



Designing a Facility with Both Good Manufacturing Practice (GMP) and Biosafety in Mind: Synergies and Conflicts

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Abstract

Designing a large-scale GMP production facility for biological production requires various types of risk assessments to be carried out. This is the main tool in obtaining a balance between the aspects where GMP and biosafety guidelines contradict each other. Only by evaluating the various risks involved in the project, can rational and optimal choices be made regarding facility design and construction.

Introduction

Defining biosafety and GMP is a first step toward understanding the similarities and differences in the approaches taken to attain safe working conditions and quality assurance in manufactured products. The definition of biosafety is: “a combination of procedures, containment systems, and construction technologies in order to minimize the risk of infecting laboratories and prevent escape of microbes into the surrounding environment.” The objective is to create a safe environment in which to research infectious diseases; to prevent escape of infectious agents, to minimize staff member’s and other people’s contact with infectious agents, both inside and outside the containment zone, and to prevent the introduction of infectious agents into nature.

Some biosafety guidelines take a performance approach. They define the intended result, not how to achieve it or how to demonstrate it. In this instance, the user develops and chooses the acceptance criteria. Other biosafety guidelines are more prescriptive. These outline specific requirements that must be met and, in some cases, they outline acceptance criteria as well. These guidelines are no doubt the most helpful in trying to convince i.e., the GMP authorities, that other interests are relevant as well.

The definition of Good Manufacturing Practices (GMP): “is the part of the quality assurance that ensures that pharmaceutical products are produced consistently

and controlled in accordance with the appropriate quality standards. These standards depend on the intended use of the product and the requirements issued by the marketing authorization (MA) or the product specification. GMP applies to both production and quality control.” The purpose is not to keep the worker safe but to protect the end user of the product. While the guidelines for GMP production are different in Europe and the USA, they all focus on the end user and the actual requirements may vary a little.

Biosafety requirements must be considered with regard to the following issues:

- Manufacturers
 - Vaccine production
 - GMO (Genetically Modified Organisms)
- Hospitals/patient care facilities
 - Isolation rooms with or without airlocks
- Test laboratories
 - Vaccine production
 - Hospitals/patient care facilities
- Bioterrorism
- Animal facilities

However, when you consider manufacturers, it is relevant to address biocontainment and GMP at the same time. A case in point is that wild type polio virus is close to being eradicated worldwide and WHO has therefore published a guideline for production of Inactivated Polio Vaccine under BSL3 enhanced conditions. This is the first guideline that has tried to address both aspects.

Biosafety and GMP Synergies and Conflicts

It is easy to design facilities for GMP and biosafety containment when synergies are present. **Synergies between GMP and biosafety guidelines include:**

- Mandatory restricted access and segregation of production areas.
- Facility design should facilitate easy cleaning and assist in minimizing the introduction of airborne contaminants in the laboratory and production area.

- Validation of processes, systems equipment, and utilities must be performed.
- Job certification and mandatory training of employees must take place before work is begun. The training must be documented and repeated at regular intervals.
- Mandatory PPE (personal protective equipment) must be worn at all times while working with the agents and hazardous chemicals, etc. Training prior to the use of PPE is required, and written policies and procedures must be easily accessible.
- Tasks not documented are considered **not** done in a GMP environment. Documentation in biosecurity is essential and has become equally important in biosafety.

It is much more challenging to address the issues where GMP and normal biocontainment practices are in conflict with each other. Several of the more notable areas that demonstrate conflict between requirements merit discussion. First, those individuals unfamiliar with a large-scale GMP production facility should realize the rooms are very large in size as compared to rooms in a diagnostic laboratory, and have ventilation criteria similar to those required for animal facilities. Most of these production areas must be ventilated by up to 20 HEPA filtered air changes per hour, well in excess of standard BSL-2 and even BSL-3 laboratories. Second, part of the production area is sterile or aseptic and has no contact with the infectious agents, e.g., the initial cell propagating steps in the production of viral vaccines. To achieve this goal, these areas are stringently maintained under positive pressure relative to their surrounding corridors and laboratories. To further complicate matters, other parts of the manufacturing or developmental process involve work with infectious agents. The primary containment barrier in a production of biologicals is a fermentor. Vent filters are essential to ensure the virus is contained within the production vessel, and does not escape to other process

areas. A relative or absolute negative pressure zone must be applied to these areas.

