

MICROBIOLOGY TOPICS

Contamination Control in the Compliance Program

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“Microbiology Topics” discusses various topics in microbiology of practical use in validation and compliance. We intend this column to be a useful resource for daily work applications.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Scott Sutton at scott.sutton@microbiol.org or journal managing editor Susan Haigney at shaigney@advanstar.com.

IMPORTANT POINTS

The following important points are discussed:

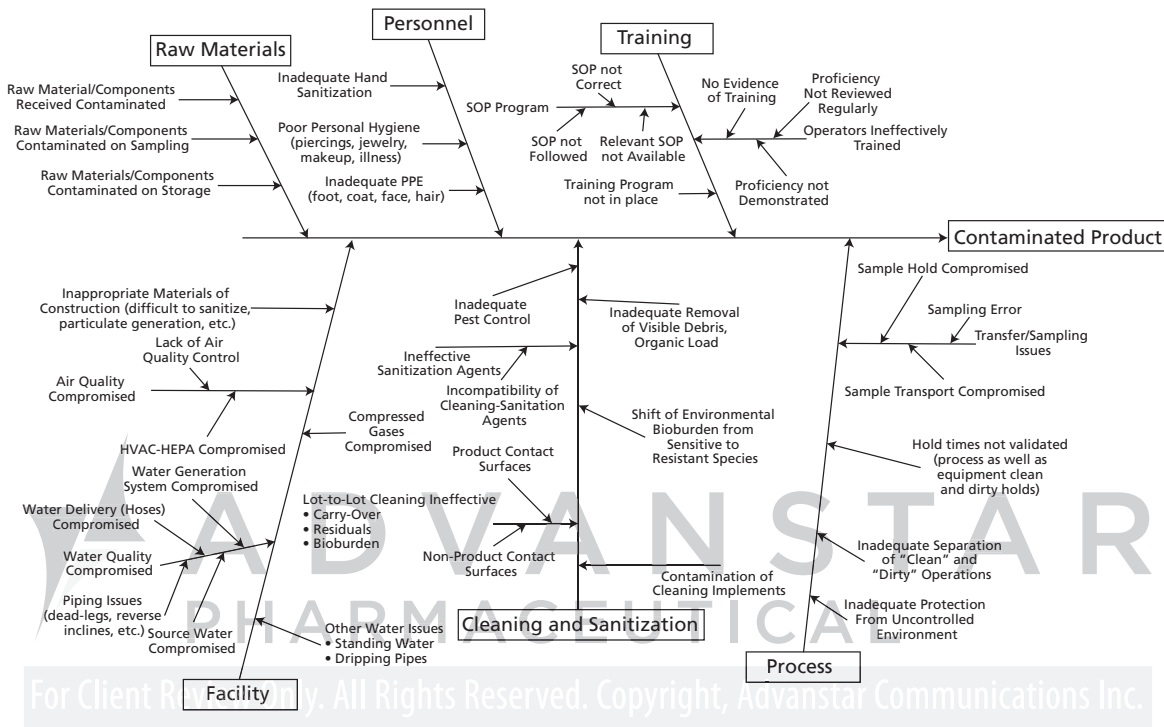
- The contamination control plan is central to good manufacturing practice, describing the procedures and policies designed to create products under controlled conditions
- The contamination control plan covers all phases of a facility’s status
- The contamination control plan is a comprehensive document, describing control of incoming contamination and measures designed to minimize their impact
- Consistency and application are key to successful execution of the contamination control plan.

INTRODUCTION

Development of a contamination control plan is critical to the success of aseptic, terminal sterilization, and non-sterile manufacturing facilities. This is most obvious in the aseptic arena, where the US Food and Drug Administration has issued clear regulatory guidance on the need for control of contamination at all stages of the process. What is less obvious is the even greater need for a plan to address contamination control in non-sterile manufacturing. This need only becomes obvious after a problem has arisen— frequently a problem in contamination control that requires product recall. The contamination challenge in non-sterile production is different from that in aseptic production. The objective in aseptic production is to exclude all microorganisms from the finished product; in the non-sterile environment it is to control the types and numbers of microorganisms in the finished

Figure 1:
Example “Fishbone” diagram for contaminated product.

Cause & Effect Diagram for Potential Causes of Contaminated Product



products. Regulatory action has extended this consideration even into the realm of personal care products (e.g., cosmetics, toiletries, and soaps).

Contamination control is central to compliance. The whole point of current good manufacturing practice (CGMP) is to produce safe and effective medications (1). As an indication, the word “contamination” or its variants appears no fewer than 24 times in 21 CFR 211. One of the most frequent cause of drug recalls, lack of sterility assurance, relates directly to the inability of the manufacturer to document adequate protection against contamination by adventitious bioburden. See the Reference section for a historical review (2) and a biotech case study on this topic (3).

