Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

AN ANATOMY OF A CONTAMINATION CONTROL STRATEGY FOR STERILE MANUFACTURING

INTRODUCTION

A contamination control strategy is a system that considers all the integral elements of pharmaceutical product manufacturing (1). This is best achieved using quality risk management principles and supporting risk assessments for contamination control and monitoring (detectability of contamination event) (2).

An effective strategy, depending on the type of pharmaceutical product being manufactured, considers (3, 4):

- Microbial contamination
- Sterility assurance
- Facility design
- Chemical contamination
- Particle contamination (visible and sub-visible)
- Viral control
- Other forms of contamination that can arise from mix-ups, damaging primary or secondary packaging, distribution problems, and environmental fluctuations.

It is recognized that any contamination control strategy represents a cyclical process, designed to prompt the manufacturers to identify and resolve risk, and hence one that requires periodic review and update. While contamination control strategies are foremost discussed in relation to sterile manufacturing, most of the elements are applicable to non-sterile processing as well.

Manufacturers of sterile pharmaceutical products are required to have a contamination control strategy, as required by Annex 1 of EU GMP. Such a strategy is also in keeping with the FDA Aseptic Filling Guidance. According to EU GMP Annex 1 (draft, 2020) (5):

> *"Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.*
>
> *Risk assessments should be used to justify alternative approaches to those specified in the Annex only if these alternative approaches meet or surpass the intent of this Annex.*
>
> *A contamination control strategy should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed.*
>
> *The strategy should consider all aspects of contamination control and its life cycle with ongoing and periodic review and update of the strategy as appropriate."*

Such an approach is also in keeping with FDA guidances, albeit in terms that are not so explicitly stated (6).

Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

Contamination control is also supported by the overall Pharmaceutical Quality System (PQS) The PQS clarifies the expectations for an effective quality system which includes ensuring that the organization has sufficient knowledge and expertise in relation to the products they are manufacturing and that decisions are documented.

A robust Contamination Control Strategy is based on three components (7, 8):

- Manufacturing control strategy: based on product type, demand, process, and risk.
- Quality control strategy: based on an understanding of risk with control of critical quality attributes in a manufacturing process meeting regulatory requirements.
- Contamination control strategy: including cross contamination control that may include requirements for containment / product segregation.

This article, in considering the key features and components, presents an anatomy of a contamination control strategy. This primarily in relation to sterile manufacturing (although there will no doubt be elements of interest to non-sterile manufacturers). The aim is to provide a framework that can be used by pharmaceutical and healthcare organizations for benchmarking purposes.

CORE PRINCIPLE

The core principle for contamination control is control. Control is achieved through a series of measures, which will include:

1. Quality by Design with Quality Risk Management: This encompasses contamination control by design via technical control measures that are applied based on science and knowledge of process and risks.
2. Organizational Control Measures: The organization of operations, as defined in the Pharmaceutical Quality System, should follow Quality Risk Management principles together with procedural control (through SOPs) and associated risks taking account of human factors.

It is important to understand the product and process in enough detail to be able to effectively assess the hazards to product quality from contamination and ensure control measures are in place which proactively mitigate the risk of the product becoming contaminated.

Once control is established, systems are in place to detect contamination events. This will include environmental monitoring systems and assessment of other forms of contamination. Central to this is trend analysis. Within EU GMP Annex 1 ‘Principle’, it is stated that a functioning contamination control strategy (CCS) will act as a 'health check' on the control and monitoring functions. In interpreting this, it is important to recognize that to collect data on the status of manufacturing operations is not enough; there is an expectation that responsible departments evaluate these data and look for trends that could be an indication of the beginning of a loss of control and, more importantly, to prevent the control breakdown from happening.

As part of the periodic review of the control strategy, the review of trend data should inform as to the development of the CCS, making this document a ‘living document’ that adjusts as required, including describing any risk mitigations. Assessing quality metrics and the reasons behind deviations can signal things that require assessing and putting into a future version of the CCS (9).

The concept of the ‘living’ document is captured in figure 1:

Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

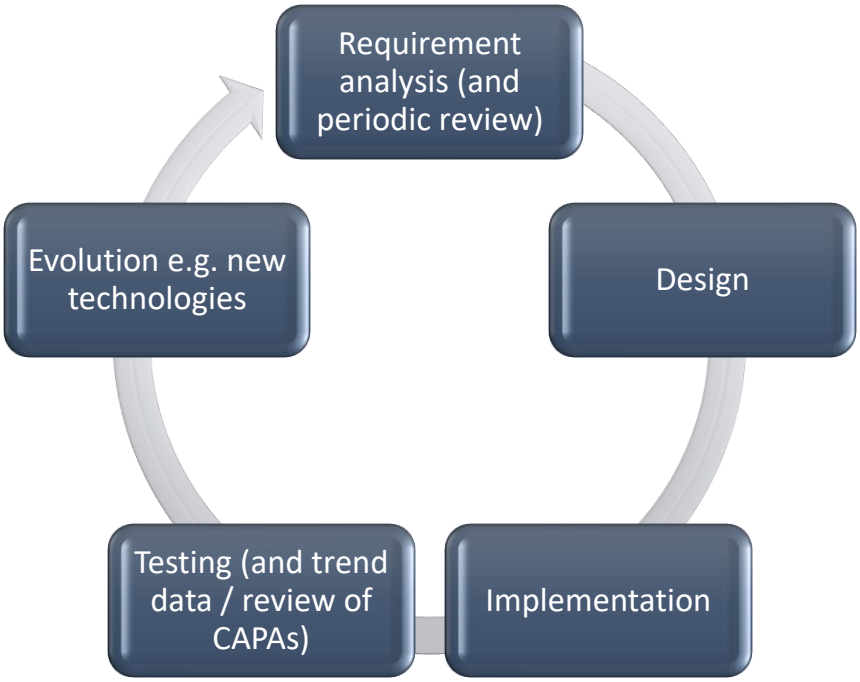

Figure 1: Contamination control lifecycle (adapted from Pharmig Irish Conference, May 2019)

