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ASEPTIC PROCESS SIMULATION: AN ASSESSMENT OF ASEPTIC PROCESSING CAPABILITY

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ABSTRACT

Aseptic process simulation (APS) is a critical validation procedure performed before implementing a new aseptically-manufactured product or aseptic process. It is the lynchpin of any qualification of an aseptic facility which requires careful consideration and design for successful implementation and thus should be carefully planned to ensure the length of the simulation and the number of manipulations performed during the fill which are representative of the actual process. APS requires their own batch records mimicking the process being simulated and includes particulars like number and type of aseptic manipulations, number of personnel, length of run, line speed, etc. It is becoming more challenging to stay on the wave of optimal and compliant sterile product manufacturing because of augmentation in technology and regulatory expectations. It is crucial for aseptic processing contract manufacturers to remain willing to seek, develop, and utilize innovative technologies, as efficiency of operations is essential to the effective operation of contract manufacturing organization. The past few years have been predominantly vigorous in context to changes that has been implemented in aseptic processing with some changes from shifts in approach to validation and process control as well apart from technology advancement.

KEYWORDS: Aseptic process simulation, media fill, validation, sterile, aseptic manufacturing, intervention.

1. INTRODUCTION

An aseptic process is defined as the steps from the sterilization of the drug to the point the product are sealed[1,2] which begins with formulation and ends with container closure, thus an aseptic process simulation (APS) is simply a process simulation. The colloquial term has

come into wide use and its mean the filling of media in any fragment or portion of a process. Although an APS is a media fill, and it's not necessarily that every media fill is an APS.[3]

Aseptic process simulations are one of the last steps and also a key element of ongoing process validation of an operational aseptic processing facility[4,5,6] as well as validation of aseptic process during pharmaceutical formulation and filling. It is commonly known as media fill because of the fact that the test replaces the sterile microbiological growth medium for sterile product.[1,2] APS is a method to determine whether aseptic process is actually an aseptic process or not. In an aseptic process simulation, media growth is used instead of the products or chemicals in the process been simulated which is then tested for sterility. If it is sterile, the process can be assumed to be performed aseptically, if not, aseptic process simulation should be repeated to investigate contamination from the source and corrective and preventive actions should be sought.[4,5,6]

2. PURPOSE OF AN APS

The Food and Drug Administration states the need of an APS to qualify the aseptic process using a microbiological growth medium manipulated as well as exposed to the operators, equipment, surfaces, and environmental conditions in an identical manner the product itself is exposed.[7,8] Parenteral Drug Association (P DA)[1] includes the purpose of an APS as.

- APS serves to demonstrate means to produce sterile drug products by the aseptic process capability.
- It aims to qualify or certify aseptic processing personnel.
- It tends to comply with current good manufacturing practice requirements.[2]

Parenteral Drug Association (PDA), the published a paper in 1988 in partial response to the publication of the Food and Drug Administration's (FDA's) 1987 guideline on aseptic processing which included response to strong interest in aseptic processing in the industry at that time.[9,10] The opening section of that document called as "evolutionary" characterized the improvements of aseptic processing operations. However, conceivably the improvements which have occurred since 1988 in aseptic processing can be characterized better as "revolutionary technology in current scenario. The practices described in 1988 are, by and large, as valid now as they were then and that the products manufactured in compliance with the under- lying principles outlined in the 1988 document are still intrinsically safe though aseptic manufacture of sterile products is the most difficult confront faced within the healthcare industry as exclusion of infectious organisms from sterile products necessitates

careful application of microbiological contamination control principles. Moreover, it is also confirmed by practicability that as stated in 1988 "the major variable arises in the control of aseptic processing are not from the sterilization processes, the clean room, or the filtration processes that are so often the subject of technical papers and regulatory guidelines rather from the workforce itself" is altogether factual. Along with the fact that human- borne contamination is the most critical risk factor in aseptic processing. Numerous industry surveys and technical articles have been published since that time all of which are in accordance with these findings.[11-16] The implementation of new technologies and aseptic processing improvements to better control human- borne contamination are have been continued by industries along with expanded microbial-test regimens and more comprehensive process simulation testing to guarantee adequate process which is consistent and as reproducible as possible within the technical constraints that are inherent in the measurement of aseptic performance are also implement on the same time.[16,17]