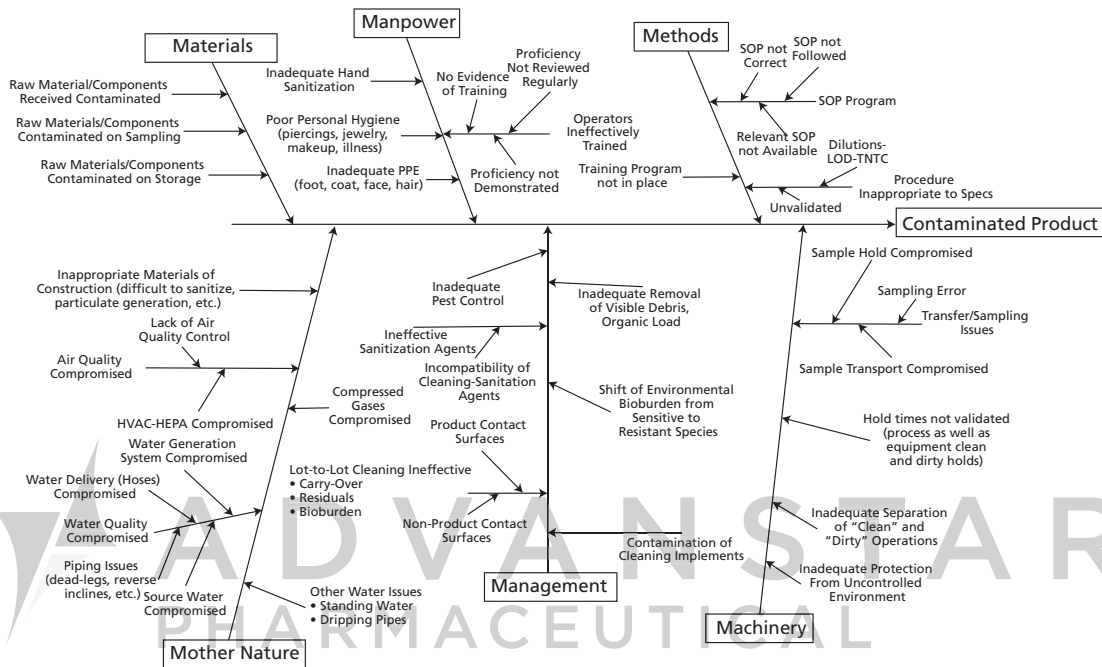
Diverse markets such as pharmaceuticals, medical devices, diagnostics, and personal care products have operated historically under different CGMP. However,

the considerations for contamination control are similar and can be approached from the perspective of root cause analysis (4). Use of a “Cause and Effect” diagram can be an excellent tool in the determination of likely routes of contamination after the fact during an investigation. It can also be used as a proactive learning tool for the development of the contamination control plan (see Figure 1). For those more comfortable with Six Sigma procedures, this can be revisited as an Ishikawa Diagram (see Figure 2). The main point here is to identify, and come to agreement, on the likely causes of potential problems.

A more traditional proactive approach to risk management might be through use of failure mode and effects analysis (FMEA), which can be extremely useful in determining the most important aspects of control for your process (5).

Figure 2:
Example Ishikawa diagram for contaminated product.

Cause & Effect Diagram for Potential Causes of Contaminated Product "6M"



COMPONENTS OF A STRONG CONTAMINATION CONTROL PLAN

The contamination control plan and the protocol governing the program are essential documents useful in providing the rationale and methods used to accomplish three tasks:

- Minimizing the bioburden throughout the manufacturing processes
- Minimizing the level of batch residual cross-over contamination
- Minimizing the level of cleaning material residual contamination.

This article examines the components of the plan in terms of specific areas of interest in meeting these three key objectives.

Phases of Manufacturing Operation

The contamination control plan must take into account different stages of facility operational status.

At a minimum, these include the following:

- Commissioning and initial start up
- Ongoing operations
- Shut-down for regular maintenance
- Start-up after scheduled shut down.

These phases will not have the same level of contamination control. A good plan will discuss the concerns specific to each of these phases.

Validated Methods

All measures of bioburden in a facility will be indirect. Bacterial cells cannot be counted on a surface or in the air. The microorganisms must be transferred to an agar plate (or some other mechanism) and colony-forming units (CFU) counted. If the assumption is made that the transfer of microorganisms from the air or from a surface to agar is consistent, then these numbers can be used to

estimate trends over time. This assumes that the nutrient agar is capable of growing the microorganisms to visible colonies. As residual disinfectant on a surface may impede the growth of microorganisms, neutralizers are frequently incorporated into the growth media (e.g., Dey-Engley Agar, MCTA). The contamination control plan should describe the sampling methods used, and how these methods are to be validated for the conditions of use (6).

