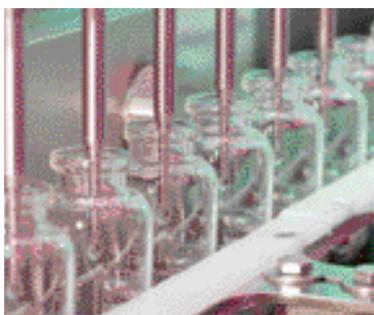


# Design of an Aseptic Process Simulation

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DSM PHARMACEUTICALS

The authors suggest a design strategy for an aseptic process simulation that focuses on the basic repeating unit of the process, establishing alert and action criteria for the unit itself, and using worst-case simulations to establish routine operational parameters for the manufacturing process.

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The aseptic process simulation (APS) is widely used for the validation of an aseptic processing during pharmaceutical formulation and filling. The test substitutes sterile microbiological growth medium for sterile product, and so is referred to as *media fill*.

It is essential, however, that the definition and purpose of an APS be clearly stated and understood before undertaking its design. Thereafter, a comprehensive design that revolves around the particular aseptic process being tested can be developed. An APS that is developed with a clear understanding of definition and purpose, coupled with a specific design for the process being tested, will result in a readily achievable and remarkably effective simulation.

## Definition and purpose of an APS

An aseptic process can be defined as all the steps from the sterilization of the drug to the point the product is sealed (1, 2). An APS is simply a simulation of that process, beginning in formulation and ending with container closure (see Figure 1). The colloquial term *media fill* has come into wide use, however, and is interpreted by some to mean the filling of media in any fragment or portion of a process. Nevertheless, although an APS is a media fill, not every media fill is necessarily an APS.

The Food and Drug Administration states that the purpose of an APS is to qualify the aseptic process using a microbiological growth medium manipulated and exposed to the operators, equipment, surfaces, and environmental conditions similar to the way the product itself is exposed (3, 4). PDA (1) adds that the purpose of an APS is to:

- demonstrate the capability of the aseptic process to produce sterile drug products
- qualify or certify aseptic processing personnel
- comply with current good manufacturing practice requirements.

These definitions and purposes together will provide a general direction for the APS's design. Before the design can begin, however, the specific aseptic process that will be qualified must be clearly defined, particularly those process parameters that will be established during the simulation.

## Aseptic process segments

In general, an aseptic process consists of two distinct segments: formulation and filling. Each part must be tested differently (2),

**Table 1: Typical APS variable or worst-case parameters with rationale and best-case settings to be used for normal operations.**

<b>Formulation segment</b>		
<b>APS setting (worst case)</b>	<b>Rationale for APS setting</b>	<b>Operational setting (best case)</b>
Sterile bulk media to be held for 7 days	Qualify a sterile shelf life longer than required for production	Sterile bulk product to be held no more than 5 days
Increase number of formulation samplings	Maximize intrusive sampling into sterile bulk	Limit formulation sampling
Increase environmental monitoring during aseptic connection	Increase intrusion into the room during aseptic connection	Environmental monitoring returned to routine during normal formulations
<b>Filling segment</b>		
<b>APS setting (worst case)</b>	<b>Rationale for APS setting</b>	<b>Operational setting (best case)</b>
Perform APS following completion of a production fill, with minimal equipment change and no post-production sanitization	APS is performed with room, equipment, and environmental conditions at less than optimal conditions	Return to routine equipment change and sanitization process
Number of personnel in the tank room and fill room $\geq 5$ during APS operations	Increase overall viable and nonviable particulates	Number of personnel in the tank room and fill room $\leq 3$ during aseptic manufacturing operations
Set filler speed at 130 units/min	Increase the window of opportunity for contamination	Set filler speed at or above 160 units/min
Increase number and/or duration of interventions into filler	Increase opportunity for contamination	Decrease number and/or duration of interventions into filler
Add additional environmental monitoring in tank room and fill room to beginning, middle, and end of each shift	Increase intrusion into the filling operation	Environmental monitoring returned to routine schedule
Use utensils, equipment, components, and closures that have remained opened (exposed) in the aseptic processing area for extended periods.	Provide utensils, equipment, components, and closures with less than optimum sterility conditions.	Limit use of utensils, equipment, components, and closures to opening their containers only when ready for use.
Increase number of breaks and shift changes	Maximize number of gown changes and fill room entries	Return to routine number of breaks and shift changes

particularly when the process involves extended formulation bulk-hold times. And each segment requires its own distinct test with its own distinct criteria. Then, both tests are run together. The design of the APS begins with defining the basic unit for each segment.

