industry for the manufacture of sterile products. For the United States, the FDA's 2004 Guidance for Industry[4] and USP General Chapter <1116>[8] include ISO classes 5 – 8 and their corresponding Federal Standard 209E classes (although this classification is obsolete, it is still mentioned for continuity), only for particles ≥ 0.5 μm. The European Union use an alphabetic classification of Grades A to D (according to EU Guidelines to Good Manufacturing Practice Annex 1[6]). For each grade, a ≥ 0.5 μm and ≥ 5 μm particle count is specified, for both at rest and in operation states. Each grade has up to two corresponding ISO classes, as follows.

Grade A – ISO 4.8 at rest and in operation, based on the reduced maximum count of particles ≥ 5 μm per cubic meter from 29 (ISO 5) to 20 (ISO 4.8);

Grade B – ISO 5 at rest, ISO 7 in operation;

Grade C – ISO 7 at rest, ISO 8 in operation;

Grade D – ISO 8 at rest, undefined in operation.

Sterile products can be manufactured by two different methods: aseptic processing or terminal sterilization. These products should be manufactured using aseptic processing only when terminal sterilization is not feasible. Therefore, when designing the manufacturing process of a sterile drug product, the first approach should be evaluating if the product can be terminally sterilized. When aseptic processing is selected over terminal sterilization, proper scientific justification should be provided in the marketing authorization dossier. The most common and plausible reason is the degradation of the drug substance and/or drug product when exposed to terminal sterilization conditions. A decision tree for sterilization choices for aqueous products is presented in Appendix 1.[3][4][6][10]

3. Terminal sterilization

Terminal sterilization usually involves performing the filling and closing processes under high-quality environmental conditions (aseptic conditions are not required), in order to minimize microbial and other particulate content in the product and to help ensuring that the subsequent sterilization process is successful. Therefore, the product and the container

closure system must have low bioburden but are not sterile. The product in its final container is then subjected to a terminal sterilization process such as heat or irradiation. The method of choice for aqueous preparations is moist heat sterilization (in an autoclave) and, therefore, it should be used whenever possible.[3][4][6]

3.1. Aseptic processing

In aseptic processing, the product and the container closure system are previously subjected to sterilization methods separately. Since the product is not sterilized in its final container, it is required that the filling and closing processes occur under aseptic conditions and following aseptic technique. Usually, different sterilization methods are applied to the individual components of the final product. Glass containers are subjected to dry heat sterilization (in a depyrogenation tunnel), rubber closures are subjected to moist heat sterilization (in an autoclave) or purchased irradiated (pre-sterilized) and liquid dosage forms are subjected to sterilizing filtration (through a sterilizing-grade filter). Each one of these manufacturing steps should be properly validated and controlled. Any manipulation of the sterilized components poses the risk of contamination and, therefore, appropriate controls should be in place, in order to avoid obtaining a non-sterile product.[3][4][6]