As well as being an evolving document, Johnson and Hansy state that the CCS also needs to contain proactive and reactive elements (10). Proactive aspects include linking the CCS to the organization's quality culture, running proactive risk assessments, and embedding continuous improvements. Reactive elements include having pre-planned guidances for contamination events and a corrective and preventive action system to help address contamination issues.

CONTROL MEASURES

The underlying requirement of the CCS is with understanding the product and process in enough detail to be able to effectively assess the hazards to product quality from contamination and ensure control measures are in place which proactively mitigate the risk of the product becoming contaminated.

This is achieved through a series of measures:

1. Effective design, qualification and validation of the facility and equipment in conjunction.
2. During manufacture of the product having systems in place to monitor and trend the performance of the process.
3. Ensuring systems are in place investigate process deviations which may impact product quality using a documented system of risk assessment. Pertinent findings from deviations should feed back into the CCS.
4. To have in place a risk assessment process in order to correct and prevent contamination deviations occurring (either for the first time or again). Ideally there will be in place a formal risk assessment for each process step. This means, beginning with the start of the manufacturing process, capturing sterile processing, through to capping and packaging. Under Good Distribution Practice, risk assessments extend to the point where the recipient receives the product (of particular concern here is packaging and container closure integrity).

Once the CCS is implemented it needs to be maintained regularly and may become part of the periodic product quality review to confirm that any changes to any part of the process have been implemented in accordance with the CCS and GMP.

Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

Sterile Manufacturing

A CCS is especially important for sterile manufacturing, and especially for aseptic manufacturing. The objective of a contamination control strategy, for aseptically filled products, is sterility assurance and the production of a sterile product (a product devoid of viable microorganisms). This is because:

- With aseptic processing the imperative is to prevent microbial ingress.
- A statistical assurance cannot be provided.
- The manufacturer is heavily reliant upon a good contamination control strategy.

Sterility assurance is a holistic concept, concerning the wider embracement of the aspects of GMP which are designed to protect the product from contamination at all stages of manufacturing (from in-coming raw materials through to finished products) and thus it forms an integral part of the quality assurance system.

DETAIL OF THE CONTROL MEASURES

The various control measures required are examined and expanded upon below, under relevant sections.

Control Of Premises

Central to the control of premises is the cleanroom(or alternative controlled environment for some types of non-sterile manufacturing). Cleanrooms should be designed to meet the requirements of ISO 14644 (11). The focus should be on the technical aspects of cleanroom design and operation including the use of barrier technology, transfer of people / materials cleanroom, cleaning and disinfection and demonstrating that the maintenance of suitable environmental conditions during qualification of the cleanroom. Including:

Facility Design

The important aspects of facility designed that need to be reviewed under the CCS are:

- Cleanroom design
- Cleanroom specification
- Contamination cascade

Which requires:

- The air supply to the cleanroom is justified and linked to the control measures for achieving the required environmental conditions for manufacturing.
- Supply of filtered air, maintenance of positive pressure to adjacent rooms of different grades (minimum of 10 pascals) and effective monitoring and warning systems in the event of a failure or reduction in pressure differentials between cleanrooms/ isolators.
- Use of airflow visualization throughout the document to verify that the air flow within the cleanroom prevents the ingress of particles and operates to protect the product.
- Establishing the environmental monitoring program, with reference to airflow.
- Cleanrooms need to be suitably qualified to demonstrate the effective control of the environment including viable and non-viable particle monitoring filter integrity testing, air flow visualization as well as physical parameters like temperature and humidity monitoring.
- Cleanrooms are classified in terms of the measurement of non-viable particle monitoring, as per ISO14644.
- An assessment is performed for critical locations in both the at rest and in operational state.

- Minimum test requirements for requalification must be met: Including airflow volume, non-viable counts, air pressure measurements and integrity testing of filters.
- Scheduled test frequencies for requalification are appropriate.
- 'For cause' requalification must be defined, for example after a major change within the cleanroom.

The CCS should recognize the need to control human interventions in Restricted Access Barrier Systems (RABS) or with isolators. This is because people are the major source of microbial contamination.

Process Flows

Contamination control measures need to be designed into each part of the production process and should include the use of contamination controls such as cleaning, decontamination, sterilization and transfer methods for primary packaging materials, consumables and intermediate product that reduce the contamination risks as far as is possible. Arguably, the implementation of a contamination control strategy should start with a risk assessment for the identification and assessment of all contamination risks present in a facility and/or process that may contribute microbiological, particulate, chemical and cross product contamination to a finished medicinal product (12).