The design of the ventilation system is more complex than the traditional directional air flow as described for biocontainment laboratories, and the correct design and implementation is vital for achieving GMP status and producing products that are safe for human and animal use. Operation and maintenance of these systems pose ample challenges and costs, as there are many varied levels of pressure and air change requirements throughout the building. The secondary containment barrier in GMP as well as biosafety is the room itself.

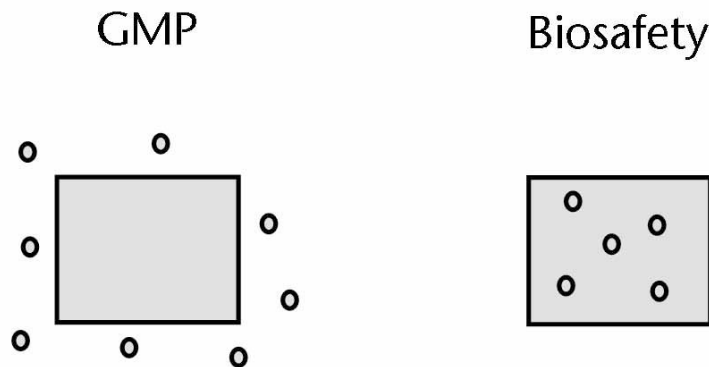
When Worlds Collide: Conflicts Between GMP and Biosafety

Most major conflicts between GMP and biosafety occur in major systems areas such as facility layout, cleaning process flow, HVAC design, and decontamination/sterilization systems.

It is important to understand the reasons why GMP and biosafety practices are sometimes in conflict. GMP focuses on preventing cross contamination and keeping environmental contaminants out of the product, (Figure 1) thereby simultaneously protecting the end user and the product. In GMP, the production flow goes from dirty to clean. Raw materials entering the facility are considered dirty. The process includes several steps of purification and inactivation, which means the product becomes increasingly “clean” during the final steps of the production.

Biosafety focuses on keeping the infectious agent in, (Figure 1) thereby protecting the employees and the environment from possible leaks. The production flow is opposite that of a GMP production, i.e., clean to dirty or non-infectious to infectious. The production process be-

Figure 1
GMP and Biosafety.



gins with propagation of a cell culture, which is then inoculated with virus. Towards the end of the process the product is inactivated. Toxoid from toxin-producing bacteria is obtained in approximately the same manner, i.e., that the bacteria is inactivated toward the end of the process.

Developing a Strategy for Merging GMP and Biosafety: Risk Assessment

Merging GMP and containment aspects when synergy is not the case necessitates a strategy. As in all strategic planning, it is necessary to read all of the pertinent guidelines and to ensure you and those you will partner with understand them fully. Understanding *why* the guidelines and requirements differ is as important as understanding *how* they differ.

Alternate solutions to achieving a goal should be considered and discussed. One way to start is by reviewing the construction of similar facilities to learn how the issues were resolved in those particular cases. Risk assessment is a valuable tool in providing weighted values where there are contradictions between biosafety and GMP guidelines. While your team prepares a logical solution be aware that authorities governing licensing and approval may not be as familiar with the approach taken and the validity of the solution, and you will be required to defend your position.

