# NON-VIABLE PARTICLE MANAGEMENT DURING BFS MANUFACTURING OPERATIONS

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BFS technology is a robust aseptic filling process that is capable of producing a product that meets high quality industry standards. This technology is recognized in the pharmaceutical industry as an advanced aseptic processing technology, which offers several operational advantages over conventional aseptic production, such as isolation of the critical filling zone. However, BFS is a process which, due to its current mechanics, creates a large quantity of non-viable particles in the manufacturing area. The Rules & Guidance for Pharmaceutical Manufacture & Distribution 1997 specifies that BFS equipment, fitted with an effective grade A air shower, may be installed in at minimum a grade C environment, provided that grade A/B clothing is used. The environment should comply with the grade C non-viable limit at rest. Table 1 lists the environmental grades and corresponding particle limits.

Non-viable particles created during the BFS process primarily originate from the electrically heated parison cut-off knife contacting the molten parison. As the knife passes through the molten parison, smoke particles are generated and dispersed throughout the area housing the BFS Machine. The quantity of particles generated is

Table 1: Non-viable Particle Standards[1]

| maximum permitted number of particles/m³ | | | | |
|---|---|---|---|---|
| | At rest | | In operation | |
| Grade | 0.5 mm | 5 mm | 0.5 mm | 5 mm |
| A | 3,500 | 0 | 3,500 | 0 |
| B | 3,500 | 0 | 350,000 | 2,000 |
| C | 350,000 | 2,000 | 3,500,000 | 20,000 |
| D | 3,500,000 | 20,000 | Not Defined | Not Defined |

typically proportional to the horizontal linear quantity of parison being extruded (total cut length). The presence of large quantities of non-viable particles in the BFS machine room may impact upon the environment within the grade A air shower. Studies challenging the technology with air dispersed viable organisms[2,3,4] have demonstrated that the quality of the environment impacts upon the quality of the product. Given that viability of a particulate does affect airborne behavior, the impact of viable airborne microorganisms on BFS product suggests a likely impact of non-viable particles. As BFS technology further progresses into injectable products control of non-viable particles is increasingly important. Table 2 summarizes the particle limits for small volume injections as indicated by the U.S. Pharmacopoeia (USP) Vol. 23.

Table 2: Particle Limits for Small Volume Injections[5]

| Particle Size (μm) | Limit (counts/container) |
|---|---|
| ≥ 10 | 6,000 |
| ≥ 25 | 600 |

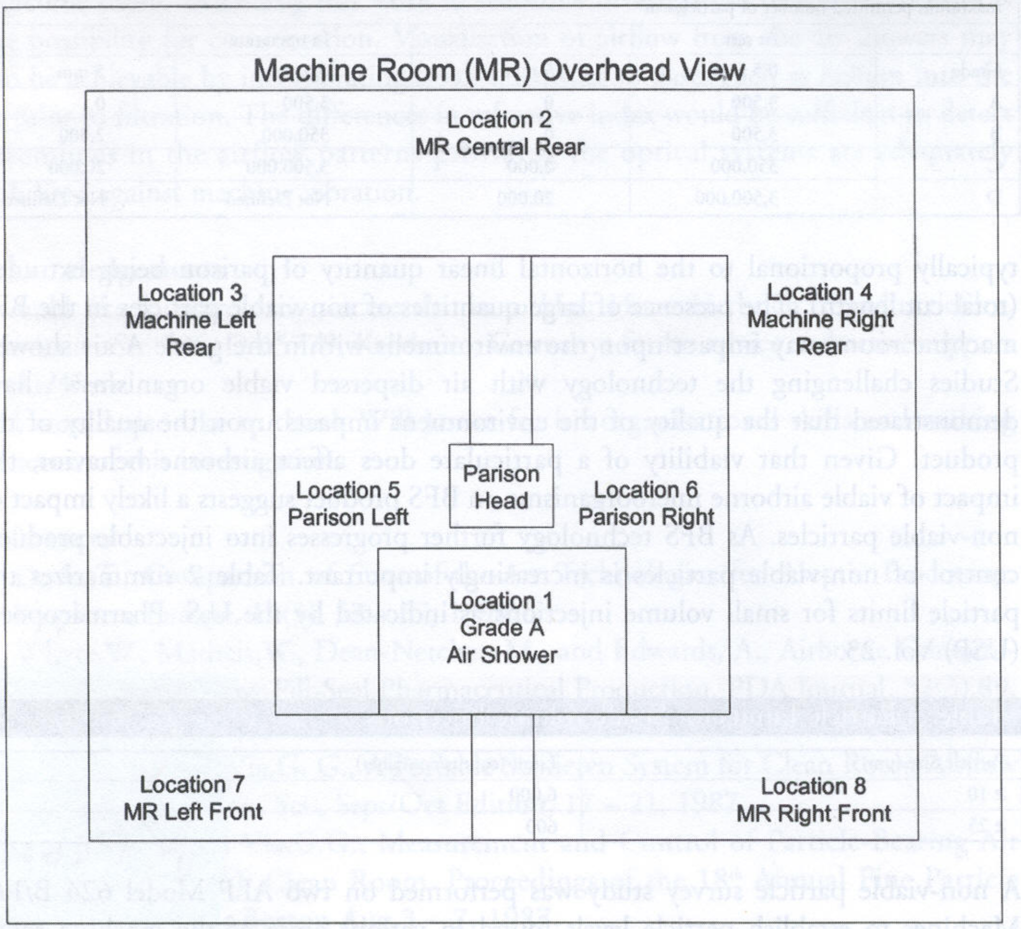
A non-viable particle survey study was performed on two ALP Model 624 B/F/S Machines to establish particle levels found in various areas of the machine room during dynamic conditions. The grade A air shower is routinely monitored during production activity and historical particle levels are known, however this area was also included in the survey study. Each machine was equipped with an electrically heated parison cut-off knife with each process utilizing low density polyethylene (LDPE) resin. Seven locations in the machine room and one location within the grade A air shower (nozzle shroud) were monitored with a Climet Model CI-500 laser particulate counter, refer to Figure 1 for a depiction of the sample locations.

