Abstract – The aim of this article is to assess the technical aspects and activities related to the transfer of an injectable pharmaceutical product from development phase to production. 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 (for new products) or from one manufacturing site to another (for marketed products).

Index Terms – injectable products, technology transfer, process validation

I. INTRODUCTION

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, provide 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.

Process validation is part of technology transfer and is used to demonstrate that the manufacturing process developed, operated within established parameters, can consistently deliver the intended product. The evidence obtained from process validation activities proves to the competent authorities that the manufacturing process is under control and that the product obtained has the desired quality. Therefore, after approval, it can start to be routinely produced for commercial purposes, with confidence. Nevertheless, it is important to recognize that process validation is not an isolated event and should occur throughout the lifecycle of the product.

II. INJECTABLE PHARMACEUTICAL PRODUCTS

According to USP Chapter <1>, “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 Pharmacopeial 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.

The preparations intended for parenteral administration are available either as liquid (solutions, emulsions or suspensions) or solid products. These preparations contain one or more drug substances, also known as active pharmaceutical ingredients (API), and may contain appropriate excipients (vehicles and/or other substances).

A. 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.

The manufacture of injectable products should occur in clean areas, which should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency (HEPA filters). Injectable products are mandatory 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.

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.

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.

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.

Some aseptically processed products are subjected to an additional manufacturing operation known as lyophilization or freeze-drying. Lyophilization is a process in which water is removed from an aqueous liquid product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process is performed at low pressure and temperature (which makes it suitable for thermolabile products) and consists usually of the following three separate and interdependent phases: freezing (solidification of water), primary drying (sublimation of ice) and secondary drying (desorption of unfrozen water).

B. Labeling and Packaging

The term labelling corresponds to all labels and other written, printed or graphic items (e.g., insert) on an article's primary packaging container or on and in any package or wrapper in which it is enclosed (except any outer shipping container). The term label designates that part of the labelling on the primary packaging container.

A container closure system (or packaging system) refers to the sum of packaging components that together contain 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.

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 should be packaged in an appropriate container closure system, which should be suitable for its intended use. Suitability means that the packaging system provides the dosage form with adequate protection, is compatible with the dosage form, is composed of safe materials and allows a proper delivery of the drug product.

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., high-density polyethylene and polypropylene). 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, which are usually accompanied with aluminum seals.

III. PROCESS VALIDATION

Process validation is part of technology transfer and is used to demonstrate that the manufacturing process developed by R&D and transferred to industrial scale, operated within established parameters, can consistently yield a product meeting its specified quality attributes. It is important however
to recognize that process validation is not an isolated event. A lifecycle approach should be applied in order to link product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control throughout routine production.

Process validation activities can be divided in three stages: process design, process qualification and continued process verification.

A. Process Design

The aim of this stage is to design a process suitable for routine commercial production capable of consistently delivering a product with the desired quality. The data gathered during pharmaceutical development provide valuable information and should be considered to the process design stage.

The Quality Target Product Profile (QTPP) is related to clinical safety and efficacy of the drug product and is the basis for pharmaceutical product and process development and optimization. The QTPP is used as a starting point to establish the final Critical Quality Attributes (CQAs) of the product. According to ICH Guideline Q8(R2), “A CQA is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality”.

CQAs are attributes considered critical for the efficacy and safety of the product and, therefore, need to be controlled to ensure product quality.

Several activities can help to obtain process knowledge and understanding which is crucial to design an efficient process with an effective process control strategy. Design of Experiments (DOE) studies are useful to gain process knowledge by revealing relationships between the variable inputs (e.g., material attributes or process parameters) and the resulting outputs (e.g., in-process material, intermediates or finished product). The results of DOE studies can provide a rationale to determine the design space, by establishing ranges of incoming component quality, equipment parameters and in-process material quality attributes.

B. Process Qualification

The aim of process qualification is to evaluate the process design in order to determine if it is capable of consistent commercial production. This stage, which has to be successfully completed before commercial distribution of the product, has two elements 1. qualification of the equipment and utilities (such as water, steam and gases) and 2. process performance qualification (PPQ).

