GUIDE TO INSPECTIONS OF STERILE DRUG SUBSTANCE MANUFACTURERS

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One of the more difficult processes to inspect and one which has presented considerable problems over the years is that of the manufacture of sterile bulk drug substances. Within the past several years, there have been a number of batches of sterile bulk drug substances from different manufacturers which exhibited microbiological contamination. One manufacturer had approximately 100 batches contaminated in a 6 month time period. Another had approximately 25 batches contaminated in a similar period. Other manufacturers have had recalls due to the lack of assurance of sterility. Although the Inspection Guide for Bulk Drug Substances provides some direction for the inspection of the sterile bulk drug substance, it does not provide the detailed direction needed.

I. INTRODUCTION

In the manufacture of the sterile bulk powders, it is important to recognize that there is no further processing of the finished sterile bulk powder to remove contaminants or impurities such as particulates, endotoxins and degradants.

As with other inspections, any rejected batches, along with the various reasons for rejection, should be identified early in the inspection to provide direction for the investigator. For example, lists of batches rejected and/or retested over a period of time should be obtained from the manufacturer to provide direction for coverage to be given to specific processes or systems. Because some of the actual sterile bulk operations may not be seen, and because of the complexity of the process, it is particularly important to review reports and summaries, such as validation studies, reject lists, Environmental Monitoring Summary Reports, QA Investigation Logs, etc. These systems and others are discussed in the Basic Inspection Guide. This is particularly important for the foreign sterile bulk drug substance manufacturer where time is limited.

In the preparation for a sterile bulk drug substance inspection, a flow chart with the major processing steps should be obtained. Generally, the manufacture of a sterile bulk substance usually includes the following steps:

1. Conversion of the non-sterile drug substance to the sterile form by dissolving in a solvent, sterilization of the solution by filtration and collection in a sterilized reactor (crystallizer).

2. Aseptic precipitation or crystallization of the sterile drug substance in the sterile reactor.

3. Aseptic isolation of the sterile substance by centrifugation or filtration.

4. Aseptic drying, milling and blending of the sterile substance.

5. Aseptic sampling and packaging the drug substance.

These operations should be performed in closed systems, with minimal operator handling. Any aseptic operations performed by an operator(s) other than in a closed system should be identified and carefully reviewed.

II. COMPONENTS

In addition to the impurity concerns for the manufacture of bulk drug substances, there is a concern with endotoxins in the manufacture of the sterile bulk drug substances. The validation report, which demonstrates the removal, if present, of endotoxins to acceptable levels, should be reviewed. Some manufacturers have commented that since an organic solvent is typically used for the conversion of the non-sterile bulk drug substance to the sterile bulk drug substance, that endotoxins will be reduced at this stage. As with any operation, this may or may not be correct. For example, in an inspection of a manufacturer who conducted extensive studies of the conversion (crystallization) of the non-sterile substance to the sterile drug substance, they found no change from the initial endotoxin level. Organic solvents were used in this conversion. Thus, it is important to review and assess this aspect of the validation report.

In the validation of this conversion (non-sterile to sterile) from an endotoxin perspective, challenge studies can be carried out on a laboratory or pilot scale to determine the efficiency of the step. Once it is established that the process will result in acceptable endotoxin levels, some monitoring of the production batches would be appropriate. As with any validation process, the purpose and efficiency of each step should be evaluated. For example, if the conversion (crystallization) from the non-sterile to the sterile substance is to reduce endotoxins by one log, then data should support this step.

Since endotoxins may not be uniformly distributed, it is also important to monitor the bioburden of the non-sterile substance(s) being sterilized. For example, gram negative contaminats in a non-sterile bulk drug substance prior to sterilization are of concern, particularly if the sterilization (filtration) and crystallization steps do not reduce the endotoxins to acceptable levels. Therefore, microbiological, as well as endotoxin data on the critical components and operational steps should be reviewed.

