Every person involved in pharmaceutical product manufacturing has the responsibility to assure the quality of the product being produced. The aim of this paper is to validate quality assurance throughout the process of manufacturing pharmaceutical products. Additionally, within aseptic manufacturing, certain monitoring and information needs to be collected on a routine basis to continually assess the state of control of the complete operation. The basis for assessing the state of control is to have rigorous and defined information flow processes. Once the information is collected, quality assurance involves the ability to assess, evaluate, and make appropriate decisions to ensure the product has the required safety, identity, strength, quality, and purity. Quality assurance study is the process of bringing all of the information together, evaluating the information, making decisions, refining systems, and applying process knowledge. This process begins in the early stages of drug development when not a lot of specific process information about the process is known, but it is important to allow for development to progress, building knowledge about process. However, even in early development, sterility assurance requirements should be largely the same at all stages of development and routine commercial manufacturing.

Key words: Validation study / How to avoid / Contamination / Pharmaceutical products.

INTRODUCTION

Quality assurance is important in the pharmaceutical industry. Those involved in pharmaceutical product manufacturing must strictly follow carefully established and validated methods of preparation and procedures. Quality assurance needs to be built into the operations and process and not just be emphasized in the end-product testing. Quality must be applied to facilities, preparation of materials, and to all aspects of processing.

Key quality systems and key aspects of those quality systems as they apply to aseptic processing will be discussed in this paper. In general, all operating conditions and treatment of materials should be such as to prevent microbial contamination and follow a proven control strategy (Quality Assurance of Pharmaceuticals, 2007). The output from the control systems of the operating conditions and treatment of materials should then be assessed as part of the lot disposition process.

To maintain the sterility of the components and the product during aseptic processing, the control strategy needs to include the following factors: environment, personnel, critical surfaces, container/closure sterilization and transfer procedures, maximum holding period of the product before filling into the final container, and sterilizing processes (Quality Assurance of Pharmaceuticals, 2007).

In general, two basic areas can be defined: physical assets and process systems. Systems to collect and track information are needed in these two basic areas to ensure sterility assurance. Physical assets include facilities, equipment, and utilities (e.g., air handling systems, compressed air, nitrogen, steam generator, and water). The process systems include key points in the quality systems such as training, material management, calibrations, validations, processes, batch records, investigations, a quality control laboratory, environmental monitoring, cleaning equipment/facilities,
and quality information management. The role of quality assurance in product development for an aspect process will be briefly presented.

The output from the control systems for routine monitoring of the physical assets (not in use and during production), coupled with the output from the process systems associated with the production batch, should be included in the quality information management system for assessing the status of each lot produced by aseptic processing.

**PHYSICAL ASSETS**

The physical assets should be designed to support the specific type of production and to reduce the chance for contamination of the product. This paper focuses on quality aspects of physical assets related to design preferences and control. Quality assurance plays a key role in physical assets in its alignment with operations and provides guidance for design, systems for monitoring, change control, and qualifying. Also, operations and quality assurance must be considered together to resolve investigations related to the physical assets.

**Facilities**

For aseptic processing, the facility layout should control the flow of materials and personnel with respect to the environment quality needed for the stage of processing. For example, the facility should have a room classifications from lower to higher as the process flows toward aseptic requirements. Air locks should be used to separate the transfer of materials and the flow of personnel into the critical aseptic processing areas to prevent the chance of contamination.

The construction materials for the production areas should be chosen for durability to allow for frequent cleaning/sanitizing. In clean areas, all exposed surfaces should be smooth, impervious, and unbroken to minimize the shedding or accumulation of particles or microorganisms (Eudralex Volume 4, EU Guidelines to Good Manufacturing Practice, 2008). The wall and room designs should have not areas that collect dust or cause difficulties for cleaning. Examples of adequate design features included seamless and rounded floor to wall junctions as well as readily accessible corners. Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination (FDA, 2004). False ceilings should be sealed to prevent contamination from the space above them. Sinks and drains should not be located in areas used for aseptic manufacture.

In quality control microbiology, the sterility testing area should have an environment of the same or better quality as the aseptic processing area. This is done to minimize the potential of false positives during testing.