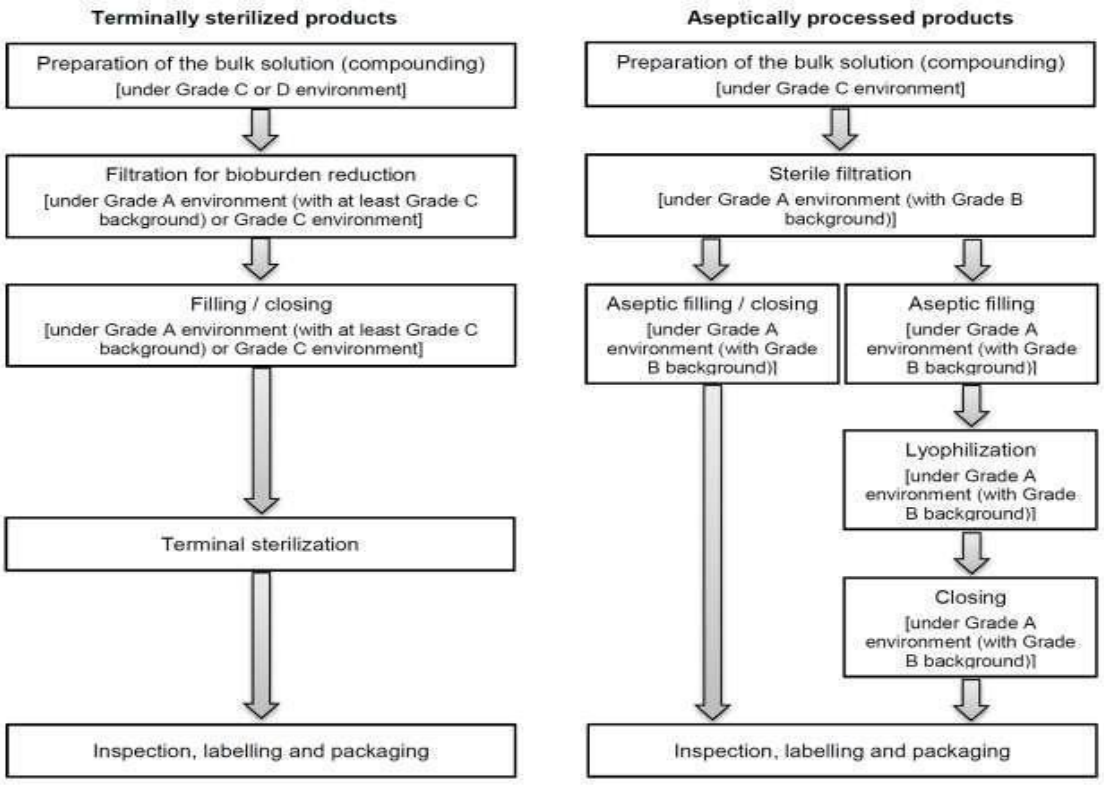

Figure 2: General steps involved in the manufacture of injectable drug products.

(terminally sterilized vs. aseptically processed products)

4. Pre-Formulation and Formulation Development

There is a significant amount of time, effort, and expense required when identifying a new drug molecule, whether it is a small molecule or a large bio-molecule. However, once the molecule is identified and a process to mass produce the molecule is created, the final product development work begins.

The initial goal is to get the product to a semi-formulated state so it can be administered to animals for safety/toxicology studies (pre-clinical). For the early phases of animal and human studies (clinical trials) it is common to use drug products that are not in the final formulated state, as they need to be stable only through the course of the trial. While these early phase studies are conducted, development scientists work to identify the final formulation that will offer the best stability, safety, and efficacy.

Pre-Formulation studies may include.

- pH stability
- pH solubility
- identifying a stability indicating analytical method
- thermal stability
- oxidation potential
- light stability
- hydrolysis potential Formulation studies may include:
- identifying both the need for and appropriate strength of a buffer system to control pH
- identifying both the need for and appropriate strength of a surfactant
- identifying both the need for and appropriate strength of a stabilizer
- identifying both the need for and appropriate strength of a bulking agent
- identifying both the need for and appropriate strength of a solubilizing agent
- identifying both the need for and appropriate strength of a preservative system
- accelerated stability studies
- Process Compatibility

Once the pre-formulation and formulation studies have identified a suitable drug product candidate, the next step includes learning how the formulation behaves/interacts in an aseptic manufacturing facility. Studies are conducted in order to understand the manner in which the

product reacts when the formulated product comes into contact with different materials utilized during manufacturing, including:

- glass
- stainless steel
- process tubing
- plastics
- other components that may come into contact with the drug product.

Product hold time studies are also conducted to determine the amount of time the product can sit in the filling vessel before it degrades or settles.

4.1 Filtration

At this point in the manufacturing process the formulated drug product enters the Class A clean room. It remains under these conditions until the product is filled, stoppered, and capped. Only then does the product exit the clean room, unless it is destined to be freeze-dried, at which point the product is aseptically transported to the freeze-dryer.

There are four primary types of filters used in the parenteral and biopharmaceutical industry (the type of filter chosen depends on the type of material to be removed). The filter types include.

- clarifying filters—large particles
- microfilter—bacteria and yeasts (used for injectable drug products
- ultrafilter—viruses
- nanofilter—small organic compounds and ions

The injectable drug industry uses microfilters to remove particles in the 0.1 to 10 micron size range from the formulated drug product. Several different types of membranes are available in this pore size range to accommodate different types of formulations, including water based formulations (hydrophilic) and solvent based formulations (hydrophobic). It is up to the development scientist to conduct studies for filter compatibility in order to determine the correct filter and filter surface area for the particular product. For most parenteral products, a hydrophilic (water loving) filter is used and may include.

- cellulose acetate
- cellulose nitrate
- regenerated cellulose

- modified regenerated cellulose
- polyamide (nylon)
- polycarbonate
- polyethersulfone
- polysulfone
- polyvinylidene difluoride (PVDF)

The next step in the process is to sterilize the solution using one of the filters listed above. Note that products that are either suspensions or large particle-sized emulsions cannot be sterile filtered and have to be aseptically formulated—all components are pre-sterilized individually and then brought together in a sterile environment. The filters are available as either flat disks or as cartridge filters, which significantly increase the filter surface area when extremely large volumes need to be filtered.