There is almost always a need from operators to manipulate sterile or sterilized products and components during an aseptic process which may be universally considered to offer the greatest potential for introducing microbial contamination[11, 12, 15, 18] that has been recognized the US Food and Drug Administration inspectors these potential which in turn has led to some substantial concerns raised in warning letters issued in 2000.[19-20] Thus implications for other firms performing aseptic processing have been observed due to the measures taken to respond for these concerns by the companies involved. The representatives of the Office of Compliance at FDA's Center for Drug Evaluation and Research (CDER) were assigned to address relevant issues and establish some ground rules for the industry to follow by PDA who held conference call in November 2001 for resolving the issue.[21, 22]

Table 1: Rank-ordered sources of microbial contamination in aseptic processing.[3,8]

Year	1986	2001
Personnel contaminants	1	1
Human error	2	2
Non-routine activity	3	4
Aseptic assembly	4	3
Mechanical failure	5	5
Improper sanitization	6	7
Material transfers	6	8
Surface contaminants	7	7
Airborne contaminants	7	6
Routine APA activity	7	7
Failure of 0.2 filter	8	8

Failure of HEPA	9	8
Improper sterilization	10	9
Other		10

3. HUMAN INTERVENTIONS IN ASEPTIC PROCESSING

There are no other factors with the same potential for introducing contamination than the human interventions performed during aseptic processing, sterilization processes, environmental sanitization, room design and heating and ventilation systems all being significantly less significant as sources of contamination which necessitates industries to focus on human interventions during aseptic processing. Personnel continuously shed microorganisms and particles to their surroundings and gowning materials far beyond the number of organisms present on a human skin. Thus significant numbers of potentially contaminating microorganisms to sterile materials, components and surfaces during the interventions is largely unavoidable in staffed clean rooms because of the proximity of personnel in production sterile preparations.

3.1. Routine and non routine interventions

Interventions in aseptic processing operations consist mainly of two categories routine and non routine. The activities that comprise inherent parts of the aseptic process and integral parts of every batch are categorized as Routine interventions.

Characteristic routine interventions include

- Aseptic assembly of the equipment before use;
- Initial product connection or introduction;
- Start-up component supply or introduction;
- Initial fill weight or volume adjustment;
- Periodic component replenishment;
- Periodic fill weight or volume checking and verification;
- Fill weight or volume adjustment;
- Environmental monitoring;
- Operator breaks and meals;
- Operator shift changes;
- Product sampling;
- Filter integrity testing;
- Product container replacement;

• Component change (different sizes);
• Fill-volume change;
• Any other interventional activity which is an integral part of the process.

Non routine interventions include activities that are predominantly corrective and may not be a part of every batch. Non routine interventions may not be necessary in theory, but actually in practice such interventions are almost always required to correct some incongruity but not in during the aseptic process.

Characteristic non- routine interventions include.
• Stopper misfeeds or clumping;
• Fallen, broken, or jammed containers;
• Defective seals on containers;
• Product spillage or leakage;
• Product filter change;
• Sensor adjustments or replacement;
• Filling needle replacement;
• Fill-pump replacement;
• Stopper bowl changes;
• Timing adjustments;
• Conveyor or guide rail adjustments;
• Any other line malfunction requiring manual correction.

3.2. The perfect intervention

The perfect intervention is not required in aseptic processing. The fewer the interventions, the lower the likelihood of contamination and thus in every aseptic process the objective is to reduce the number of interventions and operators should endeavor to achieve these goal throughout the operational life of the process. The three major means by which the interventions can be eliminated are: Process and procedural design, improvisation in component quality, and process automation.

3.3. Process and procedural design

Eliminating interventions by performing clean-in-place and sterilize-in-place procedures for the filling assembly; removing samples after process materials have been transferred; eliminating unnecessary sampling steps; and using the pressure-hold method for filter

integrity verification to obviate the need for a downstream connection are some of the process and procedural design elements that can potentially reduce interventions. Moreover, interventions also can be eliminated by improving component quality like establishing tighter acceptable quality levels for containers, seals, and other parts that must be assembled; and certain better control over component preparation to offer greater operational reliability.