Qualification of utilities and equipment refers to activities performed to demonstrate that they are suitable for their intended use and perform properly. It includes the following activities: selection of utilities and equipment construction materials, operating principles and performance characteristics; installation qualification (IQ) and operational qualification (OQ).

The aim of process performance qualification (PPQ) is to confirm the process design and demonstrate that the manufacturing process intended for commercial production consistently performs as expected. The main documents for this stage of process validation are a PPQ protocol and a subsequent PPQ report. The PPQ protocol should specify the manufacturing conditions, controls, testing and expected results. The PPQ report should be prepared in a timely manner after the manufacture of the PPQ batches, in order to document and assess adherence to the PPQ protocol. A Master Batch Record, describing all the steps to be followed during the manufacture of the PPQ batches, is also an essential document.

C. Continued Process Verification

The intention of the third validation stage is to guarantee that the process remains in a state of control during routine commercial production. All information about the process performance previously gathered is essential to detect any unplanned deviations from the process and out of trend (OOT) or out of specification (OOS) product results. This is crucial to identify eventual problems and determine corrective or preventive actions to maintain the process in a state of control.

IV. RELATIONSHIP BETWEEN PROCESS VALIDATION, QUALITY RISK MANAGEMENT AND PHARMACEUTICAL QUALITY SYSTEM

The importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a useful component of an effective pharmaceutical quality system, which can and should be implemented throughout the different stages of a product lifecycle. The use of science and risk based approaches at each lifecycle stage promotes innovation and continual improvement and strengthen the relationship between pharmaceutical development, technology transfer and manufacturing activities.

A pharmaceutical company can face various types of risk. According to ICH guideline Q9, “risk is defined as the combination of the probability of occurrence of harm and the severity of that harm”. Quality risk management allows to assess the probability (occurrence), severity and detectability of the risk. Therefore, quality risk management is essential to an effective pharmaceutical quality system, since it can provide a scientific and practical approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual maintenance or improvement of process performance and product quality throughout the product lifecycle. Quality risk management has two main principles:

- The risk should be evaluated based on scientific knowledge and related to the safety of the patient;
- The level of detail and documentation of the quality risk management process should be commensurate with the level of risk.

Appropriate risk management tools can be applied to several aspects of pharmaceutical quality and different stages of the product lifecycle, in order to facilitate and improve science-based decision making regarding the risk. These tools
are extremely useful when applied as part of process validation (particularly during PPQ), due to the high amount of validation activities required. Risk management tools help to define the process and identify crucial areas and/or steps in that process, areas of risk and/or hazard and critical control points. Risk assessment is the first part of a risk management process and consists of risk identification, analysis and evaluation. It begins with a well-defined risk question or problem description. The results from the risk assessment often dictate the effort needed to reduce specific risks to acceptable levels and it helps to distinguish between critical and non-critical process steps and parameters, which facilitates the design of a process validation study.

V. TECHNOLOGY TRANSFER

Technology transfer involves transfer of product and process knowledge to achieve product realization. It includes all the activities required for successful progress from pharmaceutical development to production (for new products) or from one manufacturing site to another (for marketed products).

Several technical aspects need to be taken into consideration to allow proper evaluation and validation of the manufacturing process prior to start routine production of the product for commercial purposes. There are inputs, outputs and controls associated with each unit operation of a manufacturing process. A proper correlation between process inputs (material attributes and process parameters), their associated manufacturing controls and process outputs (quality attributes) is crucial for successful technology transfer. Inappropriate understanding regarding the relationship between process inputs and outputs and lack of efficient controls can result in a process not properly controlled. This may lead to extensive product losses, batch rejection, difficulties with regulatory submissions and, ultimately, preclude submission approval.

Identification of all unit operations and their associated equipment is crucial when selecting those parameters and attributes that are considered critical and, therefore, need to be controlled. All relevant information about the product and the process obtained during the development phase should also be properly reviewed and evaluated.