A number of aspects must be taken into consideration while trying to establish the level of hazard associated with a particular agent. The following factors should be addressed in a risk assessment and thoroughly evaluated: reservoir, volume, concentration, possible ways of escape, route of transmission, infectious dose, susceptible hosts, incubation period, decontamination and whether immunization or treatment exists. It is important to remember that this part of the risk assessment is a subset of the total risk assessment which must be performed. For a large-scale production of biologicals, it is also relevant to perform a risk assessment on the mechanical performance of various production equipment and utilities. This part of the risk assessment highlights the most risky areas of a production by examining various possible scenarios.

Words such as: none, too much, too little, forgotten, more, less, part of, added, reversed, wrong direction, wrong component, wrong object, leaking, lost, too fast, too slow, too high, too low, too late, too hard, too soft, too long, too short, too hot, too cold, etc. should be used to evaluate production equipment regarding temperature, pressure, flow, volume, mixing, surface tension, creation of bubbles or foam, pH, redox, density, leakage, breakage, tanks, pumps, valves, pipes, computer, alarms, communication, etc. Incompatible interactions between these issues and systems should also be considered and addressed. It is important to make separate risk assessments

for normal production, plant shut down and restart for preventive maintenance, emergency or unplanned shut downs caused by, for example, fire or power failure or during CIP (Clean in Place) and SIP (Steam in Place) operations.

In comparison to a small diagnostic laboratory, a facility engaged in the production of biologicals usually involves handling of large amounts of highly-infectious material. However, despite the large quantities, a topic that needs to be taken into consideration during the design phase, a normal GMP production usually only involves one type of infectious agent. It is important to understand that a biological production facility houses many tanks containing large volumes of product, waste, and growth media. The pipes inside the facility penetrate almost every room in the production area and carry liquids such as WFI (Water for Injection) at 80°C, deionized water, growth media, etc. If a pipe breaks during a spill, it will dilute the leaked material and almost certainly lead to the creation of an even larger volume of potentially-hazardous material that must be remediated. Aspects such as high pressure and temperatures are also issues that must be considered during large-scale production of biologicals, as compared to an ordinary biocontainment research lab.

Due to various aspects of GMP, the facility and systems design also includes closed systems, double filters, and steam traps on tanks, providing an extra level of protection to ensure the infectious agent stays within the tanks. Tube welders are used for inoculation or sampling. All systems are equipped with alarms and automatic shut down procedures. All handling is performed according to GMP procedures with batch records, GMP trained employees, SOPs, log books, etc. Finally, in addition to the described safeguards, the basic understanding between GMP personnel is: "that anything not documented on paper with the proper signatures, has not happened," further ensuring proper operating procedures.

GMP or Biosafety: Which Guideline Wins?

GMP takes precedence at lower levels of biosafety risks (BSL-1/2), whereas biosafety takes precedence at higher biosafety risks (BSL-3/4). However, no compromises are acceptable in GMP production that might potentially increase the danger for the end user of the product. Both sets of guidelines must therefore be met when dealing with a large-scale GMP production and a high biosafety risk. Due to the responsibility to safeguard the end user of a product, standard technical solutions and basic design choices might have to be reconsidered. The following sections will provide examples of some conflicts to provide the reader a more detailed appreciation regarding what these issues may involve.

Airlocks

What is the best way for a door to open and how hard can it be to make that decision? (Figure 2). A higher pressure helps to keep a door closed, which means that in a GMP environment, it is normally preferred that all doors open toward the area with the highest pressure. However, seen from a biosafety point of view, all doors should open toward the largest room of the two, as this will create the smallest amount of air turbulence when doors are opened and closed. From a basic safety point of view, it is preferred that a door will not swing out into a corridor where people are expected to pass. From an emergency point of view, however, doors should always open away from areas where hazardous situations might occur.

A door can only open in one of two ways. This is fortunate as it means that at least some of the authorities will be satisfied by the end result.

How large should an airlock be? My experience is that most airlocks are too small, which means that the design does not allow room for all the equipment that needs to be installed in the area such as PPE, sinks for cleaning of hands, kits for handling of spills, emergency showers etc. Biosafety requires these items to be close by, while GMP specifies that they may not be stored or installed inside the production area, which means that storing them in the airlock might be the only option.