3.4. Process automation

Automating processes by which human intervention can be reduced includes robotic sampling for fill weights, servo-adjustable fill volumes, automated elimination of downed containers, and automated stopper seal integrity testing. Furthermore, encouraging operators to examine the requirement of an intervention before performing it is another way to reduce the number of interventions. It can be exemplified by a vial that has fallen over on a turntable should be left on its side until it presents a problem feeding other containers, and if the fallen vial still remains on the turntable at the completion of the fill, the intervention entirely can be eliminated.

3.5. Identifying interventions

It is utmost essential to review the interventions with the operating personnel and supervisory staff to ensure suitability and consistency of terminology in the ASP. Certain interventions may be removed from the list as they present an unacceptable contamination risk. Then each intervention should be discussed in detail and an appropriate means must be chosen for executing the intervention- example although two or more operators may have identified the same intervention, still they may not perform it in an identical or even fully acceptable manner and thus skilled microbiologist familiar with aseptic technique should participate in this process. Each intervention (whether routine and non routine) should be recognized within a single standard operating procedure for each fill line, process or product type and these SOP should be applied to both process simulations and routine operations.

4. PROCESS SIMULATION OF ROUTINE AND NONROUTINE INTERVENTIONS

Routine interventions should be executed during process simulation at the same frequency as in an ordinary aseptic production process because it being integral and necessary parts of every aseptic process and which is relatively easy to accomplish. identical procedures should be followed for the set up of the line for the process simulation as well as those used for production, the only difference being using air instead of nitrogen for blanketing or purging (to enhance recovery of potential microbial contaminants) and adapting in-line polishing

filters to maintain flow rates. Thus the remaining routine interventions are either prescheduled by procedure (e.g., weight checks or adjustments) or transpire at regular intervals (e.g., component replenishment). As the aseptic simulation is required to follow practices identical to those used for routine production, routine interventions will be performed at the same frequency in both which in turn will ensure that the simulation is a valid representation of the routine process. Routine interventions vary substantially from non-routine interventions. Non-routine interventions occur arbitrarily during the process in response to faults the frequency with which they occur may vary substantially because of the factors outside our knowledge or ability to control. These interventions must be incorporated in process simulations at a realistic frequency level to guarantee their correct execution during routine operations.

Non-routine interventions are compulsory in simulations. It would not be able for the operators to perform those interventions during actual aseptic production if non-routine interventions are not practiced during simulations. The most suggested means for integrating non-routine interventions into a process simulation is to schedule them as if they were integral to the process, with almost the same frequency with which they occur during normal operations are. Thus it is very important that the operators perform the non- routine intervention along with the approved procedure as closely as possible which may integrate non-routine interventions into a process simulation. The media fill observer should keep a close watch to ensure that non-routine interventions are executed correctly thus making their presence strongly recommended during every process simulation.[22]

5. THE INDUSTRY'S APPROACH TO VALIDATION OF ASEPTIC MANUFACTURING

No other segment of the pharmaceutical industry mandates control of manufacturing processes as critical as the production of aseptically produced products requires. This criticality of the processes of aseptic products has led to unrelenting development of advanced production and quality assurance systems. Industries have started to develop and implement more rigorous methods for the validation of aseptic processes[23] along with the resource and staffing requirements of validation processes have substantially being increased during the past decade and a half with comprehensive prospective validation and ongoing validation maintenance. The participation of specialists from various academic backgrounds in technical and administrative disciplines are required by the management of a sound

validation program. As the validation costs across the industry have certainly increased during these years, definitely the most costly of all operations is to maintain in a validated state is aseptic manufacturing with a part of the augmented costs attributed to increased technical complexity of aseptic operations and substantial portions due to increased regulatory expectations.[24, 17]

6. PROCESS SIMULATION TESTING

FDA has applied considerable pressure regarding the rejection of units from the media-fill population that is incubated and inspected during the past few years the concern in this regard being understandable. Industry should not biasely remove containers that might have been compromised yielding an undesirable result during media fill. There should be no room for artificial biasing of the outcome toward success as matter of fact the media-fill test must always be a scientifically valid evaluation of the aseptic process.