According to ICH Guideline Q8(R2), “A CPP is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality”. Therefore, it is crucial to identify and to determine the functional relationships that link CPPs and CMAs to product CQAs, in order to establish a proper control strategy, which can be simplified and improved by using a risk-based approach. The product quality attributes classified as CQAs usually include product appearance, assay and impurities, which are critical because they have the potential to be impacted by the formulation and/or manufacturing process variables. Bacterial endotoxins, product sterility and particulate matter are also considered to be CQAs for injectable pharmaceutical products. CQAs are generally ensured through a good pharmaceutical quality system and by implementing an effective control strategy.

A. Review of the drug product information

Information available about the drug product should be reviewed, including:

- drug product formulation;
- drug product specifications and characteristics;
- container closure system;
- proposed manufacturing process.

B. Validation of analytical methods and cleaning validation

Limit of detection, limit of quantification, precision and accuracy must be characterized for all analytical test methods. All methods should be properly validated prior to product and process characterization studies and the design and implementation of process controls. Any Microbiological method should be validated to confirm that the product does not influence the recovery of microorganisms.

Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Sufficient data from the verification should be available to support a conclusion that the equipment is clean and can be released for further use. Adequate cleaning procedures are essential to minimize the risk of contamination and cross-contamination (if the facility manufactures multiple products), operator exposure and environmental effects.

C. Materials and equipment preparation

The preparation of all materials and equipment to be used for the manufacturing process of an injectable product is critical in order to ensure the quality and quantity of the materials/components and to avoid contaminations during production. Crucial activities are: 1. washing and sterilization/depyrogenation of the container closure system components and 2. selection and weighing of the raw materials (API and excipients).

D. Compounding (preparation of the bulk solution)

For liquid parenteral solutions, compounding consists in the preparation of the bulk solution, following the defined formulation and compounding process. The API and the excipients are dissolved in a vehicle, which could be aqueous, normally water for injection, or an oil. The equipment used for compounding are jacketed compounding tanks equipped with mixers and temperature sensors. For some products sensitive to oxygen, other tank accessories are required like sparging elements for inert gas sparging and dissolved oxygen sensors. The sequence of addition of the raw materials, the mixing speeds and the mixing times used can influence the dissolution of each raw material and the homogeneity of the final bulk solution. The influence of the compounding process on the product quality should be evaluated and the process parameters used properly validated for each batch size. Ranges of mixing times and mixing speeds should be challenged to ensure that complete dissolution and homogenization occur. Usually, a range of mixing times and mixing speeds is established in the PPQ protocol for each compounding step.
based on the developmental experience as well as the current experience of the site with similar products, batch size and compounding tanks. This range is used as a reference and can be adjusted, if needed, during actual production of the PPQ batches to achieve proper dissolution or homogenization. At the end of the compounding process, samples from the top and bottom of the preparation tank are collected and tested to verify bulk solution homogeneity.

The selection of the tank to be used for each batch should be based on the product characteristics and process requirements. The compatibility of the material of construction with the bulk solution, the batch size and the compounding process controls should be taken into consideration for the tank selection.

E. Holding times

Maximum holding times have to be defined for each product/process according to the product sensitivity, the product compatibility with its contact materials during the manufacturing process and in order to avoid Bioburden growth. Different holding times may be established according to the characteristics of the product and the process.

F. Filtration

Filtration is the process by which particles are removed from the bulk solution by passing it through a porous material (filter). When the filtration process also removes microorganisms from the solution it is called sterilizing filtration. A sterilizing-grade filter has a 0.2 µm or smaller pore size. However, the classification of a filter by pore size has limited value and, therefore, this measurement has been replaced by defining the filter in terms of its bacterial retention. Typically, a sterilizing-grade filter is a filter that retains $10^7$ CFU of a standard test organism (e.g., Brevundimonas diminuta) per cm² of effective filtration area (EFA) under process conditions.