**Formulation segment design.** The basic unit for the formulation segment of the APS is essentially the entire formulation process itself. The process and its parameters are specific, using a sterile, closed system, maintained under constant positive pressure with clearly defined aseptic manipulations for sampling and connections. Time and the number of manipulations are the parameters that can be adjusted during the simulation by increasing the length of time for the bulk-hold and the number of manipulations performed, then reducing the time and number for product formulations. This is a basic formulation unit, and once qualified, is used repeatedly for each batch of drug. The acceptance criterion for the formulation segment of the APS is no less than sterile.

**Filling segment design.** When designing an APS for the filling segment, it is necessary to fully understand the basic unit of the particular process being tested, with all its elements and permutations. This unit may be executed once to fill a batch, or repeatedly in an extended filling. For example, in a manual fill-

ing process, the filling crew is the basic unit and the entire APS revolves around this one unit. Where isolator technology is used, the basic unit is the entire filling segment from docking to undocking. Between the manual filling process and isolator technology is an automated filler that uses filling operators within each shift to perform aseptic set-ups, connections, and interventions. In these automated filling operations, the basic unit is the shift (with its team of filling operators) in which all operations are executed once to fill a relatively small batch in one shift, or repeated daily in an extended filling campaign to fill a large batch. The following scenario demonstrates how the shift is used as the basic filling unit in the design of an APS:

- The filling process consists of one day-shift using one filling team. The basic filling unit here is the one shift, and, in this instance, all APS parameters and criteria will be embedded within this one shift. The initial qualification will require three consecutive day-shift simulations; thereafter requalification will require at least one day-shift simulation, twice per year (1–3).
- The filling process consists of two shifts (*i.e.*, one day and one night) using two or more filling teams. The basic filling unit here is the two shifts. In this instance, though, each shift is treated independently in that all APS parameters and criteria

**Table II: Upper 95% confidence limit for a Poisson variable with an equation for calculating contamination rate (5, 6).**

Observed media-fill failure frequency (integral, intact units)	Upper 95% confidence limit
0	2.9957
1	4.7439
2	6.2958
3	7.7537
4	9.1537
5	10.5130
6	11.8424
7	13.1481

Contamination rate is upper 95% confidence limit X 100/number of media-filled units.

Calculation to derive 6300 units:  
 $0.0475\% = (2.9957 \times 100)/\text{number of media-filled units}$

will be embedded within the day shift, and repeated again for the night shift. Initial qualification will require three consecutive two-shift simulations; thereafter requalification will require at least one two-shift simulation twice per year (1–3).

When we reflect on the concept of segments and basic units an APS design, we recognize that the concept is essentially no more than a reflection of the batch records. The entire aseptic process may already be segmented into formula tion or filling batch records, and the filling batch record may be further divided into units recording shift changes, personnel present in the fill room, interventions and stoppages (including their duration), the pulling of samples representative of the shifts, and the environmental monitoring revolving around the shifts. Once the design of the APS has captured the aseptic process to this extent, and has defined the basic unit relative to the process, then all that remains is to determine how to test the unit effectively, what parameters within the unit to vary, and the acceptance criterion for that unit. The APS must focus on the basic filling unit when determining the level of process control, and ultimately the overall acceptability of the filling segment of the aseptic process.

**Aseptic process parameters.** In the design of an APS, a distinction must be made between those parts of the aseptic process that are to remain fixed, and those that are to be varied. It is these variable components of the process that are adjusted in ways to present a worst case situation from which fixed routine manufacturing parameters are established. Manufacturing would then be limited to operations within the established APS parameters, thereby providing the highest degree of process control. The direction of the adjustment for each varied parameter, however, must be evaluated carefully (e.g., filling speed or operator fatigue) to ensure that a true worst case is presented during the simulation. Some examples of worst case situations, or variable parameters are as follows:

- simulate environmental and equipment/component fatigue associated with the longest permitted run on the processing line (2, 4)

**Table III: Two-shift APS acceptance criteria using alert and action limits based on a minimum of 6300 integral, intact media-filled units/shift versus a combined minimum of 12,600 units/two shifts.**

	Each shift 6300 units	Both shifts 12,600 units
Alert limit (<0.05% contamination rate at 95% confidence level)	<1	2
Action limit (<0.1% contamination rate at 95% confidence level)	1	6