III. FACILITY

Facility design for the aseptic processing of sterile bulk drug substances should have the same design features as an SVP aseptic processing facility. These would include temperature, humidity and pressure control. Because sterile bulk aseptic facilities are usually larger, problems with pressure differentials and sanitization have been encountered. For example, a manufacturer was found to have the gowning area under greater pressure than the adjacent aseptic areas. The need to remove solvent vapors may also impact on area pressurization.

Unnecessary equipment and/or equipment that cannot be adequately sanitized, such as wooden skids and forklift trucks, should be identified. Inquire about the movement of large quantities of sterile drug substance and the location of pass-through areas between the sterile core and non-sterile areas. Observe these areas, review environmental monitoring results and sanitization procedures.

The CGMP Regulations prohibit the use of asbestos filters in the final filtration of solutions. At present, it would be difficult for a manufacturer to justify the use of asbestos filters for filtration of air or solutions. Inquire about the use of asbestos filters.

Facilities used for the charge or addition of non-sterile components, such as the non-sterile drug substance, should be similar to those used for the compounding of parenteral solutions prior to sterilization. The concern is soluble extraneous contaminants, including endotoxins, that may be carried through the process. Observe this area and review the environmental controls and specifications to determine the viable and non-viable particulate levels allowed in this area.

IV. PROCESSING

Sterile powders are usually produced by dissolving the non-sterile substance or reactants in an organic

solvent and then filtering the solution through a sterilizing filter. After filtration, the sterile bulk material is separated from the solvent by crystallization or precipitation. Other methods include dissolution in an aqueous solution, filtration sterilization and separation by crystallization/filtration. Aqueous solutions can also be sterile filtered and spray dried or lyophilized.

In the handling of aqueous solutions, prior to solvent evaporation (either by spray drying or lyophilization), check the adequacy of the system and controls to minimize endotoxin contamination. In some instances, piping systems for aqueous solutions have been shown to be the source of endotoxin contamination in sterile powders. There should be a print available of the piping system. Trace the actual piping, compare it with the print and assure that there are no "dead legs" in the system.

The validation data for the filtration (sterilization) process should also be reviewed. Determine the firm's criteria for selection of the filter and the frequency of changing filters. Determine if the firm knows the bioburden and examine their procedures for integrity testing filters.

Filters might not be changed after each batch is sterilized. Determine if there is data to justify the integrity of the filters for the time periods utilized and that "grow through" has not occurred.

In the spray drying of sterile powders, there are some concerns. These include the sterilization of the spray dryer, the source of air and its quality, the chamber temperatures and the particle residence or contact time. In some cases, charring and product degradation have been found for small portions of a batch.

With regard to bulk lyophilization, concerns include air classification and aseptic barriers for loading and unloading the unit, partial meltback, uneven freezing and heat transfer throughout the powder bed, and the additional aseptic manipulations required to break up the large cake. For bulk lyophilization, unlike other sterile bulk operations, media challenges can be performed. At this point in time, with today's level of technology, it would seem that it would be difficult to justify the bulk lyophilization of sterile powders (from a microbiological aspect). Refer to the Guide for the Inspection of a Lyophilization Process for additional direction regarding this process.

Seek to determine the number and frequency of process changes made to a specific process or step. This can be an indicator of a problem experienced in a number of batches. A number of changes in a short period of time can be an indicator that the firm is experiencing problems. Review the Process Change SOP and the log for process changes, including the reason for such changes.

V. EQUIPMENT

Equipment used in the processing of sterile bulk drug substances should be sterile and capable of being sterilized. This includes the crystallizer, centrifuge and dryer. The sanitization, rather than sterilization of this equipment, is unacceptable. Sterilization procedures and the validation of the sterilization of suspect pieces of equipment and transfer lines should be reviewed.