Process Flow for Cleaning

The process flow for cleaning must be decided very early in the programming phase. Both the GMP and bio-

safety guidelines specify that these flows must move from the clean areas to the dirty ones, and, in the case of GMP, the cleaning carts may not be stored permanently in the production rooms. Additional rooms for cleaning carts should be taken into account during the design phase, as it is impossible to add extra space for these later in the construction phase once the walls are constructed.

Sinks should be placed strategically to ease the drainage of water used during cleaning. Daily autoclave decontamination of the cleaning carts should also be considered in GMP. Consideration should be given to adding extra space to the decontamination area to enable storage of carts in case the autoclave is out of service for a short period of time. It is wise to plan to purchase an extra cart(s) as well.

Ventilation Systems

What about airflow? The airflow should be directed toward the containment zone, which must therefore be surrounded by another area with a higher pressure. This creates a pressure differential and an inward airflow. There are 3 ways to achieve this inward directional airflow (Figure 3):

- An absolute negative pressure within the containment zone is one option.
- Pressure may be neutral.
- A positive pressure within the containment zone is also an option, as long as a higher positive pressure is ensured within the rooms that surround the zone.

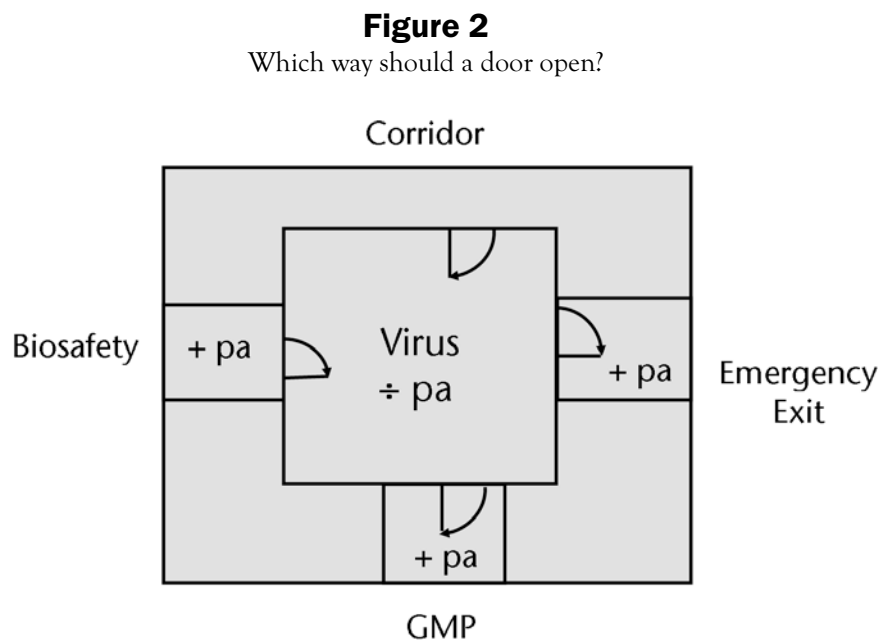


Figure 3

How to create inward directional airflow.