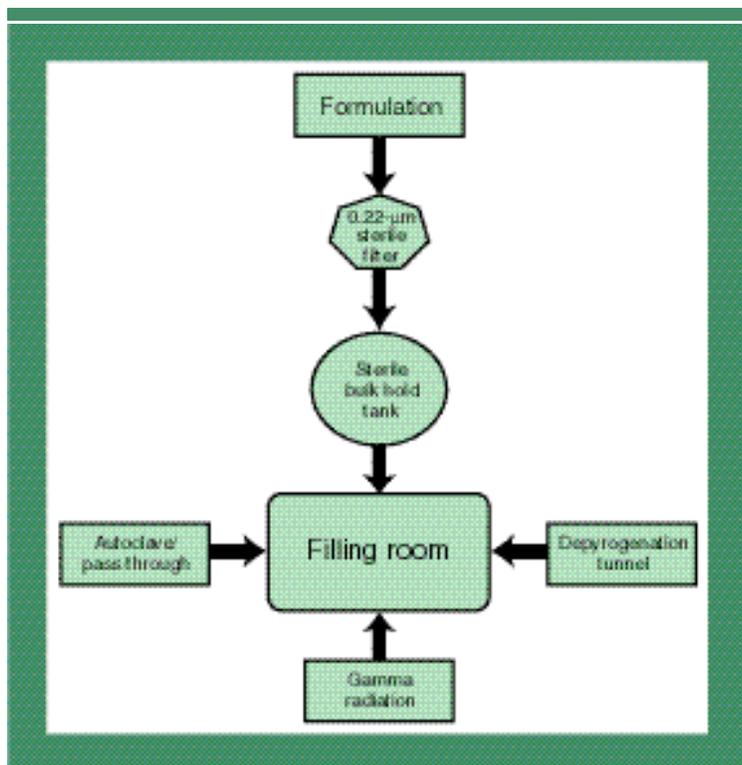
- increase bioburden of the environment (1, 4)
- set filling speed at the worst case operational range (1, 2, 4)
- increase number of interventions (4)
- increase frequency of environmental sampling
- simulate operator fatigue (4)
- increase the time period between the completion of equipment/component sterilization and the start of the process simulation (1, 2)
- increase the number of breaks or shift changes (1, 2, 4).

Again, these variable parameters are set at worst case for the process simulation, and then set at best case for routine manufacturing. Though some of these worst case situations may be universal, it is important that there be a complete and independent determination of variable parameters that are applicable for a specific aseptic process to ensure that all applicable variables are included in the simulation's design. The default use of universal parameters in the design of an APS, without a complete determination for the other applicable parameters, may result in a flawed simulation: it may lack sufficient or applicable worst case situations for a given process, leaving the test's overall effectiveness in question.

### APS batch record and protocol

The design of the APS begins with the design of the simulation batch record, which should be written in the same format as a normal batch record and contain all of the normal data: sign-off elements; typical and atypical interventions; and all the information, attachments, and documentation that normally would be attached to a batch record (1, 2). The APS protocol should be designed to give clear directions for the simulation batch record by providing at least the following:

- identification of the process being simulated (formulation or filling segment or both) down to its basic filling unit (in this case, the two shifts) (1, 2)
- identification of the room, equipment, filling line, bulk-hold tank, container and closure, and microbiological growth medium to be used, and volume of medium per container to be filled (1, 2)
- identification of incubators, incubation time, and temperatures for all samples, together with growth promotion requirements for the microbiological medium (1, 2)
- number of integral, intact units to be filled for each shift, ensuring that the number is large enough to: (a) include all required manipulations, interventions, and sampling, and (b) effectively determine the contamination rate (1, 2)



**Figure 1:** Typical aseptic process. The drug product is formulated and then filter-sterilized into a bulk-hold tank, glass containers depyrogenated, and closures autoclaved or irradiated. Then all segments are brought together in a Class 100 fill room. During an APS, the drug product is substituted with a microbiological growth medium.

- number and duration of interventions or stoppages, indicating the minimum total number and minimum duration for each (1, 2)
- clear documentation of APS participants and their activity
- a detailed list of the variable parameters to be adjusted, giving their settings for worst case, the rationale for these settings (1, 2), and the best case settings that will be used for normal processes (see Table I)
- reconciliation and accountability of bulk media and media-filled units
- acceptance criteria for all tests performed (1, 2), including the acceptable contamination rate for each filling unit or shift.