Product, personnel, material, and process flows should be outlined, and risk assessed. To do so requires an understanding and controlling the potential routes of contamination through the facility for material and personnel transfer. There should be in place:

- The need to understand product and process requirements
- The use of risk base approaches. The principal risks in product manufacturing that should be subjected to risk assessment.
- The concept of "Good Engineering Practice"
- The role of aseptic processing as mechanism for producing sterile products, if applicable.
- Management of flow and movement of people and materials through the facility
- Understanding the principles of open and closed processed and how they affect the specification of the surrounding controlled environment
- Selection of appropriate facility materials and finishes
- Whether the manufacturing process is by batch or campaign and how 'change-overs' will be controlled.
- The specified process, equipment used and how process steps are to be integrated to form a defined process design/ flow.
- The target end points for manufacturing stages.
- The extent of automation required to meet manufacturing control requirements and how the operators will interact with the process.
- How the facility/ utilities and process equipment will combine to meet manufacturing control targets.
- The country-specific regulatory requirements that applies to the given product/ process.
- The segregation of personnel and materials.
- Defined and controlled transfer of personnel through Grade D to B areas.
- There should be separate routes of entry and exit in relation to the final change areas.
- All materials need to be on an approved list.
- Transfer to Grade A/B through transfer hatches protected by effective flushing with filtered air.
- Where practicable, that materials entering the aseptic areas should be sterilized using autoclaves, depyrogenation tunnels, or purchased as triple wrapped single use sterile disposable items.

- Items not directly introduced through autoclaves, decontamination chambers or via depyrogenation tunnel are introduced using an effective transfer disinfection system.
- If any non-routine items are required within the cleanrooms these must be subject to a specific risk assessment and that any mitigation measures, be based on this assessment. The method of transferring non-routine items, normally via sporicidal disinfection, must be documented in relation to the CCS.
- All gases or liquids pass through a bacteria retentive filter.

CONTROLS AROUND CLEANING AND DISINFECTION

An important part of maintaining microbial contamination control is through the cleaning and disinfection of cleanrooms. Detergents are cleaning agents which remove soiling from a surface which requires disinfection. Cleaning is followed by disinfection; ad here disinfectants are used in cleanrooms in order to allow surfaces, walls, and floors to meet cleanroom standards and for surfaces to contain levels below the recommended maximum levels of viable microorganism. Disinfection is typically achieved through the rotation of two biocides with different modes of action. All disinfection processes should be validated with the studies demonstrating the suitability and effectiveness of disinfectants in the manner they are used, including concentration and contact time. In addition, detergents and disinfectants are sterile when used in an A/B area remain (13).

A separate cleaning related area is cleaning validation, designed to show that cleaning processes can effectively remove soil. This should be in place for representative items of equipment and demonstrated through soiling studies.

Housekeeping

Good housekeeping practices includes the cleaning and disinfection program. Cleaning is as important as disinfection, since disinfection will not work on a dirty surface, hence the requirement to consider cleaning first, prior to disinfection. This area also includes the need to maintain the environment in a tidy and safe way, with appropriate waste disposal. Here, waste disposal must always be one way; waste that has left the facility cannot be returned into the facility.

CONTROL OF UTILITIES

Utilities should be designed and controlled to the same standard as premises. Critical utilities include (14):

Pharmaceutical Grade Water

Water treatment plant and distribution systems should be designed, constructed, and maintained to minimize the risk of:

- Particulates
- Microbial contamination/proliferation
- Biofilm formation within the system
- Pyrogens

Water systems must be qualified to maintain the appropriate levels of physical, chemical, and microbial control, taking seasonal variation into account. Best design principles include:

- Water flow remaining turbulent through the pipes to minimize the risk of microbial adhesion, and subsequent biofilm formation.
- Specifications that have been defined during the qualification process, stored, and distributed.
- Water-for-Injection (WFI) storage tanks should be equipped with hydrophobic bacteria retentive vent filters, the filters are sterilized, and the integrity of the filter tested before installation and after removal following use.

- Periodic sterilization or disinfection of the water system should be undertaken following shutdown or maintenance.
- Chemical and microbial monitoring of water systems must be performed according to a written program: bioburden, endotoxin, conductivity, and total organic carbon.

Clean Steam

It is important that the feed water to a pure steam (clean steam) generator is appropriately purified. Pure steam generators should be designed, qualified, and operated to ensure that the quality of steam produced meets defined chemical and endotoxin levels. Steam can be used as a direct sterilizing agent is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

Heating Ventilation and Air Conditioning (HVAC)

HVAC systems are typically divided into separate Air Handling Units (AHUs) for control. Systems should be designed, maintained, and classified according to ISO 14644 and operated according to a local HVAC specification. For vacuum and cooling systems there should be periodic cleaning/disinfection.

Good design relates to both selecting a suitable grade of cleanroom together with a design intended to minimize contamination. This includes the use of appropriate construction materials and spending time on the suitability of the layout, covering elements like process and material flows. Good Design Control process includes the elements of planning, defining inputs such as specifications and requirements, producing outputs such as manufacturing specifications, validation, verification, design reviews, risk analysis etc.

The contamination control strategy needs to address the elements of the process design that protect the product from microbial, pyrogen, chemical, non-viable particulate, and cross product contamination.

Compressed Gasses

Gases used in aseptic processes need to be filtered with a sterilizing grade filter at the point of use. Microbial monitoring of the gas should be performed periodically at the point of use, for points used directly in aseptic processing, together with tests for particulates and other contaminants. In terms of design criteria, the mechanism(s) to prevent backflow when the vacuum or pressure system is shut off, should be in place.