The facility should be routinely inspected for the need for wall, floor, and ceiling repairs. These inspections should be documented and repairs performed promptly to keep the facilities in a good state of control to prevent the chance of product contamination. In general, the facility should be inspected before each batch and thoroughly inspected and repaired at defined frequencies (e.g., every 6 months). These inspections and repairs proactively keep the facilities in good working order to prevent contamination of the product.

Clean area control parameters should be supported by microbiological and particle data obtained during qualification studies. Initial clean room qualification should include an assessment of air quality under as-

**TABLE 1. Air Classifications**

| Clean area classification | ISO designation<sup>a</sup> | >0.5µm particles/m<sup>3</sup> | Microbiological active air settling action level<sup>b</sup> (CFU/m<sup>3</sup>) | Microbiological plates action level<sup>c</sup> (diam. 90 mm; CFU/4 h) |
|--------------------------|-----------------------------|-----------------------------|---------------------------------|---------------------------------|
| 100                      | 5                           | 3,520                       | 1<sup>d</sup>                   | 1<sup>d</sup>                   |
| 1,000                    | 6                           | 35,200                      | 7                               | 3                               |
| 10,000                   | 7                           | 352,000                     | 10                              | 5                               |
| 100,000                  | 8                           | 3,520,000                   | 100                             | 50                              |

All classifications are based on data measured in the vicinity of exposed materials/articles during periods of activity.

<sup>a</sup>ISO 14644-1 designations provide uniform particle concentration values for clean rooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU grade A. <sup>b</sup>Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels because of the nature of the operation or method of analysis.

<sup>c</sup>The additional use of settling plates is optional.

<sup>d</sup>Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

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built, static conditions and dynamic conditions. It is important for area qualification and classification to place the greatest emphasis on data generated under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing). Table 1 summarizes clean area classifications and recommended action levels of microbiological quality (ISO 14644-1).

The facility should be designed to meet room classifications appropriate for each stage of manufacturing. The facility is of great importance for maintaining appropriate environmental conditions to protect the product from contamination for routine aseptic manufacturing. The facility needs to be properly maintained, monitored, and used for the intended purpose.

**Equipment**

Aseptic processing equipment should be appropriately designed to facilitate ease of sterilization (Code of US Federal Regulations Part 21). Equipment should be designed to be easily assembled and disassembled, cleaned, sanitized, and/or sterilized. Fixed equipment (e.g., large mixing tanks) should be properly designed with attention to features such as accessibility to the sterilizing agent, piping slope, and proper condensate removal. Additionally, the effect of equipment design on the clean room environment should be addressed. For example, horizontal surfaces or ledges that accumulate particles should be avoided. Equipment should not obstruct airflow and, in critical areas, its design should not disturb unidirectional airflow (FDA, 2004).

In the aseptic processing area, smoke studies should be used to verify unidirectional airflow. Videotaping smoke studies provide thorough evidence showing airflow patterns. If changes to equipment or facilities are needed, airflow patterns need to be carefully assessed and recorded.

Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product. Ideally, product contact surfaces should be disposable or made of materials that are solely to be used in conjunction with the product (e.g., 316 stainless steel). In a multiproduct facility, key product contact surfaces should be dedicated to a product. For instance, filling needles should either be disposable or dedicated for sole use with regard to a product. This is done to prevent the chance of cross-contamination.

Adequate cleaning, drying, and storage of equipment will aid in controlling bioburden and prevent the influence of endotoxin load. If adequate procedures are not used, endotoxins can be introduced into the process by the equipment (FDA, 2004, Kevin, 2007). Records should be kept showing cleaning schedules and the performance of the cleaning procedures.

Equipment surfaces that contact a sterilized drug product, or its sterilized containers or closures, must be sterile so as not to alter the purity of the drug (Code of US Federal Regulations Part 21). Where reasonable contamination potential exists, surfaces that are in the vicinity of the sterile product should also be clean and free of microorganisms. It is important that the validation of cleaning procedures show the removal of microorganisms, the processing materials, and the cleaning agents.

Monitoring devices should be used whenever feasible. Equipment monitoring provides proof that the equipment functioned properly during use. The output from the monitoring devices should be recorded to provide assurance for the proper performance of the equipment during manufacturing.