The method of choice for the sterilization of equipment and transfer lines is saturated clean steam under pressure. In the validation of the sterilization of equipment and of transfer systems, Biological Indicators (BIs), as well as temperature sensors (Thermocouple (TC) or Resistance Thermal Device (RTD)) should be strategically located in cold spots where condensate may accumulate. These include the point of steam injection and steam discharge, as well as cold spots, which are usually low spots. For example, in a recent inspection, a manufacturer utilized a Sterilize-In-Place (SIP) system and only monitored the temperature at the point of discharge and not in low spots in the system where condensate can accumulate.

The use of formaldehyde is a much less desirable method of sterilization of equipment. It is not used in the United States, primarily because of residue levels in both the environment and in the product. A major problem with formaldehyde is its removal from piping and surfaces. In the inspection of a facility utilizing formaldehyde as a sterilant, pay particular attention to the validation of the cleaning process. The indirect testing of product or drug substance to demonstrate the absence of formaldehyde levels in a system is unacceptable. As discussed in the Cleaning Validation Guide, there should be some direct measure or determination of the absence of formaldehyde. Since contamination in a system and in a substance is not going to be uniform, merely testing the substance as a means of validating the absence of formaldehyde is unacceptable. Key surfaces should be sampled directly for residual formaldehyde.

One large foreign drug substance manufacturer, after formaldehyde sterilization of the system, had to reject the initial batches coming through the system because of formaldehyde contamination. Unfortunately, they relied on end product testing of the product and not on direct sampling to determine the absence of formaldehyde residues on equipment.

SIP systems for the bulk drug substance industry require considerable maintenance, and their malfunction has directly led to considerable product contamination and recall. The corrosive nature of the sterilant, whether it is clean steam, formaldehyde, peroxide or ethylene oxide, has caused problems with gaskets and seals. In two cases, inadequate operating procedures have led to even weld failure. For example, tower or pond water was inadvertently allowed to remain in a jacket and was valved shut. Clean steam applied to the tank resulted in pressure as high as 1,000 lbs., causing pinhole formation and contamination. Review the equipment maintenance logs. Review non-schedule equipment maintenance and the possible impact on product quality. Identify those suspect batches manufactured and released prior to the repair of the equipment.

Another potential problem with SIP systems is condensate removal from the environment. Condensate and excessive moisture can result in increased humidity and increases in levels of microorganisms on surfaces of equipment. Therefore, it is particularly important to review environmental monitoring after sterilization of the system.

The sterile bulk industry, as the non-sterile bulk industry, typically manufactures batches on a campaign basis. While this may be efficient with regard to system sterilization, it can present problems when a batch is found contaminated in the middle of a campaign. Frequently, all batches processed in a campaign in which a contaminated batch is identified are suspect. Review the failure investigation reports and the logic for the release of any batches in a campaign. Some of the more significant recalls have occurred because of the failure of a manufacturer to conclusively identify and isolate the source of a contaminant.

VI. ENVIRONMENTAL

MONITORING

The environmental monitoring program for the sterile bulk drug substance manufacturer should be similar to the programs employed by the SVP industry. This includes the daily use of surface plates and the monitoring of personnel. As with the SVP industry, alert or action limits should be established and appropriate follow-up action taken when they are reached.

There are some bulk drug substance manufacturers that utilize UV lights in operating areas. Such lights are of limited value. They may mask a contaminant on a settling or aerobic plate. They may even contribute to the generation of a resistant (flora) organism. Thus, the use of Rodac or surface plates will provide more information on levels of contamination.

There are some manufacturers that set alert/action levels on averages of plates. For the sampling of critical surfaces, such as operators' gloves, the average of results on plates is unacceptable. The primary concern is any incidence of objectionable levels of contamination that may result in a non-sterile product.

As previously discussed, it is not unusual to see the highest level of contamination on the surfaces of equipment shortly after systems are steamed. If this occurs, the cause is usually the inadequate removal of condensate.