Pressure differential

Positive room pressurization is a necessity to ensure product contamination control. Adjacent rooms of different grades should have pressure differentials of a minimum of 10 pascals. The controls around pressure differentials include:

- Indicators of pressure differences must be fitted between cleanrooms and/or isolators.
- Pressure differentials need to be monitored and recorded at regular intervals.
- The control of pressure regimes should be outlined in the site HVAC specification, where the pressure differentials and alarm parameters are justified and documented.

Barrier systems

Barrier technology refers to RABS or isolators. These form a key part of the CCS to protect the particular product manufactured. These are unidirectional airflow devices that provide an EU GMP Grade A environment.

Essential elements include:

- The entry of materials / components into the critical zone whilst maintaining the Grade A environment
- An assessment of the material transfer process
- Assessment of the decontamination methods (sporicidal for both RABS and isolator)
- Assessment of the background environment
- Methods for cleaning, disinfection, or decontamination of RABS and isolators have been assessed
- Risk assessments should be in place for the surrounding background cleanroom of the isolator or RABS, together with environmental monitoring. The cleanroom grades are commensurate with the risk in relation to the operation of the barrier devices, such that higher grades of cleanroom (Grade B) are used to house RABS devices whereas isolators are housed within Grade C environments
- Requirements are required to establish the frequency of integrity testing of the isolator; this is prior to each decontamination cycle and continuously monitored
- The frequency of testing of isolator gloves should be assessed (such as the integrity testing is at the start and end of batch and after any potential damage which may affect the integrity of the system)
- The frequency of glove replacement should be defined and based on a review of glove performance
- There should be an assessment of the risk of a disinfectant agent impacting the product

PROCESS VALIDATION

Process validation refers to the analysis of data gathered throughout the design and manufacturing of a product. Process validation needs to be an ongoing process. This means frequent (annual) review.

To undertake an effective process validation, it is recognized that those performing process validation and product reviews require knowledge of contamination rates, particularly in relation to in-process bioburden and to the supporting manufacturing environment. Process validation also details the performance of Aseptic Process Simulations.

CONTROLS AROUND ASEPTIC PROCESSING

For aseptic processing facilities, an additional layer of controls is required. This includes the use of equipment such RABS or isolators or other barrier systems. Consideration should be given to the use of technical measures to protect the product like the use of barrier technology and engineering solutions to reduce critical interventions and maintenance of grade A conditions during the transfer of materials/components. Furthermore, all product and component contact equipment must be sterilized prior to use

The design criteria should be such that aseptic manipulations are minimized. There should be an authorized list of allowed interventions, that may occur during production, and that these are practiced during aseptic process simulations (media fills).

The purpose of a media fill is to assess the process from beginning to end for weaknesses that could lead to microbiological contamination of the product. It is important that media fills are representative of the conditions during product processing and that they reflect the greatest challenge to the process. This requires an assessment of 'worst case' processing parameters that might lead to a microbial contamination event occurring and include vial size, vial neck diameter, line run speed, stoppages and the number and complexity (including time) of personnel interventions and manipulations. Hence, aseptic processing simulations are designed to assess the level of control for aseptic processing under "worst case" conditions. Medial fills are required to be conducted on each filling line every six months (at a minimum). Periodic verification of the effectiveness of the controls in place for aseptic processing include a process simulation test (media fill) using a sterile nutrient media and/or surrogate in place of the product (15).

In terms of conducting the media fill a plan is required to determine the challenges to be performed as well as the need to simulate the actual process as closely as possible including factors like shift changeovers and activities at the start and end of campaign filling (which are different from routine activities and potentially of a higher risk). Through the design process ,it is required to risk assesses the minimum number of containers to ensure that all activities and interventions are included.

In the event of recovery of a contaminated unit an investigation is required, which determines the most probable root cause, the associated corrective measures, the plan for repeating the trail and of course an assessment of all associated records since the last successful media fill.

As a further control measure, the duration of each aspect of aseptic preparation and processing needs to be limited to a defined and validated maximum time, for example:

- Sterilized equipment
- Filtration of product
- Filling time
- Maximum time open containers are exposed in the critical processing zone

There should also be controls for the finishing of sterile products. This includes outlining the requirements for sealing and capping including maintenance of environmental conditions and closure integrity validation. In examining the form fill seal operation, this requires a thorough understanding of critical process parameters associated with seal integrity during validation and that seal strength be monitored routinely. The design should also consider transport and shipping. It is important that all filled containers of products are inspected individually for extraneous contamination or other defects. Organizations should maintain a defect library which captures all known classes of defects and the need for trending results.

The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container. Container Closure Integrity Testing is a test that evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants, which include microorganisms, reactive gases, and other substances, throughout the product shelf-life. Container-closure integrity should be demonstrated as part of the stability program over the shelf life of the product for new and existing products.

Where freeze drying is required, Grade A conditions should be maintained during transfer of partially closed containers. Freeze dryers need sterilized before each load. It is also important to introduce good design principles into loading and unloading, such as ensuring that the loading patterns are specified and documented; that the transfer of partially closed containers to a freeze dryer are undertaken under Grade A conditions; that airflow patterns do not adversely affected by transport devices and venting of the loading zone; and that utensils used during transfer to and loading and unloading are subject to a validated sterilization process.