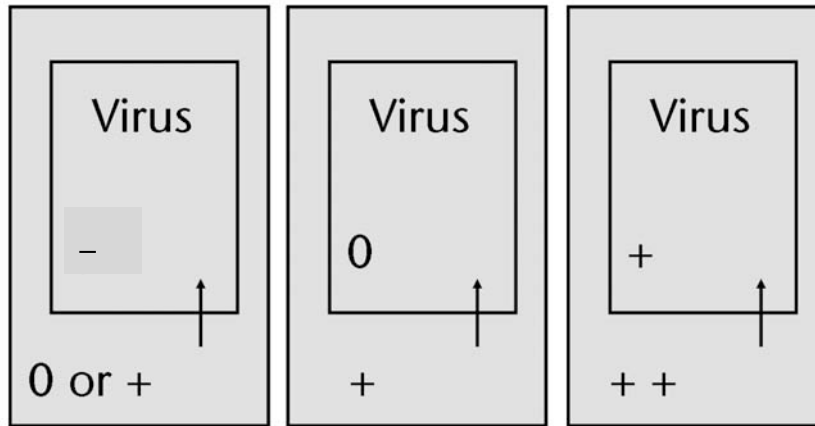
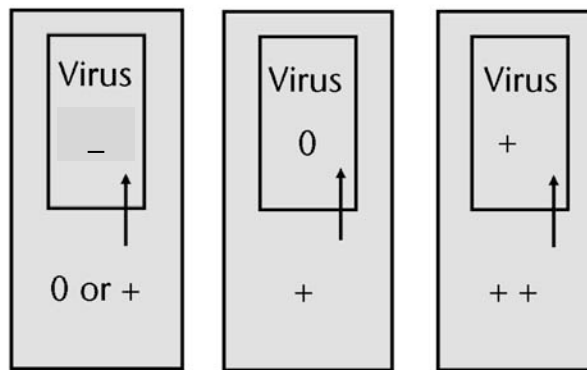


Figure 4

Three different scenarios.



Bio	Yes !	Hmmmm	?!?
GMP	WHAT ?	Hmmm	OK

Examining these 3 possibilities from both a biosafety and GMP perspective gives the following observations (Figure 4). From a biosafety point of view an absolute negative pressure is a very safe and effective design for a containment facility.

From a GMP point of view, however, this is a very creative and unusual way to ensure product safety. While the GMP guidelines do allow for this type design solution for a production of biologicals, and even though there are a lot of GMP inspectors, only a small number of them handle the inspections of biological production line or facility. Most GMP inspectors are accustomed only in visiting and assessing traditional pharmaceutical production facilities. A combined biosafety/GMP scenario is entirely new for them.

Neutral pressure is a compromise and as with most compromises, few individuals are cross trained to the degree that they understand and therefore accept a valid compromise.

Creating a directional inward airflow between two positive zones requires many biosafety professionals acting as inspectors to reassess the situation and think out-of-the-box. To many biosafety professionals, this is not a desirable solution or path, but to the GMP inspector this is an optimal scenario and they have a high level of understanding and comfort in accepting this solution.

Below, we will investigate these 3 scenarios:

An inward directional airflow must be maintained at all times no matter what happens elsewhere in the facility. This means that redundant ventilation aggregates in the

containment area are a necessity. This scenario is shown in Figure 5. If for some reason the grey fan should fail, containment will still be maintained.

In the next scenario shown in Figure 6: If the grey fan fails (6b) the pressure moves toward zero, which means that an inward directional airflow cannot be maintained. This can be rectified though, but only if there are redundant fans located outside the containment area as well (6c). Using this strategy will ensure an inward airflow.

The consequences of the last scenario (Figure 7) are more severe. If the grey fan fails (7b), the airflow will switch from an inward to outward airflow, which means that containment can no longer be maintained. The inward directional airflow can only be reestablished if redundant fans (7c) are available. Just as in the previous scenario.

There is no doubt that the first construction principle is the least expensive when assessing the ventilation cost. However, trying to run a clean room production with an absolute negative pressure is not an optimal scenario; it is more like a nightmare and raises the potential for costly failure.

The inward flow of particles from adjacent rooms in this scenario (through walls, doors, ceilings, and floors) has a heavy impact on the clean room status of the production rooms (Figure 8 "Unusual GMP"). It might prove very difficult to achieve a particle level low enough to ensure a safe product for the end user.

An air and particle tight room construction might therefore be preferred—just like a normal BSL-4 suit laboratory, however, in this case it is not to enable fumigation but to create a clean room environment.