Since processing of the sterile bulk drug substance usually occurs around the clock, monitoring surfaces and personnel during the second and third shifts should be routine.

In the management of a sterile bulk operation, periodic (weekly/monthly/quarterly) summary reports of environmental monitoring are generated. Review these reports to obtain those situations in which alert/action limits were exceeded. Review the firm's investigation report and the disposition of batches processed when objectionable environmental conditions existed.

VII. VALIDATION

The validation of the sterilization of some of the equipment and delivery systems and the validation of the process from an endotoxin perspective have been discussed.

In addition to these parameters, demonstration of the adequacy of the process to control other physicochemical aspects should also be addressed in a validation report. Depending upon the particular substance, these include potency, impurities, particulate matter, particle size, solvent residues, moisture content, and blend uniformity. For example, if the bulk substance is a blend of two active substances or an active substance and excipient, then there should be some discussion/evaluation of the process for assuring uniformity. The process validation report for such a blend would include documentation for the evaluation and assurance of uniformity. A list of validation reports and process variables evaluated should be reviewed.

As with a non-sterile bulk drug substance, there should be an impurity profile and specific, validated analytical methods. Those should also be reviewed.

Manufacturers are expected to validate the aseptic processing of sterile BPCs. Such validation must encompass all parts, phases, steps, and activities of any process where components, fluid pathways, in-process fluids, etc., are expected to remain sterile. Furthermore, such validation must include all probable potentials for loss of sterility as a result of processing. Validation must also account for all potential avenues of microbial ingress associated with the routine use of the process.

The validation procedure should approximate as closely as possible all those processing steps, activities, conditions, and characteristics that may have a bearing on the possibility of microbial ingress into the system during routine production. In this regard, it is essential that validation runs are as representative aspossible of routine production to ensure that the results obtained from validation are generalizable to routine production.

Validation must include the 100% assessment of sterility of an appropriate material that is subjected to the validation procedure. Culture media is the material of choice. whenever feasible. Where not feasible, non-media alternatives would be acceptable. Where necessary, different materials can be used in series for different phases of a composite aseptic process incapable of accommodating a single material. In any event, some material simulating the sterile BPC, or the sterile BPC itself, must pass through the entire system that is intended to be sterile. Any material used for process validation must be microbiologically inert.

Environmental and personnel monitoring must be performed during validation, in a manner and amount sufficient to establish appropriate monitoring limits for routine production.

At least three consecutive, successful validation runs are necessary before an aseptic process can be considered to be validated.

Alternative proposals for the validation of the aseptic processing of bulk pharmaceuticals will be considered by FDA on a case-by-case basis. For example, it may be acceptable to exclude from the aseptic processing validation procedure certain stages of the post-sterilization bulk process that take place in a totally closed system. Such closed systems should be sterilized in place by a validated procedure, integrity tested for each lot, and should not be subject to any intrusions whereby there may be the likelihood of microbial ingress. Suitable continuous system pressurization would be considered an appropriate means for ensuring system integrity.

VIII. WATER FOR INJECTION

Although water may not be a component of the sterile drug substance, water that comes in contact with the equipment or that enters into the reaction can be a source of impurities (e.g., endotoxins). Therefore, only water for injection should be utilized.

Some manufacturers have attempted to utilize marginal systems, such as single pass Reverse Osmosis (RO) systems. For example, a foreign drug substance manufacturer was using a single pass RO system with post RO sterilizing filters to minimize microbiological contamination. This system was found to be unacceptable. RO filters are not absolute and should therefore be in series. Also, the use of sterilizing filters in a Water for Injection system to mask a microbiological (endotoxin) problem has also been unacceptable. As with environmental monitoring, periodic reports should be reviewed.

If any questionable conditions are found, refer to the Inspection Guide for High Purity Water Systems.