Where possible, manufacturing systems should be designed to minimize the number of manual interventions and that the systems are able to maintain sterility. Aseptic manufacturers should consider the use of single use systems in order to strengthen asepsis. The increased reliance of pre-sterilized single-use set-ups and components places more emphasis on supplier management. Pharmaceutical organizations need to ensure that if the sterilization steps are being conducted by a 3rd party that the controls and validation would meet the manufacturers own sterilization policies.

Potential hazards to consider with single-use systems are:

- Handling fragile systems
- Management of leaks and holes

- Maintenance of integrity
- Any detrimental impact on product quality from surface to product contact
- The fragile nature of the system compared to fixed reusable systems
- The increase in the number and complexity of manual operations and connections made.
- The complexity of the assembly
- The performance of the pre-use integrity test for sterilizing grade filters
- The potential for compromising the system at the point of opening the outer packaging
- The risk of particulate contamination

CONTROL OF EQUIPMENT

Selecting and operating equipment correctly is of importance and equipment assessment should follow the principles of Quality by Design. A detailed description of equipment design during validation needs to be provided and a record of P&ID's is in place. In terms of monitoring equipment performance, the methods must be defined during the URS stage, with alarm and system trends being reviewed during operation.

It is also important that equipment qualification must be kept up to date

- If equipment begins to move from the validated set points, the risk of contamination occurring could increase
- The 'validation lifecycle' approach must be adopted

To support equipment operations, cleaning processes must be validated, and a detailed assessment of cleaning validation and cross contamination exists in the form of a risk assessment. Separate assessment may be needed for fixed, mobile, and single-use equipment.

CONTROL OF PERSONNEL

People are the major variable within pharmaceutical processing. The variables can be minimized through good training and educational programs. Included within 'personnel qualification' will be (16):

- Sufficient personnel are qualified, trained and experienced in the manufacture and testing of sterile products to ensure compliance with GMP
- Unqualified personnel should not enter Grade B cleanrooms or Grade A zones in operation
- With visitors, they must always be accompanied by a trained operator
- Requirements for gowning and monitoring including:
    - Knowledge of contamination risks and appropriate control measures
    - Annual initial qualification of personnel
    - Gowning assessment
    - Training on specific requirements depending on criticality of the work performed

With training, knowledge of aseptic practices is essential for avoiding product contamination, therefore this is an essential part of training, especially for staff who work in cleanrooms and who are required to perform open processing or with the taking of samples. As personnel represent the primary source of contamination in any production process, personnel training is a key contributor towards implementation of an effective contamination control strategy. All personnel who access cleanrooms should receive regular training, gowning qualification, and assessment in disciplines relevant to the correct manufacture of sterile products. Specific elements of the training should include:

- Basic Microbiology
- Hygiene

- Cleanroom practices
- Contamination control techniques
- Protection of sterile products

Personnel training should be practical, frequent, and continuous and should cover theoretical, practical and cGMP aspects with the curriculum including basic microbiology, personal hygiene, and aseptic technique. Training should cover a broad range of areas ranging from personnel movement and behavior in cleanrooms to the impact of cleanroom behaviors on the quality of the finished product.

In terms of cleanroom gowning and behavior, it is important to reinforce that wristwatches, make-up, jewelry, other personal items such as mobile phones and any other non-essential items are allowed in clean areas. It is also important that the clothing and its quality are appropriate for the process and the grade of the working area. On entering the cleanroom, outdoor clothing (other than personal underwear) should not be brought into changing rooms leading directly to Grade B and C cleanrooms.

Clean area clothing is cleaned in a dedicated laundry facility using a qualified process. In terms of specific cleanroom clothing requirements for different grades, this will include Description of clothing required for each grade:

Grade A / B:

- First sterile suit
- Second sterile suit
- Mob cap
- Beard snood if required
- Sterile mask
- Sterile Googles
- Two pair of sterile gloves
- Sterile hood
- Captive shoes
- Overshoes

Grade C / D:

- Sterile suit
- Captive shoes
- Face mask
- Gloves to be worn when there is a defined risk of contamination to the product or process.
- Beard snood if required

CONTROL OF STERILIZATION METHODS

Sterilization processes should be qualified and supported by routine re-qualification. All sterilization processes should be validated using physical measurements and where appropriate by biological indicators (BI), for depyrogenation devices endotoxin indicators are required.

For sterilizers, validated loading patterns must be established for all sterilization processes and these are subject to periodic revalidation. If sterilized items are not used immediately after sterilization, these need to stored using appropriately sealed packaging. Where sterilized items, in sealed packaging, need to be transferred into the Grade A zone, these are to be performed

using validated methods. Where such items are sterilized in sealed packaging, the packaging sealing process should be validated.

Sterilization methods include moist heat and dry heat (depyrogenation). It is required to understand critical process parameters during validation.

Dry heat sterilization (or depyrogenation) is a process aimed at the reduction in the level of pyrogens with the use of hot air in temperature ranging. The position of the temperature probes used for controlling and/or recording needs to be determined during the validation. It is important that sufficient time is allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period starts. After completion of the high temperature phase, precautions should be taken against contamination of a sterilized load during cooling.

With steam sterilization, undertaken using an autoclave, the basic principle of steam sterilization is to expose each item to direct steam contact at the required temperature and pressure for the specified time. There are four parameters of steam sterilization, each of which needs to be controlled. These are:

1. steam
2. pressure
3. temperature
4. time

It is important that pure steam generators are designed, qualified, and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels. In addition, a sampling schedule should be in place to ensure that representative pure steam samples are obtained for analysis on a regular basis.