Records need to be kept for equipment showing routine and nonroutine maintenance, usage, and calibration of monitoring devices. If the equipment does not operate within intended limits, an investigation should be performed.

**Utilities**

Utilities for an aseptic processing facility should be designed to prevent contamination.

Utilities actually bring processing materials into contact with the product. These materials should be sterilized. For example, the compressed air system may introduce air into a lyophilizer before the product is stoppered. Thus, the air becomes the headspace of the product vial. Quality aspects will be illustrated for the following utilities: air systems (heating, ventilating, and air conditioning:HVAC), the compressed air system, nitrogen gas supply, water, and steam generator.

**HVAC**

The main purpose for the HVAC system is to provide clean air into the processing areas. The HVAC system needs to be designed to deliver particulate-and microbial-free air. Most systems contain prefilters with > 95% efficiency filters with terminal or final filters > 99.9% efficiency (HEP A). In the aseptic areas, HVAC systems should deliver single-pass air. Therefore, the system should not recirculate air and the air supply should consist of 100% fresh makeup air. This is done to prevent cross-contamination.

The HVAC system should be capable of keeping the processing areas very cool for operator comfort.
Typically the cleanroom environment should be around <18°C and <60% RH. The main reason for this type of temperature and humidity control is to keep the operators, who are generally double gowned, comfortable and free from perspiration to decrease shedding.

Monitoring systems should target continuous monitoring for temperature, humidity and pressure differentials across filters and pressure differentials between rooms. The continuous monitoring should have appropriate ranges of values. If conditions fall outside of the set ranges, an investigation should be triggered with an assessment of the impact on the product.

**Compressed Air System**

Like the HVAC system, the compressed air system should be designed to provide essentially a source for sterile air. The air system should be monitored at frequencies to show that air is delivered free from contaminates like microorganisms and hydrocarbons. At use-points that come into contact with the product terminal, sterile filters should be used. These filters should be tested for integrity. Records should be maintained for the proper routine performance and lot performance of the air system.

**Nitrogen Gas**

Nitrogen gas is often used during the production process to control equipment and sometimes used to produce an environment free from oxygen. The nitrogen gas supply should be tested for identity and moisture. Often a plant may use a bulk liquid nitrogen tank coupled with evaporators to supply nitrogen gas. In these systems, each charge of the bulk nitrogen tank should be tested at a minimum for identity. If by accident the wrong liquid were to be loaded into the bulk tank, this could cause major damage to the nitrogen system and contaminate the production facility. The nitrogen system needs to be routinely monitored for performance. Routine and nonroutine maintenance should be documented. Additionally, at key locations throughout the nitrogen system, point-of-use sterilizing filters should be used and the integrity tested.

**Water**

From the perspective of quality, the water system should be monitored before use to ensure that the appropriate quality of water is used during processing. Ideally, the water system should be continuously monitored for key parameters like pressure, temperature, conductivity, and total organic carbon. Additionally, the water system should be sampled throughout at key points in the system and points of use. Records need to be kept for routine and nonroutine maintenance. To ensure the proper control of the water system, the monitoring data should be analyzed for trends, and reviewed routinely. During the course of monitoring a water system, limits that raise alerts and set action into motion need to be established. If a limit is exceeded, an appropriate action/investigation should be performed.

**Steam Generator**

Steam systems should be supplied with clean water that is free from hydrocarbons, salts, and microorganisms, ideally, water-for-injection (WFI) quality. The steam quality needs to be routinely tested throughout the distribution system and at key points of use. Like the other utility systems, records should be kept for the maintenance and performance of the steam generator.

**QUALITY SYSTEM**

Quality assurance needs to remain proactive in aseptic processing by providing guidance to operations for developing systems. A proactive quality system for aseptic processing has rigorous monitoring, evaluation, and response/corrective action components. In proactive quality, the right systems are in place to react before major problems happen. The monitoring aspects of the quality system should be evaluated for trends and reviewed frequently by quality and operations management. The quality of the output from the physical assets and quality systems for each batch manufactured should be evaluated and assessed. Components of the process system that are discussed below include the following: training, material management, calibration, validation, process, batch records, investigations, quality control laboratories, environmental monitoring, cleaning equipment/facility, and quality information management.