Several issues may be related to the filtration process, such as, product losses by adsorption to the filter, presence of leachables from the filter in the product and sterile filtration not being effective leading to an increase in bioburden and to a non-sterile final product. To assure sterility and to guarantee that the product quality is not negatively affected by the filtration process, the functionality of the filter should be demonstrated by the filter manufacturer and by the filter user (i.e., the pharmaceutical company responsible for the drug product manufacturing). Usually, qualification documentation provided by the filter manufacturer is used to support performance qualification conducted by the filter user as part of process validation, which is particularly critical for aseptically processed products. Sterile filtration validation includes several elements but is usually achieved by focusing on the following:

- **Bacterial retention** – The aim of the bacterial retention validation study (also known as bacterial challenge) is to have documented evidence demonstrating that the filtration process will consistently remove a high level of a standard test organism, suspended within the actual drug product or a surrogate fluid, under simulated worst-case process conditions of contact time, temperature, pressure and/or flow rate. Brevundimonas diminuta is the mainly used microorganism for bacterial challenge tests. Nevertheless, other bacteria can be used provided that they are small enough to challenge the retentive capability of the filter and that they simulate the smallest microorganism found in production. The size of the test organism should be confirmed by demonstrating passage through a 0.45 µm rated membrane as a positive control. When it is not possible to inoculate the challenge organism into the product due to its bactericidal activity, a surrogate fluid is used instead, which should match the product as closely as possible in terms of its physicochemical characteristics (e.g., viscosity, surface tension and pH), without adversely affecting the test organism.

- **Extractables/leachables** – Extractables are chemical compounds that can be extracted from product contacting surfaces when exposed to an appropriate solvent under exaggerated conditions. Extractables studies are usually conducted to ensure that the filter does not adversely affect the product, using model solvents that bracket the properties of pH, ionic strength and/or level of organic components of the actual drug product. These studies should be performed with the entire filter device under specific laboratory conditions that simulate worst-case process conditions of contact time, temperature and pre-treatment (e.g., sterilization of the filter). Leachables are compounds that migrate from the filter material in the presence of the actual product formulation under normal process operating conditions. The need for leachables testing should be assessed on a case-by-case basis by the filter user and, if applicable, potential leachables are identified and evaluated to ensure they do not compromise the product quality.

- **Compatibility** – Chemical compatibility between the filter and the product should include the entire device and depends on the fluid, filtration temperature and contact time. After product exposure, the filter should be subjected to a physical test to verify if the integrity of the filter had been compromised. Additionally, the filter should be visually inspected for any signs of discoloration, distortion or damage to ensure that no observable physical change occurred.

The filtration process may also have some influence on the assay and pH of the bulk product, which is typically evaluated during process performance qualification, as part of dead volume evaluation or filter conditioning. Dead volume or filter conditioning is translated in the amount of bulk solution that needs to be discarded prior to the start of filling in order to obtain a product within specifications. Typically, the evaluation involves the testing of the first units filled (dead volume), which should be sequentially numbered when they are collected, or the testing of a sample of bulk product collected immediately after the filter at determined contacted
times, in order to determine the amount of bulk solution to be rejected prior to the start of filling, if any. Dead volume and filter conditioning time evaluation is typically performed in the first PPQ batch manufactured, in order to establish an appropriate amount to be discarded in the subsequent produced batches.

The assay and pH of the first units filled may be affected by the filtration process, particularly in the case of online filtration (i.e., when filtration and filling occur simultaneously instead of the whole bulk solution being previously filtered to a holding tank). If steam sterilized filters are not properly dried prior to use, the first units filled may have lower assay results and/or higher pH due to the residual water that remained in the filtration assembly. The use of an inappropriate drying procedure is particularly critical for filters with a higher EFA, since a larger amount of water may remain in the filter. In this case, a high amount of product has to be discarded as part of initial set up activities (i.e., prior to start actually filling), which leads to excessive product losses. In order to avoid this situation, adequate drying procedures should be qualified and validated for each filter or, as an alternative, the use of gamma-irradiated filters may be considered.