The pure steam used should also assessed periodically against validated parameters. These parameters should include the following:

- non-condensable gases
- dryness value (dryness fraction)
- and superheat

Where sterilizing grade filtration is required, this involves passing product through a sterilizing grade filter; this is a filter (with a nominal pore size of 0.22 am or less). The filter should have been appropriately validated to obtain a sterile filtrate and subsequently aseptically filled into a sterile container. Consideration must be given to the critical parameters or process conditions during validation of the step including the use of product and the selection of the most appropriate bacterial challenge organism during retention testing.

In terms of integrity testing of the filters, it is important to perform the verification of the sterilized filter assembly before use and after use. Within Europe, pre-use, post-sterilization integrity testing (PUPSIT) is also required. It may be possible to use risk assessment to justify methods other than PUPSIT to verify filter integrity due to process constraints. In this situation is required to consider all the contamination risks throughout the supply chain, the methods of integrity testing and levels of product bioburden.

Where parts of sterilization are outsourced, the level of control must be the same as if the sterilization is conducted in-house. Typically, a number of items are purchased sterile from suppliers, including cleanroom clothing, single-use disposable items, laboratory test kits etc. For this, the key control measure is through the technical agreement and audit. Furthermore, sufficient

evidence must be provided to the contract giver to ensure the process is operating correctly, which requires an expert review of the sterilization process.

CONTROL OF OUTSOURCED ACTIVITIES

Control of outsourced activities is required to ensure that contract activities, contract testing, analysis and services are adequately controlled, and that they comply with GMP and Marketing Authorizations or Clinical Trial Authorization.

The following steps should be followed in order to control the process:

- Initial Contract Assessment: An initial assessment is undertaken to confirm that the proposed contractor has suitable knowledge and experience and holds necessary license to carry out the work required
- Assessment of the contractor: A more detailed assessment should be undertaken depending on the nature of the work to be done.
- Transfer / Exchange of Information: In order for the contractor to make a valued judgement about their ability to carry out the contract, sufficient technical information is provided specific to the product under consideration.
- Technical Agreement: The technical agreement is prepared for each specific contract manufacture arrangement by competent personnel suitably knowledgeable in pharmaceutical technology.

The assessment necessary will depend on the nature of the work to be undertaken but may involve one or more of the following:

- Audit
- Questionnaire
- Periodic Visits
- Comparability studies
- Assessment of contractor documentation

Specific types of technical risks with outsourcing include a lack of planning in the technology transfer, incomplete process validation, and changing specifications when outsourcing a project.

BIO-CONTAMINATION CONTROL

Biocontamination control concerns the control strategies relating to manufacturing, quality, and contamination control. These are interconnected and need to be considered for facility design and daily operations. Control is typically assessed through a risk-based microbiological monitoring program. The important principle at BPL is that control is the most important aspect, and that monitoring is in place to verify that control is being maintained.

Under this concern falls bioburden control. This is should be assessed through testing of intermediate product, including at applicable hold times, to assess bioburden levels in intermediate product up to and including the final formulated bulk prior to sterile filtration. In addition, in-coming raw materials are assessed against Raw Material Specifications for bioburden using the Microbial Limits Test and chemical composition should be in place.

Environmental monitoring programs must produce meaningful data which can be trended, reviewed, and acted upon to ensure the manufacturing operation is under continuous control. Environmental monitoring can only provide a snapshot of the manufacturing conditions due to the inherent limitation of the monitoring methods, so it is important that the suitable instruments and appropriate media are selected to minimize inaccuracies in results achieved (17).

Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

The objective of an environmental microbial monitoring plan is to determine suitable locations within the manufacturing operations which provide meaningful data to provide assurance that appropriate environmental conditions were maintained. The monitoring locations need to be close to the action so a review is required of the operations within the manufacturing areas to identify high traffic areas, hot spots, potential dead zones, critical contact surfaces, high traffic areas and surfaces within the cleanroom. Environmental monitoring plan has been determined through risk assessment. Considerations include:

- Sampling locations (Qualification and Routine)
- Frequency of monitoring
- Monitoring method (effective and does not introduce contamination)
- Incubation conditions
- Historical data and significant changes
- Air visualization studies
- Trend analysis, Alert and Action levels
- Routine monitoring of cleanrooms, clean air equipment and personnel needs to be performed in operation throughout all critical stages, including equipment set-up
- For aseptic processing, personnel monitoring is required following critical interventions and on exit from the Grade B area (gloves, gowns, and sleeves)

One of the key requirements is to really understand the data and to take appropriate actions in the event of increased numbers of alert/ action level breaches or consecutive breaches or changes in the microbial flora within the facility.

Microbiological testing of finished products is also required. Sterile pharmaceutical products have three requirements relating to sterility assurance:

- Sterile
- Apyrogenic
- Particle free

In order to test the following requirements, the following controls are in place:

- Sterility test
- Endotoxin test (or other test for pyrogens like the monocyte activation test)
- Product container inspection in finished product manufacturing

QUALITY CONTROL (QC)

Contamination is monitored through quality control activities. It is important that there are personnel with appropriate training and experience in microbiology, chemistry, and knowledge of the process to support the design of the manufacturing process, environmental monitoring regime and any investigation assessing the impact of microbiologically or chemically linked events to the safety of the sterile product. All samples tested should be detailed in written plans supported by rationales to justify sample selection. Where limits are exceeded, investigations must be conducted using Out of Specification procedures.