To ensure that the filter membrane is completely intact (no holes), integrity testing must be performed both before and after filtering the product. This is accomplished through a process known as bubble point testing, a non-destructive integrity test measuring diffusive flow or water intrustion over the filter membrane.

4.2 Filling

Once the product has been filtered into a sterile filling container and the filter passes the post-fill integrity test, it is now ready to fill into its primary container. Sterile tubing is placed into the sterile solution, which leads first to pumps and then to filling needles. There are several different pumps that can be used to fill the product, and the type of pump used depends upon the type of product being filled. The types of pumps include.

- gravity (solids and liquids)
- piston (liquids and gases)
- peristaltic (liquids and gases)

The product is generally filled into glass vials; however, different types of containers can be filled depending on the product. Product can be filled into these containers using one of three main methods.

- volumetric—a fixed volume is added
- time/pressure—a fixed pressure is administered over a certain amount of time
- net weight—each container is weighed while being filled

Vials that have been pre-sterilized travel down the filling line and stop below the filling needles. The needles descend into the vials and slowly rise as the required amount of product is dispensed. This method of filling minimizes splashing of product on the sides of the container. In special circumstances, where emulsions or suspensions are being filled, these products must be constantly recirculated to prevent settling of the solids at the bottom of the filling container. The weight of the vials must be initially checked after filling to ensure the proper dose is being dispensed; it should also be checked periodically throughout the run to ensure nothing has changed with the filling equipment that would cause either a low or high product fill.

The label should not cover the whole length or circumference of the container, which should be labeled so that a sufficient area remains uncovered to allow visual inspection of the contents.

5. Packaging

A container closure system (or packaging system) refers to the sum of packaging components that together contains and protect the dosage form. A primary packaging component is a packaging component that is in direct contact with the dosage form, while a secondary packaging component is a packaging component that is not in direct contact with the dosage form.[3] 14]

The selection of the container closure system is more critical for a liquid-base dosage form than for a solid, since the liquids are more likely to interact with the packaging components. Nevertheless, each drug product (either solid or liquid) should be packaged in an appropriate container closure system, which should be suitable for its intended use. Suitability means that the packaging system complies with the following criteria.[3][14]

- Protection: provides the dosage form with adequate protection from factors that can cause its degradation throughout the shelf-life, such as, exposure to light, exposure to oxygen, loss of solvent, absorption of water vapor and microbial contamination;
- Compatibility: is compatible (i.e., does not interact) with the dosage form;
- Safety: is composed of materials that are considered safe for use with the dosage form and the route of administration;
- Performance: is functional and allows a proper delivery of the drug product.

5.1. Primary packaging components

Since the primary packaging components are intended to be in direct contact with the dosage form, special attention should be given to their materials of construction.

5.1.1. Containers

Parenteral preparations are usually supplied in the following containers: vials, ampoules, bags, bottles and syringes. These containers are commonly made from glass (clear or amber type I glass) or plastic (e.g., HDPE and PP). The material of construction must be compatible with the drug product formulation and should allow the visual inspection of the contents.

Glass vials are the main containers for injectable pharmaceutical products (refer to figure 3), due to their high chemical resistance, impermeability to gases, temperature resistance and ease of cleaning and sterilization. Their capacity usually ranges from 1 mL to 100 mL and they usually have a neck diameter of 13 mm, 20 mm or 32 mm.[3][14][15][16]

Figure 3: Clear and amber glass vials.[16]

5.1.2. Closures

Closures for parenteral preparations must fit the container properly, in order to preserve the quality of the product and this combination should be validated to prove container/closure integrity. The more common closures are rubber stoppers (refer to figure 7), which are usually accompanied with aluminum seals (refer to figure 8).[3][14][17][18]

Figure 4: Rubber stoppers.[18]

Stoppers are typically made of elastomeric materials (such as, bromobutyl and chlorobutyl rubber) and are available in different sizes and styles, according to the type of container they are intended for (refer to figure 9). Several types of coating can be applied to the top and/or bottom surface of the stoppers. Coating with fluorinated polymers (e.g., PTFE and ETFE) is widely used to reduce the risk of chemical interactions between the closure and the drug product (i.e., to improve compatibility) but applying coating to stoppers can provide many other advantages, such as.[3][14][17][18][19]

- Lower level of extractable from the rubber;
- Reduced particulate matter (visible and sub-visible particles);
- Enhanced machinability, which usually leads to increased line speeds.

