General Discussion

What are the "worst case" attributes to be considered in an aseptic process simulation (*i.e.* media fill program) for aseptic filling of sterile drug products within conventional cleanrooms?

Aseptic process simulation tests (*e.g.* media fills) "are used extensively and are recognized as an effective way to validate aseptic filling" processes for the purpose of complying with regulatory GMP expectations. A media fill begins at the point where the final sterilization of the product takes place (*i.e.* where aseptic operations are performed) through the completion of filling operations with the sealing of the filled containers.

Media fill operations involve aseptic filling using microbiological growth medium in place of the product. It is important that the microbiological growth medium is exposed to direct product contact surfaces of equipment and container closure systems (*e.g.* stoppers).

The media fill should be performed within all critical environments where sterile product would be exposed as well as include all process manipulations by operators into the critical environment (*i.e.* interventions) without introducing conditions that could potentially compromise the process. Thus a media fill serves as a direct simulation of the aseptic filling process and is affected by all elements involved in actual product filling operations (e.g. facility, equipment, and personnel). Additionally, all components that have the potential for direct product contact should be prepared and staged within the critical environment as part of media fill and are an important consideration to account for as part of the overall media fill design.

While a media fill can certainly provide a great deal of assurance of the overall capability of an aseptic filling operation, it is still only a simulation and therefore it is not expected to simulate actual production activity in all circumstances. Conversely, any required adaptations to allow a media fill to properly simulate a routine production operation "should be accomplished in a manner which will not improve the results of the simulation, relative to routine operations".

Also, since aseptic manufacturing processes can be complex and consist of a number of stages, in some circumstances (*e.g.* sterile bulk manufacturing) it is permissible and "may be more practical to validate the various segments of the process individually". There is no expectation that a media fill be performed in one session that includes all applicable steps from product compounding through the end of aseptic filling and sealing.

This document presents the common "worst case" attributes to be considered within a media fill program for aseptic manufacturing processes. Recommendations to address these attributes are also included.

First it is important to note that the definition of "worst case" does not mean execution of a media fill at processing failure points where media fill failure would likely occur.

Remember that other compounding activities that involve "any aseptic manipulations performed during and at the end of the holding period" such as sampling, weighing, multiple filtrations, etc. should also be included in the design of a bulk holding time simulation. Obviously, in the event of a process change, additional holding time simulation(s) would be indicated to support the change in the process that may have an impact on the bulk holding tank operation.

2. **Aseptic Process Times:** The time it takes to perform all necessary aseptic processing operations is a major consideration in media fill design. The maximum aseptic process filling time required to fill the largest batch size for any given container/closure size should also include other activities that are part of a normal aseptic processing operation (*e.g.* operator breaks, necessary equipment change-outs, etc.).

   The most conservative position or "worst-case" for assessing the required time to complete a media fill operation would be the full batch size and duration since it most closely simulates the actual production operation. Other media fill design options can be used and may include performing the media fill immediately following the completion of routine production operations, which is also known as "piggybacking", or alternating the filling of media fill vials with just operating the filling equipment (without vial filling) to allow for continuous processing time while minimizing the total number of media filled vials.

   This provides an acceptable alternative for a "worst-case" scenario to simulate the maximum anticipated filling time. In this situation, the containers should at a minimum be filled at the start of the filling run and at the end of the desired filling time to fully encompass operation.

   In any case, a supporting rationale document should be generated that explains the duration of a media fill process simulation in the event that the anticipated duration differs from the actual filling process duration. Any rationale that is developed for aseptic operations that do not employ true personnel separation from the process (*e.g.* restricted access barriers, isolators, blow-fill-seal) "should be carried out so as to cover all shift operations" since the introduction of new personnel may be a potential source of contamination due to differences in how operations may be performed.

   Remember, a very important consideration exists if the intent of performing a media fill is to justify extended continuous production (i.e. aseptic filling campaign). In this case, the media fill should encompass the full duration of the aseptic filling campaign. For instance, a "worst-case" condition relative to total aseptic processing time could include the longest operations and manipulations that could potentially occur in a single routine production run. Additionally, routine processes may occur on different shifts and the "worst-case" would account for all of the operational shifts that the routine process would run so as to account for differences on each operational shift.

fill weight adjustments, addition of stoppers, removal of downed vials, sampling, environmental monitoring, etc.). Non-routine interventions occur sporadically and do not necessarily occur during every production batch. Non-routine interventions of this type include unexpected processing equipment failures or any occurrence that hinders routine operations of the process (*e.g.* line jams, vial guide adjustments, removal and replacement of damaged components, etc.). Non routine interventions should be included in the intervention plan of the media fill program and performed at least once per year. Media fill documentation "should list all interventions that are permitted during normal batch processing".

It is important that the "interventions representative of each shift, and shift changeover, should be incorporated into the design" of a media fill. However, remember that "justifying mechanical interventions through environmental monitoring and media fills is not a good practice; the process design focus should be on eliminating interventions".

The media fill should not be used to justify poor practices. The frequency to perform an intervention during a media fill should also be representative of the number of times the intervention occurs in an aseptic manufacturing operation[9].

Conclusions

The media fill program design should consider and is expected to "emulate the regular product fill situation in terms of equipment, processes, personnel involved and time taken for filling as well as for holding". As part of media fill design, there is an expectation to consider "worst case" conditions. A number of these have been presented including: holding times, aseptic process times, number of units, line speed, container size, process matrix, personnel, process setup, and interventions. Within each of these highlighted categories an attempt has been made to provide guidance on what to consider a "worst-case" condition within the media fill program.

Remember that "worst-case" conditions are expected to be included within the media fill program, but there is a certain degree of latitude in how you can accomplish implementing these conditions.

Finally, it is imperative that any media fill program be supported by a documented rationale that includes the reasoning for conditions that are selected and their frequency. A rationale document may state that the frequency to perform a "worst-case" condition should be based on criticality of specific processing activities. As guidance, it is logical that the frequency consider both the number of times the condition may occur during routine production and the potential risk the condition presents to product quality.