VIRAL CONTROL

Viral control is required for some types of biologics. Manufacturers will use a variety of strategies to eliminate or destroy viruses and has in place measures to prevent viral contamination through the viral secure area cleanroom suite. This may include a virus secure processing area, formed of cleanrooms with dedicated air supplies and maintained over-pressure to adjacent areas. In terms of the product, pasteurization, dry heat inactivation, solvent detergent treatment and filtration are each

possible and used in combination to address both enveloped and non-enveloped viruses. These processes should also be validated to show they can effectively reduce the viral load in products.

PEST CONTROL

Pest control refers to the arrangements for preventing the entry of insects and other animals into the premises by way of building design and facilities. Within cleanrooms, protection will be afforded either by airlocks, controlled access, self-closing doors, or a combination of the three. In other areas, rollers should be in place for delivery areas exposed to the outdoor environment. Other measures should be put in place like rodent traps and ultra-violet electric fly killers.

CONTROL OF STORAGE CONDITIONS

Processes associated with the finishing and transport of sterile products should not compromise the finished sterile product in terms of container integrity or pose a risk of contamination and ensure that medicinal products are stored and maintained in accordance with registered storage condition. This can be assessed through careful monitoring. Arrangements for monitoring include:

- Continuous alarm monitoring
- Alarm to security (including appropriate call-out instructions)
- Minimum annual check of alarm operation
- Continuous chart / electronic recording of temperature

PROCESS IMPACT EVENTS

During manufacturing events can happen that can cause a potential product or process risk, such as engineering repairs (these can be planned maintenance or unplanned activities). Each event should be assessed before the activity starts, with appropriate recommendations made for controls, cleaning, and monitoring. The event should also be assessed afterwards to address any unforeseen impact or where the operation has been extended (e.g., through 'scope creep'). A means to achieve this is through a process impact assessment, which is a formal and documented process to ensure the impact of unscheduled activities on the GMP status of the facility are considered, any necessary mitigation actions agreed and implemented prior to activities. This approach can also be extended to pharmaceutical facility shutdowns.

This aspect of the CCS includes preventive maintenance, which is a risk-centric approach to ensure that equipment is maintained and services to ensure that it is fit for its intended purpose, is safe to use and that adequate records are kept. In keeping with the CCS such activities must not add significant risk of contamination. This means engineering staff need to be knowledgeable about contamination and before any activities are undertaken, a risk assessment is performed in the form of a process impact assessments prior to any works being undertaken. As part of quality oversight, the impact post-works is examined to assess the extent of any residual risk.

For instruments and equipment where a maintenance program is effective, there are six variables that should be evaluated as they can significantly affect the cost of the procedure:

- Labor source: Where dedicated personnel are not used, the contractor must be evaluated for suitable knowledge and hygienic skills
- Parts: Care must be taken to ensure that the specifications are equivalent to the original, and that the items are not of lower quality
- Preventive maintenance delivery methodology: Most manufactures produce preventive maintenance kits and to replace every part in the kit whether it is worn or not

- Frequency: This needs to be based on recommendation from equipment manufacturer, installation qualification and usage of equipment
- Scheduling: The schedule should be reviewed annually and shall be updated in case of any change
- Compliant documentation and reporting: Preventive maintenance documents should be reviewed and retained by the Quality department

It is also important hat before making any change, the potential requirement for a change control is considered. Where maintenance has been undertaken against a change control or in response to a deviation, the assessment and any subsequent data should be reviewed by the Quality department.

INVESTIGATION CONTAMINATION CONTROL

Contamination control incidences and microbial data deviations are investigated need to be documented and assessed. Such investigations should address (18):

- Root cause analysis
- Process or product impact
- Risk
- Suitable corrective and preventative action

The CCS needs to be supported by place a good system for addressing corrective and preventive actions. This is supported by having systems in place for:

- Trending
- Conducting investigations
- Arriving at root causes
- Suggesting and implementing appropriate corrective and preventive actions
- Applying effective investigational tools

The strategy should be able to prevent an event from happening again and adjust its risk profile in the CCS accordingly (this may result in the risk status of different items described in the CCS as altering and this may also lead to changes in risk profile.

CONTINUOUS IMPROVEMENT

A continual improvement process, also often called a continuous improvement process is an ongoing effort to improve products, services, or processes. The CCS are actively updated and should drive continuous improvement of the manufacturing and control methods.

VENDOR APPROVAL

Procedures for the qualification of suppliers and quality agreements, are essential components of supplier-management program. These procedures are sufficiently detailed to ensure adequate control of the materials and supply chain. With vendor approval, this extends to key component suppliers. The main things to consider with purchasing are:

- Understanding where materials come from
- Knowing whether materials have been prepared and processed properly
- Knowing whether materials remain the same as those components used in previous validation
- The need to understand the sterilization of components and the suitability of single use systems, and services

Author: Tim Sandle

Published on IVT Network (www.ivtnetwork.com)
GXP Volume 25, Issue 2 – March 2021

IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY
an informa business

PEER REVIEWED

The initial qualification of a supplier will typically consist of an audit, along with characterization and qualification of the supply. The frequency of these audits should be based on the compliance history of the supplier, and as stated above, the criticality of the supply.

Once qualified, the quality agreement provides the basis from which on-going supplier management is achieved. The supplier quality agreement will provide details related to periodic audits, re-evaluation, etc. It should also require that any subsequent subcontracting decisions, or changes that the supplier intends to initiate, are notify to the company for review and approval.