On the other hand, it is irrational for regulators to hold all media-filled units particularly those that would be rejected because of lack of container/closure integrity, rather should be incubated even as a separate population. It is however, agreed that units should not be rejected from the media-fill test population for cosmetic defects only, even if they would normally be rejected in product manufacturing. Moreover, it is always possible to determine whether a media fill is representative in terms of rejects by comparing the normal lot rejection rate for container/closure integrity with that of the media-fill test and that neither the reject rate should be higher in media fills than in normal production runs of comparable size nor should they be expected to be consistently lower. Consistency of performance should be ensured by the alignment of intervention practices for production and media fills. The number of units incubated by most firms in a media-fill test was almost always 3000 or slightly more in 1988. But since 1988 the number of media-filled units has increased because of introduction of higher throughput aseptic processing filling systems. In operations with fill speeds at least 200 units/min and media fill duration with target population of only 3000 would result in media fill that might last considerably less than 30 min excluding set up. However process capability is not assessed by media-fill tests that are a high percentage of the total number of units filled in a batch. Furthermore, media-fill populations of more than 10,000 units are rarely required that too for high-throughput operations.

Industries has conducted media-fill tests under a broad diversity of conditions, including so called “piggy-back” media fills done at the end of a normal production fill during last 25

years. Industries have also conducted longer duration fills for testing operator fatigue. However, no compelling evidences indicate that the operator fatigue is a factor in environmental control, media-fill outcome, or product safety.[25] Nonetheless, there is no need to fill enormous quantities of media for evaluating fatigue as the more automated an aseptic operation is the less likely chances of fatigue will be an issue in asepsis. Risk analysis should be performed by each industry to ensure that their media-fill tests are representative evaluations of their processes; adjusting media- fill sample size accordingly. It not required for each operator to participate in a media-fill test before being admitted to aseptic production work because profuse means exist to qualify personnel for aseptic operations without the requirement for at least one media-fill test. Each employee can be evaluated in provisions of gowning effectiveness with laboratory simulations used for evaluating their aseptic techniques.[14,16] In addition, operators can be expansively trained on equipment operations and relevant operating procedures as well as work instructions. However, critical personnel, including those required for performing equipment set-up and critical aseptic assembly, should successfully participate in a media-fill test before taking up their work assignment.

However, it is not necessary to conduct more than one media-fill test per operational shift per year, more-frequent media fills on validated production lines are also unnecessary. It is also not essential to test each container type each year rather a rationale for their container/closure system selection on the basis of a careful analysis of risk should be develop by industry.[14] Media-fill tests are quite useful with some limitations to conclude whether an operation is much better or much worse than it actually is. However a media-fill test is not always predictive of future outcome or informative regarding previously manufactured product as it is a snapshot in time. Definitely media-fill positives should occur rather rarely and thus a zero contamination target is appropriate, but it does not imply that a single contaminated unit should be the cause of product quarantine or rejection. Modern aseptic clean rooms are outstanding but not perfect. It is wasteful and scientifically unacceptable to quarantine or dispose safe product because of unwarranted concerns about “sterility assurance”. However, it is quite tricky to support the documented improvements in aseptic processing performance in a quantifiable manner and thus tighter limits has been placed on media fills since 1980 to determine industry performance. Furthermore industries are willingly reducing their acceptance criteria for media-fill contamination rates below 0.1% sustain unrelenting improvements in aseptic processing which also shore up recommendations found in USP where two out of three media fills should be devoid of contamination.[26] Consequently all

these measures coupled with near absence of documented evidence indicating presence of actual microbial contamination in sterile products proposes that a perfectly sterile and safer products are manufactured by aseptic processing.[25,27,28]

7. MEDIA FILL

The media fill is most common aseptic process of stimulation wherein a representative number of dosage units, typically >5,000 units, are filled, sealed, and placed in one or more incubators and incubated for 14 days (usually 7 days at 20–25°C, followed by 7 days at 30–35°C) at the proper temperature(s) to promote microbial growth by a media fill and unit are than inspected for microbial growth. A growth promotion study is performed on the media if all units for growth are found to be negative. Thus the media fill is concluded to be successful if the growth promotion study passes and it if growth promotion study fails, the failure needs to be investigated and the media fill is repeated. The source of the contamination must be investigated, corrective and preventive actions made, and the media fills must be repeated in case positive units are found in the media fill vials.