Figure 5

First scenario, redundancy strategy.

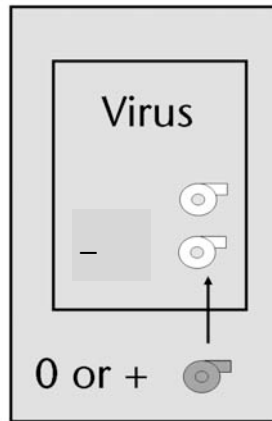


Figure 6

Second scenario, redundancy strategy.

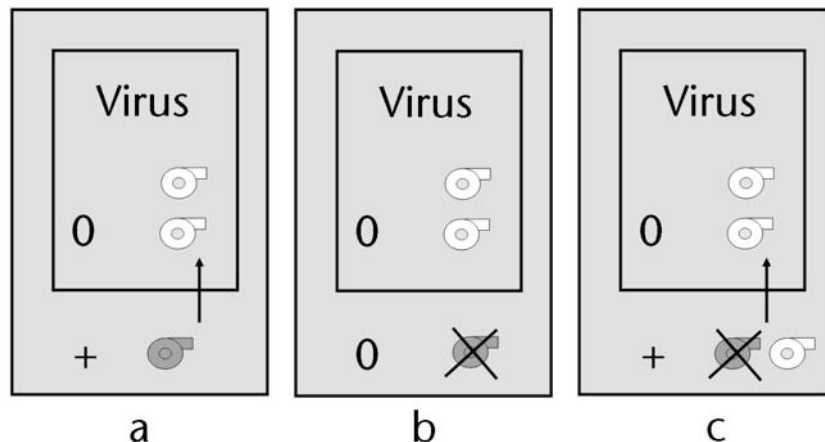


Figure 7

Third scenario, redundancy strategy.

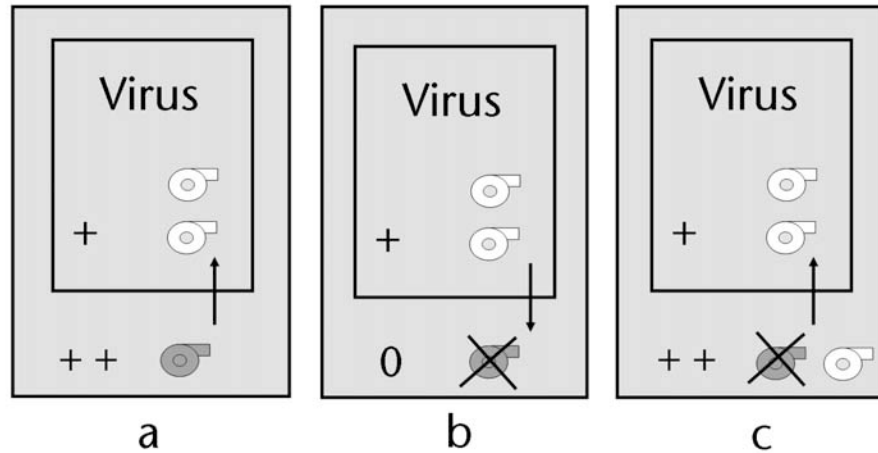
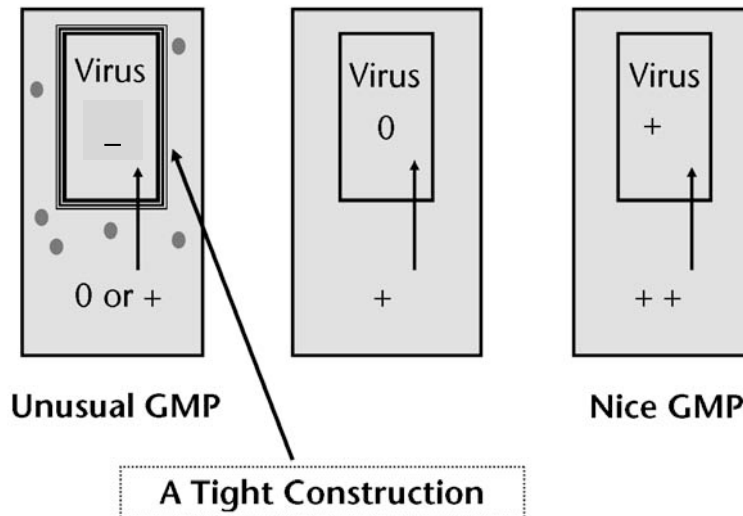