5.1.3. Capping

If the vials are not scheduled to be freeze-dried they travel down the filling line to the capping station. Caps are used to secure the stopper in the neck of the vial to prevent the stopper from coming out either over time or during handling. The caps are comprised of a plastic cap and an aluminum skirt (Figure 2).

Figure 5: Aluminum crimp caps.

The caps are fed down a chute to the vials as the vials travel down the filling line. One cap is loosely placed on the top of each vial. The vials then travel to the crimping station where rotating blades crimp the bottom of the aluminum skirt around a lip on the neck of the vial, producing a tight fit that locks the stopper into the neck of the vial. At the time of use the plastic cap is removed; this exposes the top of the stopper, which is then pierced with a needle to remove the contents inside the vial. At this point in the production process the vials exit the Class A environment through a port in the wall and are ready for inspection and final packaging.

5.2. Secondary packaging components

Common secondary packaging components are overwraps and cartons, which generally have one or more of the following functions.[3][14]

Avoids excessive transmission of moisture or solvents into or out of the packaging system.

Provides protection from excessive transmission of gases (atmospheric oxygen, inert headspace filler gas or other organic vapors) into or out of the packaging system.

Provides light protection for the packaging system (extremely important in the case of drug products that are sensitive to light and are filled in clear containers).

Provides protection for a packaging system that is flexible or needs extra protection from rough handling.

For instance, overwraps are usually used with bags, in order to avoid solvent loss, to protect the flexible packaging system from rough handling and to provide light protection (in the case of drug products sensitive to light). Cartons are more commonly used with vials, ampoules and syringes. Labels and leaflets (inserts) are also considered secondary packaging components.

Since secondary packaging components are not intended to directly contact with the dosage form, there is usually less concern regarding the materials from which they are made. Nevertheless, if the packaging system is relatively permeable, there is a possibility that the dosage form could be contaminated by the migration of an ink, adhesive component or from a volatile substance present in the secondary packaging component. In these cases, the secondary packaging component should be considered a potential source of contamination and the safety of its materials of construction should be taken into consideration.[3][14]

6. Lyophilization

If the product is destined to be freeze-dried the vials bypass the capping station and are directed to a special collection table. After enough vials are placed on the collection table, an operator picks up the tray and places it on one of the shelves in the freeze-dryer. It should be noted that many newer systems have been equipped with robotic loading systems, which eliminate the need for human intervention in loading and unloading the freeze-dryer. Lyophilization, or freeze-drying, is performed in order to extend the shelf life of poorly stable drug products. Since some products suffer degradation through a process known as

hydrolysis—a chemical reaction with the water in the product—removing the water by freeze-drying significantly extends the shelf life of the product. It should be noted that prior to using the drug product the dried solids must be reconstituted with sterile water, or another suitable diluent, in order to bring the dried solids back into the solution state in regards to the scientific principles of freeze-drying, there are several distinct phases of the freeze-drying process, including.

- freezing
- annealing (not always performed)
- primary drying
- secondary drying

Water changes form (solid, liquid, and vapor) based upon temperature and pressure. For example, water will change to vapor (boil) when the temperature exceeds 100°C; however, water will also boil at room temperature if the pressure is reduced. This is easily explained using a phase diagram of water as a function of temperature and pressure, which is detailed in Chapter 14.

In the sealed freeze-dryer chamber the product temperature is reduced to a predetermined point until all of the liquid phases have solidified. At this point a vacuum is applied to the chamber, which causes the ice to convert directly from a solid to a vapor through a process known as sublimation. The vapor leaves the product, travels through the open port of the partially inserted stopper, and travels to and collects in another part of the freeze-dryer away from the product. Once the product is completely dry, the shelves in the freeze-dryer compress and force the partially inserted stoppers further into the necks of the vials and seal the product. The vials are then removed from the freeze-dryer and sent to the capping line, where the caps are crimp sealed onto the necks of the vials.

Most freeze-dryers have several similar components, including.

- condenser
- temperature controlled shelves
- temperature monitoring devices
- vacuum monitoring devices
- vacuum systems
- bleed valve
- data recording device

After freeze-drying, there are certain attributes that the dried products must possess, including.