The facility should be disinfected regularly using validated sanitizers and sporicides. The contamination control plan should describe the methods for testing and rationale for acceptance of materials to be used in the ongoing program of disinfection. The plan should ideally describe the *in vitro* or laboratory tests to evaluate the sanitizers, including the identification of the most resistant microorganisms found in the facility as well as the most difficult-to-disinfect materials in the facility. This is also where the method for on-going evaluation of the sanitizers based on environmental monitoring data will be recorded. The choice of disinfection regimens should be reevaluated annually, and the contamination control plan should describe how this evaluation will occur.

It is also critical to have appropriate microbiological methods for the relevant specifications—plate counts less than 20 CFU are notoriously unreliable. Traditionally the “countable range” for a standard sized petri dish is 25-250 (or 30-300) CFU/plate. These lower limits (limits of quantification) are routinely ignored when setting product and environmental specifications, thereby sacrificing accuracy and precision. Similarly, the upper limits (250 or 300 CFU/plate) are set for particular microorganisms on standard-sized plates, smaller plates, or organisms that produce larger colonies will have lower numbers as their upper limit. These will require dilutions as appropriate to measure the same specification.

Know the Enemy

A successful contamination control plan is intended to provide the most useful information on the microorganisms present while at the same time show-

ing fiscal responsibility. The FDA aseptic processing guidance document recommends genetic identification of all organisms isolated from the manufacturing environment on a regular basis. This is a laudable goal, but few of us have anything near the required budget to accomplish this task. In all honesty, it is reasonable to wonder if the effort is really necessary. The numbers of CFU from validated sites (i.e., viable air and surface, non-viable) is sufficient to provide a measure of the state of control of the facility. However, periodic cataloging of the resident microflora (at least to the species level) will provide a good check on the continued effectiveness of the disinfectants in use (7). Shifts of bioburden to spore forming microorganisms will be strong evidence of the need for use of a sporicidal agent. Occasionally, this effort will also pick up shifts among non-spore-forming organisms—this is not due to “resistance” but rather ecological shifts towards species more naturally resistant to the disinfectant in use.

The considerations in the non-sterile facility are similar, as we need proof that the sanitization program used is effective and the regular use of sporicidal agents appropriate. The contamination control plan must address how the sanitization program will be monitored for efficacy.

Control Incoming Bioburden

The first step in any control program is to control contamination at the very beginning of the process. This includes raw materials (e.g., excipients, API, water) and the primary containers. All materials should be tested for incoming bioburden against documented acceptance criteria. Part of the incoming bioburden will also include water used as an excipient to the process. The GMPs for pharmaceuticals, biologics, medical devices, and diagnostics all provide instruction on this point.

Appropriate Gowning

The gowning methods and materials are of critical importance to minimization of contamination. The primary source of contamination in most controlled areas will be the personnel. The contamination control plan must address whether it is designed for

aseptic gowning procedures or protection of personnel in non-sterile manufacturing facilities. All personnel should be well trained in appropriate gowning practice and behavior. The contamination control plan should describe the rationale for the level of gowning chosen, the frequency of gown cleaning, personnel behavior, and the acceptable gown materials for the type of manufacturing process.

Training

Operator training is critical to contamination control. No supervisor can be present at all locations at all times. Each operator must be aware of his or her role in contamination control and how to minimize the risk to batch integrity. Minimal skill sets in relation to product protection and sampling should be described by job function in the contamination control plan. This is most effectively accomplished using a well-designed and enforced standard operating procedure (SOP) system (8).

Controlled Environments

Control and monitoring of the environment is another critical element of the contamination control plan. Large portions of this can be addressed by the corporate environmental monitoring (EM) master plan (which provides rationale and consistency for a single EM philosophy across the different facilities of the corporation) or the site environmental master plan (which provides consistency and detailed instruction for the various manufacturing buildings at a given site). The contamination control plan should cite the relevant documents and their role in contamination control.

The appropriate EM plan for non-sterile manufactures and for active pharmaceutical ingredient (API) manufacturers is not well defined from a regulatory perspective. There are no strong recommendations such as those seen for the environmental monitoring of aseptic facilities; however, the absence of regulatory guidance is not the same thing as the absence of need for the activity. EM is useful for determining the state of control of the facility and so is an important part of the monitoring program for all manufacturers (6).