G. Filling

Filling is the process of bringing the product in its final container. The effects of the filling process on the product quality should be evaluated by analyzing samples collected at different time points (usually, beginning, middle and end) considered representative of the whole filling process and after machine stoppages. The filling uniformity can be affected by the characteristics of the product, which may influence the dosing system (for instance, more viscous products can be more difficult to fill leading to fill volume discrepancies). Therefore, the filling process has to be validated to assure that the filling machine is accurate and that the pumps and needles used are adequate for each product. Usually, the filling pumps and needles are selected based on the fill volume and the physical characteristics of the product (particularly, viscosity).

The filling process is directly related to the filling line. If a product is produced in more than one filling line, the filling process should be validated in all of them. The effect of line stoppages on the product quality should be evaluated in order to assess eventual unintentional stoppages that might occur during the filling process (which may be particularly relevant in the case of products sensitive to oxygen and viscous products). A line stoppage with appropriate duration (e.g., one or two hours) is usually incorporated into the filling of one PPQ batch and the first units collected after the line stoppage are analyzed to evaluate its impact on the product quality. The duration of the line stoppage should be enough to allow proper intervention and resolution of eventual mechanical problems but without having an impact on the product quality.

H. Lyophilization (if applicable)

When a lyophilized product is to be manufactured, an appropriate lyophilization cycle should be developed. Cycle development is done during the R&D phase however adjustments in cycle times and parameters may occur when transferring from an R&D lyophilizer to an industrial lyophilizer. Therefore, manufacturing of engineering/test batches is advisable before production of the PPQ batches.

Lyophilization involves heat and mass transfer, which must be taken into consideration for process design and optimization, since these phenomena vary according to lyophilizer load condition (partial or full load), lyophilizer design and container closure system. Monitoring and control of CPPs, such as, shelf temperature and chamber pressure, is essential to achieve proper process control and to obtain a cake with the desired appearance and quality. Freeze drying is typically an expensive and time-consuming process. Therefore, it is usual to try to improve the process by reducing the cycle time, focusing particularly on optimization of the primary drying phase, which is the longest of all the three phases. Once a lyophilization cycle is developed and optimized, process performance qualification is performed as part of process validation in order to demonstrate that the lyophilization process allows obtaining a product within specifications. The uniformity and efficiency of the lyophilization process is evaluated by collecting samples from several positions of the lyophilizer, which are usually tested for cake appearance, reconstitution time and water content. Evaluation of the lyophilization process is important not only to assure uniform product quality within the batch but also from batch to batch.

I. Terminal sterilization (if applicable)

Terminal sterilization is a process whereby the product is sterilized within its final container. This process is typically used for heat-stable products and is usually accomplished by moist heat sterilization (in an autoclave). The efficacy of the sterilization process is dependent on heat exposure, number of microorganisms present in the load (bioburden) and heat resistance of those microorganisms. Sterilization must lead to a SAL \(^1\) of at least \(10^{-6}\) (less than one non-sterile unit per one million units). The determination of the sterilization method to be used for product sterilization (steam sterilization or aseptic filling) is done during R&D stage. Sterilization in the final container is the preferred sterilization method which is considered to provide a great assurance of sterility.

Two main design approaches are used for the development of moist heat sterilization cycles to be applied in pharmaceutical manufacturing: overkill approach or product-specific approach. Usually, the design approach is selected based on the thermal stability of the product and the materials to be sterilized. The overkill design approach requires less information on the bioburden of the items to be sterilized than the product-specific design approach. A greater heat input is required, which has a greater potential to degrade the product and materials subject to sterilization. Therefore, this approach is normally employed to products and materials that can withstand high heat without affecting their quality. On the

\(^1\) Sterility Assurance Level expresses the probability of occurrence of a non-sterile unit after exposure to a sterilization process.
other hand, the product-specific design approach requires a greater amount of information regarding the items to be sterilized, the indicator organisms (the test organisms shown to be most resistant to the sterilization process) and the bioburden levels than the overkill approach. Gathering all this information provides confidence in the values determined in development to use a lower thermal input than required for the overkill design approach. This is advantageous for the terminal sterilization of products that cannot withstand the higher temperatures required for the overkill approach, which provides greater stability and potentially increases the shelf-life of these products.