**Training**

Each employee has a responsibility to the company to ensure records and training activities are current. All regulations delineate requirements for the training and qualifications of personnel. For example, 21 CFR 211.25 (a) states that “Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions.” (Code of US Federal Regulations Part 21). Training shall be in the particular operations that the employee performs and in current good manufacturing practice on an ongoing basis.

Another point about training that extends to each employee is contained in 21 CFR 211.2S(a), stating that “Personnel engaged in the manufacture,
processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination” (Code of US Federal Regulations Part 21). Additionally, 21 CFR 211.2S(b) states that “Personnel shall practice good sanitation and health habits” (Code of US Federal Regulations Part 21). These types of regulations are particularly important for aseptic manufacturing to protect the product from contamination from the employees.

A well-designed, maintained, and operated aseptic process minimizes personnel intervention (e.g., isolator or barrier use). As operator activities increase in an aseptic processing operation, the risk to the finished product sterility also increases. To ensure product sterility, it is critical for operators involved in aseptic activities to use aseptic technique at all times.

Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, clean room behavior, microbiology, hygiene, gowning, patient safety hazards posed by a nonsterile drug product, and the specific written procedures covering aseptic manufacturing area operations.

After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator’s conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations. Some of the techniques aimed at maintaining appropriate levels of sterility assurance include the following:

1. Contact sterile materials only with sterile instruments
2. Move slowly and deliberately
3. Keep the entire body out of the path of unidirectional airflow
4. Approach a necessary manipulation in a manner that does not compromise sterility the of the product
5. Maintain proper gown control

Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas. Training activities should be clearly documented in records for each employee.

**Material Management**

Attention in material management is required with respect to aseptic processing. The main focus for material management is to always ensure that the integrity of the material delivered to the aseptic process has not been compromised. When materials are received the condition of the containers should be carefully inspected for damage or any possible breach of container integrity. The materials should be placed into a state of quarantine until they can be released by confirmation of their quality according to specifications/procedures.

Samples for release testing need to be carefully removed under aseptic conditions to prevent any possible chance of contamination of the material during the sampling procedure. The sampling needs to be performed in an environment of the same or better classification under which the material will be processed. The material needs to be delivered to the production areas in a controlled manner to prevent any possible chance of mix-up or contamination. Records need to show complete accountability, traceability, and handling of the material.

**Calibrations**

Careful attention must be paid to calibrations on monitoring devices for equipment and facilities. The calibration devices should be routinely reviewed and the information recorded. Monitoring devices are integral for documenting the performance of the process in relation to sterility assurance.

Monitoring devices need to be calibrated to tolerances that allow for reliable accuracy over the monitoring range of measurement. For example, a thermocouple should not be calibrated with a tolerance of ±2°C if the accuracy of the measurement needs to be ±0.1°C. Also, the calibration should span the range of measurement that the monitoring device will routinely record.

Records need to be kept for monitoring devices. The records need to clearly show calibration results as well as any adjustments made to and maintenance done on the device. Monitoring devices should be routinely verified before use in manufacturing. For example, a balance should be checked for accuracy by weighing a check weight and recording the results. If a device exceeds tolerance valves, corrective actions should be taken. Also, an assessment should be documented for the impact of the out-of-tolerance device has had on the facility and processes.

**Validations**

From a quality perspective, validations should be done on facilities, utilities, and equipment. For aseptic manufacturing, validations need to clearly show that the item will routinely perform in a way needed to assure
product integrity.

As mentioned previously, it should be proven that facilities provide an environment suitable for the specific type of manufacturing. Typical parameters for validation of facilities are temperature, relative humidity, pressure differentials, and particulate matter (viable and nonviable).

Equipment validation should thoroughly confirm that the performance is appropriate for the process/product. Standard equipment should be subject to the traditional validation plan of the supplier regarding installation qualification, operational qualification, and performance qualification. The qualification process should prove that the monitoring and control aspects of the equipment are suitable and in a state of control for the process.

Custom designed equipment should be subject to validation plan that ensures the equipment is designed correctly for the intended use. An approach for customized equipment involves design qualification, factory acceptance testing, installation qualification, operational qualification, and performance qualification. Equipment should be requalified on a routine basis defined by procedures or when significant changes are made.

