Overview

Development and Manufacturing of Injectable (Parenteral) Drug Products Unit

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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 years 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.

Types of Injectable Drug Products

Injectable drug products can be developed into several different types depending upon the characteristics of the drug, the desired onset of action of the drug, and the desired route of administration. The following presentations are typically used:

- injectable solution: a drug dissolved in water (or other solvent) that may include additives, known as excipients, to help stabilize it
- injectable suspension: drug crystals are not soluble in water, so the surface of the crystals are wetted to prevent them from floating on the solution surface; this is

typically accomplished using a surfactant; suspending agents are then added to prevent the crystals from settling to the bottom and forming a solid (concretion), which is difficult to re-suspend.

- injectable emulsion: a drug that is not soluble in water so it is dissolved in an oil, which is then added to water with an emulsifying agent; this is then mixed with a high shear mixer to reduce the oil droplets to micron-sized drops which remain in drops due to the emulsifying agent (surfactant)

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.

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.

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.

Stoppering

Once the vials have been filled, they travel down the filling line to have pre-sterilized stoppers inserted. If the product is not scheduled to be freeze-dried, a stopper is fully inserted into the neck of the vial and the vial is transported to the capping station. If the product is going to be freeze-dried, a special stopper with a vapor port is partially inserted into the neck of the vial. The freeze-drying process, described in more detail below, allows for the removal of water; the ice created during the freezing phase of the process is converted to water vapor, which leaves the product via the open port in the specialized lyophilization stopper. The difference between a standard serum stopper and a lyophilization stopper is illustrated in Figure 1.

Figure 1. (L—R) Standard serum and lyophilization stoppers

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 2. 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.

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.

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:

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

Labeling

Once the product is released from Inspection by Quality Assurance, it moves to Labeling. Labeling is performed in order to provide accurate information regarding the product and avoid

misrepresentation of the ingredients or effects of a drug, whether accidental or intentional. Stringent controls are placed on the printing and handling of labels in order to prevent errors. Both the label and the information on the label must be approved by the FDA, and each batch of labels to be used for a drug product must be inspected, approved, and released by QA before labeling begins.

Small batches of drug product may be labeled by hand, but in most cases labeling machines are used. The machines also inspect the labels and insure they are placed correctly and contain the correct information.

Packaging

After labeling, the product is packaged. Packaging includes a box or blister pack to hold the product and any associated materials (package inserts, swabs, needles, syringes, etc.). Once packing is complete and approved by QA, the product is shipped to the warehouse for storage.