The terminal sterilization process should be properly qualified in order to ensure that it consistently meets the design criteria determined for the cycle. Qualification must include both physical and biological qualification. Biological qualification demonstrates, by use of biological indicators, that the required lethality is achieved consistently through the load, which is measured in terms of actual kill of microorganisms. The most common microorganism used as a biological indicator is Geobacillus stearothermophilus due to its high heat resistance but other resistant bacteria may be acceptable. Nevertheless, the biological indicator selected should contain a higher population and resistance than the expected product bioburden and only spores should be used as microbiological challenges. Physical qualification demonstrates that predetermined physical requirements, including sterilization temperature and time, minimum F$_0$ and minimum exposure time, are achieved consistently from load to load.

Physical attributes of the drug product, such as, container size, fill volume, mass and physical configuration may affect temperature distribution, heat penetration and microbiological inactivation. Therefore, it is crucial that temperature distribution and heat penetration studies are performed for each sterilization process and load pattern (number of containers per tray and number of trays in the load). Adequate operational parameters must be established for the sterilization process to ensure that the required physical and biological lethality are achieved while maintaining integrity of the container closure system and product quality. These parameters consist of a set point and an operating range, which should be carefully evaluated since the lower end of the range can affect the sterilization process efficacy and the upper end may affect the product stability.

J. Inspection

All finished product batches should be 100% inspected in order to verify the level of rejects due to particles and/or defects (liquid products are inspected for particles and defects while lyophilized products are only inspected for defects). The inspection results can be used to specify a tentative rejection rate and they are extremely useful if properly evaluated since the rejected units might be related to the process or to the product itself. When a particular type of particle or defect appears often, an investigation should be conducted in order to understand if it is associated with any issue related to the process or to the product formulation. Once the root cause is identified, proper corrective measures can be established in order to decrease the number of defective units.

Finished product units should be also subjected to non-destructive leak testing, in order to confirm the integrity of the container closure system. One of the most commonly used methods is high voltage leak detection, which ensures product seal integrity by identifying small pinholes, cracks and seal imperfections that cannot be detected by visual inspection.

K. Scale-up and scale-down considerations

When there is the intention to change the validated batch size of a certain product, several aspects need to be taken into consideration to evaluate its feasibility. Both scale-up or scale-down can be considered for existing products, usually due to changes in market demand or line transfer.

For new products, scale-up can be done based on submission batches of a specific product manufactured in a specific line. Adopting a systematic approach might be useful to determine the proposed scale-up batch size based on pilot-scale batches previously manufactured for submission or process validation purposes, for instance, by schematizing all data available in a table.

L. Stability studies

After manufacturing, samples from all process validation batches should be placed in stability chambers. The purpose of stability studies is to provide evidence on how the quality of a drug product varies with time under the influence of different environmental factors (e.g., temperature and humidity) and to establish a proposed shelf-life or confirm the shelf-life for the drug product and the recommended storage conditions.

The design of the stability studies for the drug product should be based on knowledge of the characteristics of the drug substance, from stability studies on the drug substance and on experience gained from earlier phases of pharmaceutical development. Generally, a drug product should be evaluated under storage conditions that test its thermal stability and its sensitivity to moisture or potential for solvent loss, if applicable. Data from stability studies should be provided on at least three batches of the drug product, which should have exactly the same formulation, packaged in the same container closure system and produced using the same manufacturing process as proposed for commercial batches. Preferably, all batches used for process validation purposes should enter stability studies.