Sterilizing equipment cycles should be validated as to the specific load or cycle to support the process. Additionally, sterilizing cycles need to be routinely revalidated, and if a change occurs to the equipment or the utilities, revalidation should be considered.

**Process**

Process validation in aseptic manufacturing has two key aspects involving whether the process can reliably manufacture product and maintain sterility. Validation should prove that following the parameters outlined in a control strategy, the process can manufacture a product that has the safety, identity, strength, quality, and purity required. The reliability of the manufacturing process traditionally is shown from three validation lots.

To ensure the effectiveness of product sterilization, aseptic filling and closing operations must be adequately validated (Code of US Federal Regulations Part 21). The goal of even the most effective sterilization processes can be defeated if the sterilized elements of a product (the drug formulation, the container, and the closure) are brought together under conditions that contaminate any of those elements and attain SAL of $10^{-6}$.

An aseptic processing operation should be validated using media fill, a microbiological growth medium in place of the product. Normally a media fill test includes exposing microbiological growth medium to surfaces of the equipment in contact with the product, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo during the manufacturing process. The sealed containers filled with the medium are then incubated to detect microbial contamination. Results are then assessed for the potential of a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, and closing). Environmental monitoring data from the process simulation can also provide useful information for the processing line evaluation.

A media fill program should incorporate the contamination risk factors that occur in a production line and accurately assesses the state of process control. Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations. Media fill programs should address applicable issues such as:

1. Run time
2. Representative interventions, routine and nonroutine
3. Lyophilization, when applicable
4. Aseptic assembly of equipment
5. Number of personnel and their activities
6. Representative number of aseptic additions or transfers
7. Shift changes, breaks, and gown changes (when applicable)
8. Type of aseptic equipment disconnections/connections
9. Aseptic sample collections
10. Line speed and configuration
11. Weight checks
12. Typical environmental conditions
13. Run size
14. Container closure systems

A batch record should be followed for media fill studies. Additionally, documentation should be created that notes production conditions, operations, and simulated activities. A video recording can be very useful during media fills. The recording can be used as a record of the event and referred to during training exercises.

In general, a microbiological growth medium, such as soybean casein digest medium, should be used. Use of anaerobic growth media (e.g., fluid thioglycollate medium) should be considered in special circumstances when a nitrogen environment is required for the process. The media selected should be demonstrated to promote growth of gram-positive and gram-negative bacteria, yeast, and mold. The QC laboratory should determine if indicator organisms sufficiently represent production-related isolates. Environmental monitoring and sterility test isolates can
be substituted (as appropriate) or added to the growth promotion challenge.

The records from the media fill study should be carefully reviewed in the same way a production batch record would be reviewed. If any aberrant result is observed, an investigation should be initiated.

**Batch Records**

Batch records are the basic production record. Batch records should provide clear directions to execute the process as well as be the collection point for appropriate information throughout the process. The batch record should have adequate information and verification of all collected information to reliably produce the desired product. During aseptic manufacturing, output from the environment, facility, equipment, and personnel should be collected. This output should be assessed and compared to proven limits.

During the production run, if any value is collected and is outside of set ranges, this aberrant value should be investigated. The investigation needs to be referenced in the batch record. Any aspect of aseptic manufacturing should be investigated and assessed for its impact on the product before the lot disposition decision is made.

Following the compilation of the batch record, it is typically peer reviewed by a lead operator. Once the peer review is completed, the manufacturing authority needs to review the record for completeness and accuracy. Any questions or comments should be resolved by the operators. Following the manufacturing review, quality control personnel should review the record and verify that all collected data meets the control strategy requirements.

**Investigations**

In quality assurance, investigations need to be approached from a science and risk-management perspective. Investigations tend to be a huge learning opportunity in terms of conducting most operations. The focus of an investigation should be on science and risk to generate an understanding of root causes and formulate a corrective and preventive action. Basically, when an aberrant result/trend is observed or a nonroutine event occurs, an investigation should take place to understand, learn, and make corrections.

In aseptic manufacturing, an investigation should be done when any aberrant result is obtained or an unexpected event takes place involving physical assets and/or from process systems.