IX. TERMINAL STERILIZATION

There are some manufacturers who sterilize bulk powders after processing, by the use of ethylene oxide or dry heat. Some sterile bulk powders can withstand the lengthy times and high temperatures necessary for dry heat sterilization. In the process validation for a dry heat cycle for a sterile powder, important aspects that should be reviewed include: heat penetration and heat distribution, times, temperatures, stability (in relation to the amount of heat received), and particulates.

With regard to ethylene oxide, a substantial part of the sterile bulk drug industry has discontinued the use of ethylene oxide as a "sterilizing" agent. Because of employee safety considerations, ethylene oxide residues in product and the inability to validate ethylene oxide sterilization, its use is on the decline. As a primary means of sterilization, its utilization is questionable because of lack of assurance of penetration into the crystal core of a sterile powder.

Ethylene oxide has also been utilized in the treatment of sterile powders. Its principal use has been for surface sterilization of powders as a precaution against potential microbiological contamination of the sterile powder during aseptic handling.

There are some manufacturers of ophthalmics that continue to use it as a sterilant for the drug used in the formulation of sterile ophthalmic ointments and suspensions. If used as a primary sterilant, validation data should be reviewed. Refer to the Inspection Guide for Topical Products for further discussion.

X. REWORK/REPROCESSING/

RECLAMATION

As with the principal manufacturing process, reprocessing procedures should also be validated. Additionally, these procedures must be approved in filings.

Review reprocessed batches and data that were used to validate the process. Detailed investigation reports, including the description, cause, and corrective action should be available for the batch to be reprocessed.

XI. LABORATORY TESTING

AND SPECIFICATIONS

The sterility testing of sterile bulk substances should be observed. Additionally, any examples of initial sterility test failures should be investigated. The release of a batch, particularly of a sterile bulk drug substance, which fails an initial sterility test and passes a retest is very difficult to justify. Refer to the Microbiological Guide and Laboratory Guide for additional direction.

Particulate matter is another major concern with sterile powders. Specifications for particulate matter should be tighter than the compendial limits established for sterile dosage forms. The subsequent handling, transfer and filling of sterile powders increases the level of particulates. It is also important to identify particulates so that their source can be determined. Review the firm's program for performing particulate matter testing. If there are no official limits established, review their release criteria for particulates, and the basis of their limit.

With regard to residues, since some sterile powders are crystallized out of organic solvents, low levels of these solvents may be unavoidable. In addition to evaluation of the process to assure that minimal levels are established, data used by the firm to establish a residue level should be reviewed. Obviously, each batch should be tested for conformance with the residue specification. Refer to the Inspection Guide for Bulk Drug Substances for additional direction regarding limits for impurities.

XII. PACKAGING

Sterile bulk drug substances are filled into different type containers which include sterile plastic bags and sterile cans. With regard to sterile bags, sterilization by irradiation is the method of choice because of the absence of residues. There are some manufacturers, particularly foreign, which utilize formaldehyde. A major disadvantage is that formaldehyde residues may and frequently do appear in the sterile drug substance. Consequently, we have reservations about the acceptability of the use of formaldehyde for, container sterilization because of the possibility of product contamination with formaldehyde residues.

If multiple sterile bags are used, operations should be performed in aseptic processing areas. Since the dosage form manufacturer expects all inner bags to be sterile, outer bags should be applied over the primary bag containing the sterile drug in an aseptic processing area. One large manufacturer of a sterile powder only applied the immediate or primary bag in an aseptic processing area. Thus, the outer portion of this primary bag was contaminated when the other bags were applied over this bag in non-sterile processing areas.

With regard to sterile cans, a concern is particulates, which can be generated due to banging and movement. Because of some with trace quantities of aluminum, companies have moved to stainless

steel cans.

The firm's validation data for the packaging system should be reviewed. Important aspects of the sterile bag system include residues, pinholes, foreign matter (particulates), sterility and endotoxins. Important aspects of the rigid container systems include moisture, particulates and sterility.