Apart from the above-mentioned processes there are some other processes where aseptic process simulation may be performed as each of these processes has inimitable requirements that make it essential to perform aseptic process simulation useful.

- Aseptic compounding
- Aseptic crystallization
- Aseptic precipitation
- Bioreactor and fermenter charge and inoculation
- Other aseptic processes in the biotech and parenteral industries.

8. SETTING UP AN ASEPTIC PROCESS SIMULATION PROGRAM

The over- all process validation programs for a new facility should include aseptic process simulation and should make a part of the facility master plan or a separate aseptic processing procedure. Following are the Steps for setting up an aseptic process simulation program.

8.1. Define the aseptic processes

Manufacturing processes should be reviewed to determine the number of aseptic processes and the number of aseptic unit operations.

8.2. Perform a risk assessment on each aseptic process

A high level risk assessment for each aseptic process should be performed to assess its effect on patient safety and product quality. Processes that may result in a non-sterile product e.g. filling of a final product should be separated from that processes which may cause loss of product but little or no risk to patients, such as addition of growth factors or nutrients to a bioreactor.

Each process should be evaluated for key control points and factors that could present a hazard of microbial contamination of the product. Some important objects to be considered are.

- Length of the process
- Number of people involved in the process
- Shift changes or breaks involved in the process
- Line speeds (if applicable)
- Line configuration
- Operator interventions in the process (e.g., removal of tipped vials from a filling line, weight checks, manual addition of a sterilized powder to a sterile suspension formulation, aseptic sampling, etc.)
- Any special conditions, such as lyophilization, product recirculation for suspensions, etc.

8.3. Determine the frequency and number of runs for each aseptic process simulation

Although most aseptic process simulations are performed on a routine, usually semi-annual basis there are certain aseptic process simulations which are performed only as a verification activity during commissioning of new equipment like bioreactors or fermenters. However, three media fills are performed before proceeding to the process validation or conformance lot phase of the start-up during initial qualification during start-up of a facility.

8.4. Develop batch records or process instructions for each aseptic process simulation

Each aseptic process simulation requires detailed instructions on how to perform it which can be typically accomplished by a specialized batch record or manufacturing instruction for the aseptic process. A good aseptic batch record usually include the number and type of aseptic manipulations observed in the manufacturing process, line speeds, duration of runs, the number of people in the aseptic processing area for each run, environmental monitoring during the run, growth media used for process simulation, incubation times, and temperature, etc.

8.5. Develop a schedule for aseptic process simulations

Aseptic simulations are required an on a semi-annual basis for vital aseptic processes like aseptic filling and should be included in the routine production schedule as they need to be considered a part of the routine manufacturing process. The factors such as line speed, vial size, aseptic manipulations, etc., should be taken care of when aseptic process simulation is scheduled so that any bracketing or matrix approach can be covered on a routine basis is ensure by an aspetic stimulation process.[4,5,6]

9. ADVANCED ASEPTIC PROCESSING

A technology that through automation or environmental separation actively or passively reduces the risk from human-borne contamination is known as advanced aseptic processing. The only risk of consequence in human-scale clean room aseptic processing is human borne contamination, it should be apparent that technologies reducing the likelihood of operators releasing microorganisms near open product or components can further improve the already impressive safety achieved in aseptic processing. Isolators, restricted access barrier systems (RABS), blow or form–fill–seal technologies, and different types of machine automation are included in advanced aseptic technologies the upsurge in the implementation of which is visible throughout the industry.[16] The drastic advancement is evident from the fact that in 1988 the first isolator-based aseptic filling systems were just being implemented, with today these systems number in the hundreds. In industry, Blow– or form–fill–seal technologies have been used for more than 30 years and continue to undergo incremental improvements. The likelihood of human-borne contamination in critical operations is reduced by RABS system which provides a means of upgrading existing aseptic processing systems. Quite evident examples are available to show reduced risk through automation abound like loading of lyophilizers, component replenishment, and checking and adjustment of container fill weight.