Figure 8

Tight construction.



Liquid Effluent Decontamination System (AKA kill system)

This is not an area where the biosafety and GMP guidelines conflict, but building a liquid effluent decontamination system for GMP production adds some additional aspects that should also be taken into consideration as compared to a normal BSL laboratory or AG or animal BSL facility. A kill system for GMP production should be designed very carefully because, once again, more than one equity is at stake.

From a containment point of view, the kill system should be designed to handle large volumes of highly-concentrated virus harvest (and other infectious materials) when a full batch has to be discarded due to bacterial

infection. Steam traps should therefore be installed above and beneath the tanks in order to be absolutely sure that the contaminated material will be kept inside the tanks, even if some of the valves develop a leak.

From a GMP point of view, the system should be designed “backwards” compared to normal systems seen in other BSL3 and BSL4 laboratory and animal facilities, meaning that the waste should flow directly into the treatment tanks. If a buffer tank is considered necessary, it should be placed after the treatment tanks—not prior to them. This enables the pipes leading toward the combined collection and treatment tanks to be steamed at regular intervals, ensuring that no bacterial infection can reach the production rooms through these pipes.

All collection pipes should be designed for routine

steaming and be drainable, from the production hall down into the basement in order to limit the risk of bacterial infection to the production area. Most of the waste running through these pipes is growth media, which means that any type of bacteria will be able to grow in them, and thereby potentially form biofilms that reach the production hall and contaminate the clean rooms.

Depending on the types of waste entering the kill system from the different production rooms (sometimes simultaneously) with other waste materials, the pH inside the treatment tanks prior to the heat treatment will be somewhere between 2-11. The waste inside the tanks is therefore pH adjusted before the heat treatment is initiated. The waste from cell production generates almost no solids. Grinding or homogenization is, therefore, not an issue.

It is also important to understand the types of waste that enter the plumbing system to the kill system. Sinks are used to drain water used during floors cleaning, the autoclave generates condensate, the CIP process (Clean in Place, carried out on all tanks) generates a lot of waste, with both nitric acid and sodium hydroxide. The upstream waste is mainly growth media, the SIP process (Steam in Place, of tanks with clean steam) generates waste in steam form, a waste that can lead to an increase in pressure or vacuum. The downstream process generates waste consisting of sodium hydroxide, acetic acid, saline, and acetate buffer. It is important to conduct all these types of waste down to the kill system through separate pipes into the manifold and further on into the tanks. The manifold should be designed as a backflow preventer—ensuring that a waste stream cannot go backwards up another pipe due to pressure differences.

Design Responsibility

Of course, there are many other issues to be considered before designing a facility or line for the GMP production of a product listed in a high-risk group. The topics described above represent a subset of examples of what should be considered before starting the initial programming phase. There are many additional issues that will have to be considered and discussed with an engineering company regarding the design of a new biological production facility. The chief of production is responsible for having considered synergies and possible conflicts. He or she is, in collaboration with the Biosafety Officer, also responsible for developing a thorough risk assessment (which includes addressing risk perceptions) and advocating the various design choices necessary. No engineering company or contractor, however skilled they may be, can make these decisions for the user. In the end, it is the facility manager that will have to defend and rationalize the design choices in front of both GMP inspectors, the biosafety professionals, and possibly the general public.

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