The initial part of the investigation should assess what lots are impacted by the aberrant result and hold all lots in question until the investigation results are fully understood and appropriate corrective actions are taken. In general, investigations usually take the following steps:

1. Discovery of an investigational situation
2. Confirmation of the need for an investigation
3. Notification of the investigation to hold the product and operations
4. Clearly record the cause/reason for the investigation
5. Information collection
6. Formation of hypothesis for why the aberrant result was obtained
7. Conformational testing of hypothesis
8. Validate hypothesis
9. Assess impact to product
10. Formulate corrective action
11. Test corrective action
12. Implement corrective action

The basic concept of the investigation process is to follow the scientific model and learn more about the process/facility capabilities and to formulate a decision on the initial aberrant result or unexpected event.

**Quality Control Laboratories**

Regulations generally state that the quality control unit has the authority to approve or reject all components and materials used in processing and products produced. 21 CPR 211.22 (a) states that: There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

The quality control laboratory needs to have the same level of control as the manufacturing operations. The laboratory should be able to perform testing and provide very accurate results. The laboratory systems should be able to collect, store, and handle samples without compromising the integrity of the sample or having any mix-ups. Production operational points should be applied to the operations of the quality control laboratory (Table 2).

As shown in Table 2, many of the operational concepts about manufacturing apply to the quality control laboratory. The focus may be slightly different in that in operations focus is on product while the laboratory focus is on the test result. However, the concepts are comparable and when working together allow for the production of a quality product.
H. SHINTANI

Environmental Monitoring

In aseptic processing, one of the most important concerns in laboratory control is the environmental monitoring program. This program provides key information on the state of control of the aseptic processing environment during operations as well as the steady routine state. Environmental monitoring may be able to identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs.

Evaluating the quality of air and surfaces in the clean room environment should start with a well-defined written program and scientifically sound methods. All environmental monitoring locations should be described in procedures with sufficient detail to allow for reproducible sampling of a given location surveyed. Procedures should also address elements such as the following:

1) Frequency of sampling
2) When the samples are taken (i.e., during or at the conclusion of operations)
3) Duration of sampling
4) Sample size (e.g., surface area, air volume)
5) Specific sampling equipment and techniques
6) Alert and action levels
7) Appropriate response to deviations from alert or action levels.

The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures. Locations that present the most microbiological risk to the product need to be a key part of the program. Data should be collected to ensure that the microbiological quality of the critical areas shows whether or not aseptic conditions are maintained during filling and closing activities.

Environmental monitoring data needs to be analyzed for trends. From a practical point of view, if the data show all zero values then a review of sampling and testing needs to occur. If the data show more positive values in an area, a review of the cleaning procedures needs to occur. In a robust sampling and environmental monitoring program the data will show positives in a more random fashion. However, in the aseptic areas (ISO 5), the data should confirm the required

| Environmental Monitoring | Operations | Quality control laboratory |
|---------------------------|------------|----------------------------|
| Training                  | Employees need appropriate training and experience to perform assigned responsibilities | Same |
| Material management       | Materials are handled to ensure appropriate integrity is maintained and to prevent mix-ups | Samples are handled to ensure their integrity, storage, and traceability in laboratory systems |
| Calibration/validation    | An appropriate level of control of production equipment and monitoring devices must be shown | Laboratory equipment need to be treated in a way to ensure reliability of results |
| Process                   | The operations to produce a sterile drug product | The activities to produce reliable test results |
| Records                   | Batch records provide directions and a point of collection for all process information | Test records are kept to provide accuracy for testing |
| Investigations            | Focus is on the process performance And the product | Focus is on the method performance and test results |
| Environment               | Production environment needs to be clean, monitored, and kept in a way so as not to contaminate the product | The laboratory environment needs to have appropriate conditions to ensure samples can be handled without causing contamination |
| Equipment                 | Clean, maintained, calibrated/qualified | Same |

**TABLE 2**. Comparison of Aspects of Operations with Those of the Quality Control Laboratory
VALIDATION TO AVOID CONTAMINATION

conditions.

The collective output from the environmental monitoring program needs to be carefully evaluated on a routine basis. Additionally, environmental monitoring data should be assessed during the routine manufacturing of one batch.