Validated Sanitization and Sporocidal Procedures

The efficacy of the sanitizers and sporicides used in the program must be demonstrated in a study designed to test their efficacy on the materials of construction and against resident microorganisms found in the facilities governed by the contamination control plan. This can be done optimally in the following four-step process:

1. **Suspension test of efficacy.** This is a screening effort using your candidate agents against lab strains of indicator organisms as well as a variety of the microorganism species found in your facility. The goal of this assay is to determine the “most resistant” microorganism(s) for the next step.
2. **Coupon study.** Using the representative organisms (e.g., gram positive, gram negative, spore former, yeast, and mold) and organism(s) identified in the previous study, test the efficacy of the sanitizing agents on coupons of materials found in the facility. The purpose of this test is to demonstrate efficacy on these materials using the appropriate application procedures.
3. **“Mock” sanitization study.** This study provides real-world evidence of efficacy. Let a representative room go untouched for a period of time to become “contaminated.” Take bioburden samples throughout the room, and then sanitize the surfaces and repeat the bioburden sampling. The samples taken after cleaning should be far less contaminated than the first set.
4. **Confirm efficacy from environmental monitoring.** The final step in validating the sanitization program will be ongoing evidence that the program allows the facility to operate in a state of control.

The sanitization program will ideally consist of a qualified disinfectant and sanitizing agent, used appropriately (concentration and contact dwell time observed) as the primary agent. This will then be periodically rotated with the use of a sporicidal agent (also validated for effectiveness) (9, 10).

Well-Defined and Understood Manufacturing Processes

The manufacturing process should be evaluated for its potential to limit or eliminate bioburden. The two common methods for performing this are either a HACCP-type or a FMEA approach. The use of organic solvents, heat, or other inhospitable activities can greatly reduce bioburden of a process. For example, the contribution of compression (and associated shear) should be evaluated for a potential reduction in risk of excessive microbial contamination. The contribution of the finished product water activity should also contribute to this analysis. Process bioburden reduction steps should be factored into the contamination control plan on a process-by-process basis.

Of particular importance in this evaluation for the potential for microbial contamination of the process are cleaning steps, equipment hold times, HVAC, control level of environments for critical tasks, open-system versus closed-system operations, bioburden monitoring, and others specific to the process. As an example of the importance of the bioburden control point issue, there is a strong regulatory expectation in Europe that products sterilized by filtration should have a pre-filtration bioburden of not more than 10 CFU/100 mL immediately before the sterilizing filter (or be subjected to dual filtration in series).

Finally the contamination control plan should cite the need for clear SOPs on all aspects of manufacturing, monitoring, and control. These SOPs are critical for training, documentation, and batch release.

Minimization of Batch Residual Crossover Contamination

The contamination control plan should also address the potential for a batch to be contaminated by material from the previous batch manufactured using the same equipment. The contamination control plan should describe the methods by which this likelihood is minimized.

The concern over batch residual crossover is most relevant when there is more than one product

manufactured at a site. This concern has little to do with the sterility of the finished product and is relevant to sterile and non-sterile manufacture alike.

Minimization of Cleaning Material Residual Contamination

Validation of cleaning procedures is essential to demonstrate not only that the cleaning procedure effectively cleans and sanitizes the manufacturing equipment, but also that residual cleaning material is removed to prevent contamination of the next batch manufactured.

DANGER SIGNS IN CONTAMINATION CONTROL

Compliance professionals must be vigilant in terms of contamination control. Contamination control is a sure area of regulatory enforcement interest and one where the short-sighted might be tempted to institute “cost-savings.” Frequent manifestations of cost savings mentality deal with validation aspects—the sanitizer and cleaning qualifications in particular can be expensive. The temptation is real to pull back from a full program. Some examples of these approaches include accepting without confirmation bioburden information on incoming raw materials, assuming efficacy of sanitizers, neglecting to clean floors and other non-product contact surfaces (especially in non-sterile production), and other relatively high-cost “overhead” activities. These are not optional safeguards to be ignored with impunity, as several companies have recently come to realize (10-15).

A second major area to be constantly examining is in the general topic of consistency. A well-constructed contamination control plan will include reasons for various activities. For example, if you require facility “scrubs” in a non-sterile production, there is a reason for this that should be described. Requiring all operators to be in scrubs and booties is not consistent with allowing maintenance personnel to enter the area in boots, denims, and flannel shirt for a “quick signature on a work order.” Likewise, requiring shoe covers (booties) to protect against tracking soil organisms through the facility is not effective if operators fail to change the boo-

ties during the day (i.e., entering, leaving, going to lunch, using the restroom, walking in them until they hang in tatters from their ankles). Consistency is key.

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ARTICLE ACRONYM LISTING

API	Active Pharmaceutical Ingredient
CFU	Colony Forming Units
CGMP	Current Good Manufacturing Practice
EM	Environmental Monitoring
FDA	US Food and Drug Administration
FMEA	Failure Mode Effects Analysis
GMPS	Good Manufacturing Practices
MCTA	Microbial Content Test Agar (Soybean Casein Digest Agar with Lecithin)
SOP	Standard Operating Procedure

ABOUT THE AUTHOR

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