"A dogmatic approach could stifle the development and implementation of technology which could markedly improve the SAL of sterile products" was cautioned by PDA in 1988.[29] However, regrettably, neither the industry nor the regulatory community noticed PDA's advice[30] the evidence of which can be in the case of isolator technology bad decision made by industry advocates and regulators have hindered implementation, particularly in the United States. Industry believes that groups made the fault of setting a target of performance for isolators equivalent to terminal sterilization which was a very unfortunate strategy as the

demonstration of equivalence in terms of absolute sterility is quite impossible. This erroneous target setting resulted in a surfeit of validation expectations far from understandability and implementation. Moreover, targeting perfection also resulted in the expectation of a perfectly sterile enclosure environment, perfect transfer technologies, and perfect system integrity and in the case of leaks, the actual microbiological significance of so-called "breaches" was unconsidered and instead a theoretical notion of perfection replaced a practical approach to systematic technological improvement.

Nevertheless, advanced aseptic systems have met more than the expectations since 1988 yet industry and regulatory authorities need to see these technologies as an important incremental improvement in asepsis arising from reduced human-borne contamination risk. Thus the improvement over conventional clean rooms but not equivalence to terminal sterilization should be the target for validation of these systems and so it is illogical and inappropriate for industries to concern with abstract or theoretical risks that cannot be measured.[31] Although their process capability is higher, the validation techniques for the systems should not be substantially different than those used for conventional clean rooms and this higher capability should be reflected in the in-process control and validation acceptance criteria which are employed for these more technologically advanced systems. Conversely, it has to be restated that the perfection is not currently attainable and that the tools necessary to measure perfection are still short of.[17]

10. NEW PROCESS VALIDATION GUIDANCE (PVG)

The FDA issued its final version of the revision to the 1987 Guidance on General Principles of Process Validation on January 24th, 2011. On November 2008 this revision was first issued for public comment. Numerous comments to the draft revision were presented by industry. In this final version the FDA appears to have addressed most of the major categories of comment.[32] FDA through PVG encourages companies to use a science and risk based approaches for validation of critical processes. FDA also persuades companies to ask and answer the questions: *Do I have confidence in my manufacturing process? What scientific evidence assures me that my process is capable of consistently delivering quality product? How do I demonstrate that my process works as intended? How do I know my process remains in control?*[33] In another way FDA expects companies to decide on different approaches to process validation which will best accomplish the objective of confirmation of process control. The documentation focused approach where a series of consecutive batches

are run and if they pass the process is deemed validated is a traditional documentation focused approach which has now disappeared and has allow for new approaches which can more effectively be used on new technologies.

There are three stages or parts of new guidance for a true life cycle approach. In Stage 1 process design, variables affecting product quality are identified. The process variables do not adversely affect product quality is assured by developing control strategies. In Stage 2 process qualification, the process control strategies and systems providing and supporting the said control strategies, are tested and verified to be effective. In Stage 3 continued process verification, the commercial manufacturing process is examined to guarantee proper performance outcome. Some of the activities and sequence of the three stage approach is illustrated by figure 1.[34]