- fast reconstitution time: the amount of time it takes to get the solids back into solution once sterile water is added
- extended stability: how long the drug is stable in the freeze-dried state
- good appearance: a pharmaceutically elegant dried product is desired
- low residual moisture: the product should be extremely dry in order to achieve good extended stability

A formulation destined to be freeze-dried usually has several different components. In addition to the active ingredient, there may be numerous excipients added in order to ensure that the product has good long term stability and functions as expected. When these components solidify during the freezing phase of the freeze-drying process, they take on a specific solid form that is characteristic of the material. When solids form during freezing they take on one of the following forms.

- ❖ crystalline: an extremely ordered system
- ❖ amorphous: a non-ordered system
- ❖ metastable: an amorphous system that should have formed a crystalline system
- ❖ lyotropic liquid crystal: some order to the system but behaves as amorphous

Each of these forms has a “critical temperature” associated with it when it melts and/or collapses. The samples must not be allowed to melt or collapse during freeze-drying or the product will be ruined. Keeping the product temperature too far below the critical temperature significantly increases the time it takes to freeze-dry, so finding this critical temperature is important. Two instruments typically used to accomplish this are.

- ➢ Differential Scanning Calorimetry (DSC)
- ➢ Freeze-Dry Microscopy (FDM)

These two techniques allow the development scientist to identify the existing forms (crystalline amorphous, etc.) along with the associated critical temperatures, including the glass transition temperature and eutectic melting temperature.

Development scientists can then use this information to design an optimized lyophilization cycle around their formulation. Since different drug products require distinct formulations,

each of which has different critical temperatures, each product will also require a custom lyophilization designed around it.

7. Inspection

After the product has been manufactured, tested by Quality Control (QC), and released by Quality Assurance (QA), it moves to Inspection. Inspectors look for defects in both the container (cracks, poor seals, etc.) and the product (particles, discoloration, etc.). Every vial of product must be individually inspected.

The three types of inspection include

1. manual inspection: human inspection (by hand) in a light box
2. semi-automated inspection: human inspection with the vials delivered on a conveyor
3. automated inspection: camera/computer inspection with the vials on a conveyor

EVALUATION

pH

pH is the measure of concentration of protons (H+) in a solution that is the potential of hydrogen. It is the identification of a substance how it is acidic or alkaline by using a scale of acidity from 0 to 14. More the acidic solutions having lower pH, and more alkaline solutions having higher pH values. pH value less than 7 are acids and pH of greater than 7 are alkaline. The neutral solutions that are the substances which are not acidic or alkaline have a pH value of 7.

Particulate matter

In injections and parenteral infusions particulate matter are considered as, the mobile undissolved particles, other than the gas bubbles, unintentionally that present in the solutions. There are two procedures involved in the determination of particulate matter.

Sub-visible particles

various oxides such as potassium, sodium, calcium, magnesium, aluminum, boron, and iron. Silicon oxide tetrahedron forms the basic structural network of glass. Boric oxide will enter into the basic structural network and the other oxides do not enter into this structure.[19]

Method 1 (light obscuration particle count test)

Method 2 (microscopic particle count test)

Injections and parenteral infusions are examined for sub visible particles usually method 1 is preferred mostly. Then also some preparations by light obscuration particle count test that followed by microscopic particle count test is necessary to test. No all parenteral are examined by method 1such as preparations that reduced clarity or increased viscosity, since these tests are carried out according to method 2. For example: colloids, emulsions. Particulate matter contamination is still having a potential cause to the harm patients.[19-21]

Sterility

Sterility testing is to identify the presence or absence of viable micro-organisms in the sample. 26 A. Immersion (Direct inoculation) It requires the test article to be inoculated directly into test media. 27 B. Membrane Filtration It requires the test article to pass through a size exclusion membrane which capable of retaining microorganisms. Filter should be rinsed. Then the membrane is transferred to the test medium.[19] Media types: mostly used Soya-bean casein digest (SCD) and Fluid thioglycollate media (FTM).[20-21] Incubation period: all test containers should incubate at temperatures as specified in the pharmacopoeial method, that is for each test media at least 14 days, depends on whether filtration or direct inoculation test is used.

Stability

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period. The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability testing also gives information about drug vulnerability to degrade by oxidation, hydrolysis, isomerization, polymerization, decarboxylation, moisture, heat and light. Stability study is performed for specific time at specific environmental condition according to ICH guideline.[21]

CONCLUSION

The most effective route for the delivery of the active pharmaceutical substances is the parenteral rout of administration, prescribed to unconscious patients. The present article describes that design, manufacturing of sterile products. Parenteral preparations are the pyrogens free liquids, which manufactured and stored accordingly to cGMP guidelines. An excellent parenteral product will require proper area, good environmental control and personnel observation, to attain their described therapeutic effect.

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