### APS contamination rate

For the filling segment of the APS, a full statistical approach for assessing the probable contamination rate is available. The method not only provides more confidence in establishing the acceptable contamination rate, but also defines the use of alert limits (5, 6).

The use of an alert limit in the acceptance criteria can provide a means for determining the minimum number of units to be filled during the APS, and for adjusting an aseptic manufacturing process toward a no-failure rate in a process simulation. For example, with an action limit set at the recognized contamination rate of  $<0.1\%$  at the 95% confidence level, an

alert limit could be set below this at 0.0475% at the 95% confidence level. From Table II, we can calculate that a minimum of 6300 units must be filled to detect a positive at this alert limit. Further stipulations within the protocol then would state that exceeding the alert limit would require a review of those adjustable variable parameters and manufacturing practices to determine if adjustments can be made to prevent exceeding the alert limit.

An example of the criteria that would be set for a shift scheduled to fill a minimum of 6300 units is shown in Table III. These same criteria would be applied to each shift in a two-shift simulation, where each shift is scheduled to fill 6300 units for an overall two-shift total of 12,600 units. In this scenario, if each shift produced one positive unit, then each shift must exceed the alert limit, but not the action limit. On the other hand, if one shift produced both positives, it must exceed the action limit while the remaining shift would have exceeded no limit.

Consider for a moment the alert and action limits applied to a combined two-shift simulation instead of each shift. The total number of filled units required at the end of the two-shift simulation would be set at a minimum of 12,600, with each shift contributing approximately half of these. Again, using Table II to calculate the number of contaminated units exceeding each limit, we find that each shift could produce two positives for a combined two-shift total of four positive units, which would exceed the alert limit, but not the action limit (see Table III).

Using the approach of accessing each shift independently, however, would result in a failed simulation, because either shift producing two positives would have been identified as exceeding the action limit (see Table III).

### Summary of APS design strategy

The pivotal points in the APS's design are its focus on the basic repeating unit; the manipulation of numbers, time, and speed to increase challenge to the microbiological growth medium; and the effective application of an acceptable contamination rate for each shift within the basic unit.

When applied to an aseptic process in which the basic filling unit consists of two shifts, a simulation exercise should be completed in the first shift, and then repeated in the second shift, with the criterion for contamination rate established at the shift level and not at the basic filling unit level. To do otherwise could mask a dysfunctional shift, giving the impression that the overall two-shift process is acceptable.

Critical to the simulation design is the identification of all process parameters to be varied and the adjustment of these parameters to present a worst-case situation during the process simulation. Essentially, the parameters are adjusted toward microbially challenging an otherwise sterile microbiological growth medium, and then adjusted in reverse to present a safer situation during normal aseptic processing to ensure reproducibility of the process control achieved during the simulation.

Finally, the simulation design must incorporate a credible acceptance criterion for the contamination rate. Much discussion exists in this area, primarily about how many failed units, if any, are acceptable in establishing a reasonable level of process control, although many agree that a no-failure rate should be achievable for a process that produces a sterile product (1, 2, 4). A well-designed aseptic process,

however, should have little difficulty in approaching a no-failure rate during simulation, and when coupled with a well-designed APS, the simulation will leave little doubt as to the degree of process control being achieved.

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### FYI

#### New Drug Development and Delivery Center

Researchers at the Georgia Institute of Technology (Atlanta, GA, [www.gatech.edu](http://www.gatech.edu)) have launched the Center for Drug Design, Development, and Delivery. By integrating the work of more than 20 faculty members from 6 fields, the center is expected to focus Georgia Tech's interdisciplinary efforts on bringing new drugs to market.

Research areas will center on developing new chemical, biological, and physical means for delivering drugs into the body. Chemical technologies will include encapsulation, a delivery method that uses microscopic polymer particles to protect drugs or genes from degradation in the body. The technique provides extended release over time.

Researchers also will be using modified viruses to deliver genes that can treat cancer without inducing immune reactions or other problems. Finally, the center will host a research project that uses physical means—including electric fields and arrays of microscopic needles—to painlessly deliver therapeutic genes, proteins, and drugs through the skin.

In addition to these projects, the center will create educational projects and industry collaborations to give undergraduate and graduate students a broad understanding of the pharmaceutical industry. With funding from the US Department of Education, the center has already launched a program of doctoral fellowships to support 12 students.