Cleaning Equipment/Facilities

Cleaning and sterilizing are important activities for aseptic manufacturing. Equipment cleaning procedures should be validated and routinely verified. Critical product contact surfaces need to be sterilized before being used in the manufacturing process. Some key points to consider from a quality perspective of an aseptic cleaning validation program are the following:

1) Training of operators
2) Sampling methods to account for process materials and microorganisms
3) Sanitizing agent contact times should be confirmed for effectiveness (e.g., do a small study on samples of process surfaces spiked with known levels of microorganisms and use agent for the contact time to verify the absence of microorganisms)
4) Equipment/material hold times before use
5) Transfer and setup of equipment

Ideally, whenever possible in aseptic processing, disposable or single-use critical product contact items should be used. If disposable items cannot be used, then dedicated to a certain equipment use should be used to protect the product from cross-contamination. If such equipment cannot be used, then the importance of a rigorous cleaning validation and verification plan is extremely critical.

It should be verified that the equipment and facilities have been cleaned and are within the allowable hold times before use. This information should be recorded in the batch records.

Quality Information Management

The principle philosophy of quality information management begins early in product development. The combination of ICH QS, Q9, and Q10 has provided a road map of key features of information management and how the organization should use that information (ICH, 2006a; ICH, 2006b; ICH, 2007a; ICH, 2007b). Early in product development, the design space for processing parameters should start being developed. As the procedure goes through the development process, refinements are made and knowledge is gained. This information needs to be collected and used to develop the design space and process control strategy.

For aseptic processing, key elements of the control strategy and process knowledge are the following:

1) Process hold times
2) Product contact surfaces
3) Container closure assurance
4) Confirmation of material handling
5) Sterilization/sanitization procedures of equipment
6) Equipment hold times
7) Sterilization cycles
8) Equipment normal operating parameters
9) Confirmation of sterility assurance for the process
10) Product interactions with filters and process surfaces

Once the control strategy is set, information should be collected for each batch. The information should be compared with the past information collected. If any parameter is outside of the normal operating ranges for the process, an investigation should be commenced to understand why the aberrant result was obtained.

At a set frequency, the information collected according to the control strategy should be reviewed. This information needs to be evaluated for trends over a number of batches. Ranges should be assessed for applicability to the aspects of the process related to quality control. Related or repeated events should be assessed and corrective and preventive actions should be done to minimize reoccurrence.

Quality information management systems may include the following:

1) Building Management System
2) Laboratory Information Management Systems
3) Document Information Management Systems
4) Equipment Information Management Systems for calibration and validation
5) Batch Records
6) Deviations and Investigation
7) Material Management Systems

A key aspect of the information management systems is change control. The systems need to evolve as more knowledge and information is gained about the process and systems. During the change control process, a key concern is the impact the change will have on the process, as well as on the aseptic processing. Any impact to aseptic processing needs to be carefully assessed and tested to ensure the appropriate sterility assurance levels (SALs) are maintained throughout the process (SAL of 10^-6).

The fundamental point of quality information management is that information is to be collected and this information is used to assess the state of control of the entire process. This is the fundamental philosophy behind quality assurance science. Each batch should be assessed with regard to the entire information set collected, about the physical assets and process systems outputs.
QUALITY ASSURANCE ROLE IN PRODUCT DEVELOPMENT

Quality assurance has an important role in product development. Decisions about lots must be able to be made on the basis of the information available about the process with regard to quality considerations. In early development, when the drug under development has only been manufactured once or twice, a lot may not be known about the process. For aseptic processing, facility and process controls also apply and must be in place so that batch results and process observations represent the specific product/process for which little is known at the outset.

Guidelines from health authorities have been developed to help refine the approach to clinical manufacturing (Good Manufacturing Practices, 2003; FDA, 2008). Quality specialists need to draw upon all their experience and provide input to the development team about paths forward when issues occur during manufacturing. As the process is developed, quality specialists can play a key role to the development team by helping with the management of the information collected. This information can be used to help define the design space for the process. Once the process is close to becoming commercial, a control strategy should be prepared. The control strategy should define all monitoring and control parameters for the process.

It is important in product development when the product must be manufactured by aseptic techniques that sterility assurance aspects be the same across all phases of development. The difficulty in the early stages of manufacturing a drug that has just been developed is the lack of process experience. If the drug has only been made once or twice, the development team needs to use its experience and knowledge to make decisions.

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