Specific types of stability studies may be performed on at least one batch of the drug product, such as, photostability and freeze thaw studies. The photostability characteristics of new drug products should be evaluated to demonstrate that light exposure does not result in unacceptable change. This evaluation should allow to clearly define if the product is photostable or photolabile. If the results of the study are equivocal, testing of one or two additional batches should be

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2 F$_0$ is the number of equivalent minutes of steam sterilization at a temperature of 121°C delivered to a unit of product. This is calculated using a z-value of 10°C. If, for instance, a cycle has a stated F$_0$ of 8 minutes, then the sterilization effectiveness of that cycle is equivalent to 8 minutes at 121°C.
conducted. Usually, photostability studies are carried out in a sequential manner starting with testing the directly exposed drug product and, afterwards, continuing as necessary to the product in the primary packaging and then in the secondary packaging. This evaluation should progress until the results demonstrate that the drug product is adequately protected from light exposure. Freeze thaw studies are performed to predict the impact of temperature excursions on the drug product quality during the transportation / distribution process. These studies are done by placing samples of the drug product at extreme temperatures (i.e., samples are exposed at freezing temperatures followed by exposure at accelerated storage conditions) to evaluate if the product is stable after cycles of temperature excursions.

A stability protocol needs to be issued for each drug product. The stability protocol defines the number of samples needed, the storage conditions to be followed, the sample storage orientation (upright or inverted), the testing points, the tests to be performed and the drug product shelf-life specifications. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are expected to influence quality, safety and/or efficacy. Several stability chambers with different storage conditions of temperature and relative humidity can be used to perform these studies, according to the container closure system, product storage conditions and the climatic conditions of the target markets.

VI. CONCLUSION

All pharmaceutical products undergo several stages prior to start being routinely manufactured for commercial purposes. During pharmaceutical development, the product and the related manufacturing process are designed in order to deliver the intended performance and meet the needs of patients and healthcare professionals and regulatory authorities’ requirements.

Once a product and a process are developed, several technical aspects need to be evaluated and numerous activities need to be performed to ensure that the process performs reproducibly and consistently delivers a product with the desired quality. Technology transfer follows pharmaceutical development and involves transfer of product and process knowledge to achieve product realization. It includes all the activities required for successful progress from pharmaceutical development (R&D) to production (for new products) or from one manufacturing site to another (for marketed products).

Process validation is part of technology transfer and is used to demonstrate that the manufacturing process developed, operated within established parameters, can consistently deliver the intended product. A proper correlation between process inputs (CMAs and CPPs), their associated manufacturing controls and process outputs (CQAs) is crucial to successful process validation. Since there are several inputs, outputs and controls associated with each manufacturing operation, a systematic approach that emphasizes product and process understanding, based on quality risk management, is crucial to identify and to evaluate the process validation activities to be performed during technology transfer.

Nevertheless, it is important to recognize that process validation is not an isolated event and should occur throughout the lifecycle of the product, in order to assure that the manufacturing process is continuously in a state of control and delivering consistently a product with the desired quality.

VII. FUTURE PERSPECTIVES

The manufacture of injectable pharmaceutical products is particularly complex and each manufacturing unit operation should be properly validated and controlled in order to assure obtaining a sterile drug product. Any scientific / technological advancement should be considered as an opportunity to ease and improve the process.

PAT is an advanced strategy that is extremely useful to provide a higher degree of process control, since it allow real-time monitoring and control to adjust the processing conditions so that the output remains constant. However, PAT tools are not being as extensively used as they could. Probably, in a near future, these tools will start to be more and more used in the pharmaceutical industry, both for process validation activities and routine process control.

The tendency should be to decrease sampling and off-line testing, which slows the manufacture and validation activities of pharmaceutical products, particularly injectable products (which are complex per se). Additionally, PAT can be used to ease and accelerate batch release, which ultimately leads to a product entering the market much more quickly, which can represent an advantage over other pharmaceutical companies that do not apply this technology.

REFERENCES


[35] D. Lewis, "Current FDA perspective on Leachable Impurities in Parenteral and Ophthalmic Drug