QUALITY SYSTEMS

The CCS should be set around an understanding of the product, process, and critical quality attributes in manufacturing. It is of importance that the CCS is not be used to try to mitigate or support bad design or practice. Instead, where risks are apparent and deemed significant, these must be addressed and where acceptable residual risks exist, these should be assessed through appropriate monitoring to ensure that the level of risk does not increase.

SUMMARY

Why have a contamination control strategy? The answer is not simply to stay ahead of the regulatory curve (important though this is), but also to gain product and process knowledge, drawing on sound science, to seek the optimal improvements and controls over each stage of purchasing, manufacturing, and product distribution. Through this products and patients can be best protected.

This article has outlined the essential elements of contamination control required for a contamination control strategy. In doing so, only generalized points can be made. However, the guidance contained herein will enable those seeking to devise such a strategy a basis upon which to do so and for those with strategies place to modify their documentation, if appropriate.

Contamination is a wide subject area, and will include:

1. Microorganisms
2. Microbial by-products, such as endotoxin
3. Chemicals
4. Particles
    a. Visible
    b. Subvisible
    c. Non-visible
5. Pests
6. Cross-contamination of product or other residues

These are the forms of contamination that any strategy should seeks to address. The article has presented the areas to include and the types of detail and information required. While mostly European terminology has been used, the elements listed make for a global contamination control strategy adaptable for any region and product stream.

REFERENCES

1. Sandle, T (2017) Establishing a Contamination Control Strategy for Aseptic Processing, *American Pharmaceutical Review* 20(3), pp22-28

2. ICH Q9, Guideline on Quality Risk Management (ICH, September 2015) - https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf
3. Sandle, T. (2019) *Biocontamination Control for Pharmaceuticals and Healthcare*, Academic Press, London, UK
4. Baker, H (2016) Aseptic Technology Trends Series: Sterile Product Facility Design, *DME*. At: https://www.dmeforlife.com/wp-content/uploads/2016/07/DME-Aseptic-White-Paper-Sterile-Product-Facility-Design_FINAL.pdf
5. EMA (2020) Second targeted stakeholders' consultation on the revision of Annex 1, on manufacturing of sterile medicinal products, of Eudralex volume 4, at: https://ec.europa.eu/health/medicinal_products/consultations/2020_sterile_medicinal_products_en
6. FDA (2004) "Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice", U.S. Food and Drug Administration, Bethesda, MD, USA: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM0703 42.pdf
7. EU Annex 1, Manufacture of Sterile Medicinal Products, December 2017 - https://ec.europa.eu/health/sites/health/files/files/gmp/2017_12_pc_annex1_consultation_document.pdf
8. Drinkwater, J (2014) Control strategies in the manufacturing of sterile pharmaceutical products, *European Pharmaceutical Review*, Issue 5 - https://www.europeanpharmaceuticalreview.com/article/27741/control-strategies-sterile-pharmaceutical-product-manufacturing/
9. Keen, D. (2020) The evolving role of a contamination control strategy in Annex 1, *Cleanroom Technology*, at: https://cleanroomtechnology.com/news/article_page/The_evolving_role_of_a_contamination_control_strategy_in_Annex_1/169469
10. Johnson, L. and Hansy, C. (2020) Establishing a Contamination Control Strategy/Program: From Global Development to Site Implementation, *American Pharmaceutical Review*, at: https://www.americanpharmaceuticalreview.com/Featured-Articles/564173-Establishing-a-Contamination-Control-Strategy-Program-From-Global-Development-to-Site-Implementation/
11. Sandle, T. (2016) ISO 14644 Parts 1 and 2 - The revised cleanroom standard and contamination control. In Madsen, R. E. and Moldenhaurer, J. (Eds.) *Contamination Control in Healthcare Product Manufacturin*g, Volume 4, DHI, River Grove, USA, pp3-32
12. Schmitt, S. (2019) Developing an Effective Contamination Control Strategy, *Pharmaceutical Technology*, 43 99): 57-58
13. Sandle, T. (2019) Disinfectants and Biocides. In Moldenhauer, J. (Ed.) *Disinfection and Decontamination A Practical Handbook*, CRC Press, Boca Raton, pp7-34
14. Sandle, T. (2020) Utilities Design and Testing. In Roesti, D. and Goverde, M. (Eds.) *Pharmaceutical Microbiological Quality Assurance and Control: A guide for non-sterile manufacturing*, Wiley, USA, pp189 – 230
15. Sandle, T., Leavy, C. and Needham, G. (2012). A Risk Matrix Approach for Media Simulation Trials, *Journal of Validation Technology*, 18 (4): 70-78
16. Sandle, T. (2018) Personnel Monitoring for Controlled Environments. In Masden R. E. and Moldenhauer, J. M. (Eds.) *Contamination Control in Healthcare Product Manufacturing*, Vol.5, pp357-400
17. PHSS (2018) PHSS Control Strategy 'White paper' In manufacture of Sterile Pharmaceutical / Drug Products, Pharmaceutical Healthcare Sciences Society, UK: https://phss.co.uk/store/viewproduct.aspx?id=3533973
18. Sandle, T. (2015) Contamination Control Risk Assessment. In McCullough, K.Z. and Moldenhauer, J. (Eds.) *Microbial Risks and Investigations*, DHI/PDA, River Grove, USA, pp783-836