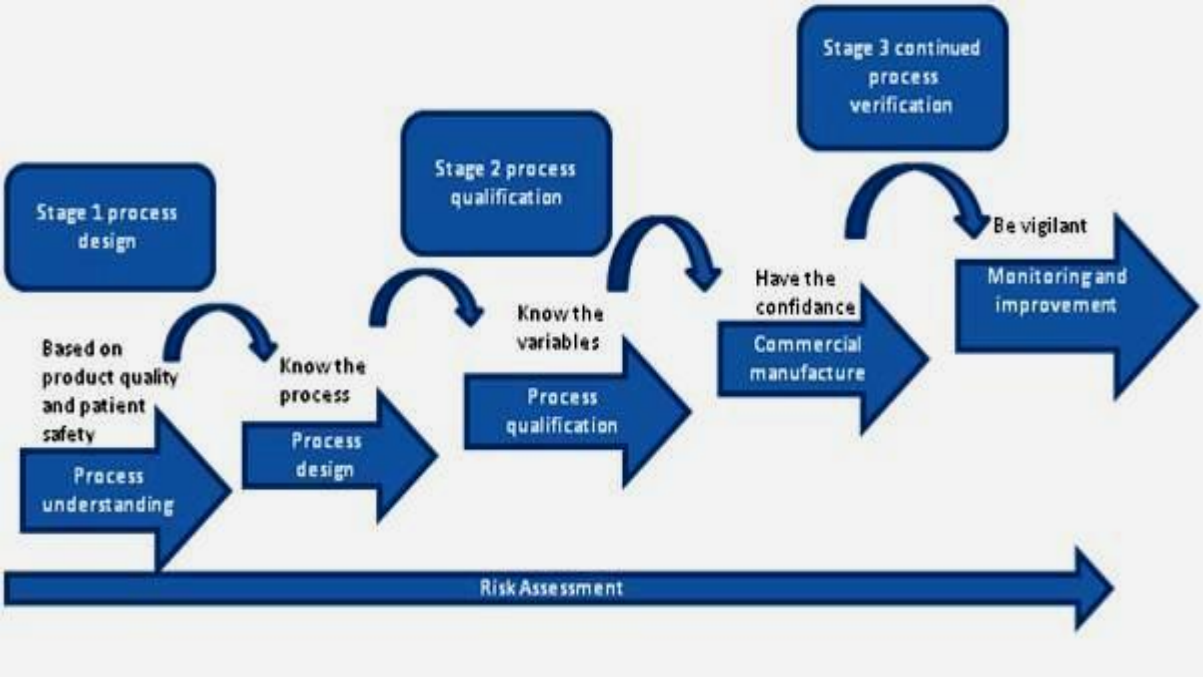

Figure 1: Process qualification sequence.

Table 2: Aseptic process validation (APV) and life process approach to APV.

Stage 1 Process Design		**Stage 2 process qualification**	**Stage 3 continued process verification**
Parameter or condition	**Control strategy**	**Process qualification test**	**Continued process verification**
Personnel/interventions	HEPA air Positioning and flow aseptic technique	Unidirectional air Velocity, smoke/air flow profile studies personnel, qualification, aseptic process simulation	Process observation, Personnel monitoring, sterility test result
Environmental condition	HEPA air flow room pressurization clean room temperature and humidity, sanitization	HVAC qualification, HEPA certification, clean room qualification, disinfection, qualification	Environmental monitoring result, differential, pressure, periodic clean room, certification
Sterility of product and product contact surfaces/part/components	Sterilization procedure, bioburden, component wrapping, handling and holding	Clean steam system qualification, steam in place qualification, autoclave qualification, sterilized parts hold time studies	Sterility test results, bioburden monitoring, periodic, requalification of utilities and equipment
Condition of non product contact surface	Clean and sanitization	Disinfectant efficacy, cleaning	Environmental monitoring results
Production yields and quality of output	Filling process speed and duration	Fill line qualification, aseptic process simulations	Production yields, analysis of product defect and rejection rates, production downtime, customer feedback/complaints

11. CONCLUSION

The adequacy of the aseptic process can be demonstrated by successful media fills, provided that intervention practices are detailed in procedures used in an identical manner for both process simulation and routine operation. Aseptic processing capability can be assessed by process simulation and are not definitive determinations of sterility assurance. In order to improve efficiency and effectiveness of operations, it is required to embrace new technologies and the aseptic processing industry needs to be more innovative. The commercial climate is right for the use of improved technology and the regulatory climate is right for the use of more creative and effective ways to validate such technologies. Contract manufactures will handle more aseptic processing and it is important that contract manufactures take the lead in the use of such advances.

12. DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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