A total of five consecutive sample volumes were taken at each location and particle counts averaged, results are summarized in Tables 3 and 4.

A comparison of particle levels resulting from operation of the two machines reveals a large variation in mean counts. This is likely due to the horizontal linear quantities of plastic used for each process. The Model 624 with the 24 cavity set-up utilizing 6 parisons with a total cut length of approximately 71 cm, as opposed to the Model 624 with the 12 cavity set-up utilizing 12 parisons with a total cut length of approximately 43 cm. Currently there is no guideline for non-viable particles in the machine room under dynamic conditions, however, the results demonstrate that neither machine would meet grade C dynamic condition specifications. The results also indicate that the design of the Model 624 air shower is effective in maintaining a controlled environment despite the high level of particles in the machine room, as the particle results in the air shower were well below the grade A dynamic condition specifications during the study.

Although the technology currently meets published guidelines, process improvements to reduce particle levels should be actively reviewed. It is expected that a reduction in particle levels in the machine room would correspondingly reduce particle levels in the grade A air shower, thereby improving machine performance and raising product quality. There are several routes that may be followed to achieve process improvements in this area.

Figure 1: Non-Viable Particle Monitoring Locations




- *Modification of the Grade A Air Shower*

  Efforts have been made to improve performance of the grade A air shower by design modification[6,7]. Although these modifications appear to have a positive effect on the grade A air shower, the adjacent environment has not been improved and still presents a quality risk to the product. Furthermore, the true impact of these modifications has yet to be quantitatively assessed under controlled challenge conditions.

- *Implementation of Gray Side/White Side B/F/S Machine Design Concept*

  The machine design concept of gray side/white side, isolation of areas that present a contamination risk to controlled environments, is an alternative attempt to control non-viable particles[8]. Application of this design concept requires extensive facility modification and purchase of completely new BFS Machines. Due to the existing installed machine population, this option may not be practical for most companies to implement. While perhaps a viable process improvement for new facility construction, the gray side/white side machine design concept does not directly address the source of non-viable particle generation.

- *Modification of the Parison Cutting Process*

  As previously stated, the primary source of non-viable particle generation is from the parison cut-off process. Modification of this process to eliminate the particle generation source offers the most logical choice for improvement. Automatic Liquid Packaging (ALP) is currently field testing an alternative parison cut-off mechanism (Kleen Kut™) which can be fully integrated into new/existing ALP BFS systems.

| Table 3: ALP Model 624 with a 24 cavity set-up with electrically heated cut-off knife | | |
|---|---|---|
| Sample Location | Mean 0.5 mm particles/m³ | Mean 5 mm particles/m³ |
| 1 - Grade A Air Shower | 353 | 0 |
| 2 - MR Central Rear | 20,933,654 | 86,630 |
| 3 - Machine Left Rear | 23,761,102 | 100,994 |
| 4 - Machine Right Rear | 22,921,614 | 93,042 |
| 5 - Parison Left | 55,217,997 | 456,226 |
| 6 - Parison Right | 61,593,669 | 582,827 |
| 7 - MR Left Front | 16,817,828 | 65,211 |
| 8 - MR Right Front | 9,707,807 | 39,519 |

| Table 4: ALP Model 624 with a 12 cavity set-up and tip/cap insertion with electrically heated cut-off knife | | |
|---|---|---|
| Sample Location | Mean 0.5 mm particles/m³ | Mean 5 mm particles/m³ |
| 1 - Grade A Air Shower | 1,126 | 0 |
| 2 - MR Central Rear | 4,483,134 | 5,261 |
| 3 - Machine Left Rear | 4,949,367 | 3,390 |
| 4 - Machine Right Rear | 2,515,859 | 2,055 |
| 5 - Parison Left | 4,086,683 | 2,634 |
| 6 - Parison Right | 2,009,054 | 2,691 |
| 7 - MR Left Front | 4,475,613 | 2,599 |
| 8 - MR Right Front | 1,990,750 | 1,328 |

| Table 5: ALP Model 624 with a 24 cavity set-up with Kleen Kut™ | | |
|---|---|---|
| Sample Location | Mean 0.5 mm particles/m³ | Mean 5 mm particles/m³ |
| 1 - Grade A Air Shower | 138 | 0 |
| 2 - MR Central Rear | 94,595 | 92 |
| 3 - Machine Left Rear | 7,818 | 28 |
| 4 - Machine Right Rear | 2,712 | 0 |
| 5 - Parison Left | 9,322 | 177 |
| 6 - Parison Right | 1,758 | 21 |
| 7 - MR Left Front | 1,469 | 7 |
| 8 - MR Right Front | 10,664 | 42 |

| Table 6: ALP Model 624 with a 12 cavity set-up and tip/cap insertion with Kleen Kut™ | | |
|---|---|---|
| Sample Location | Mean 0.5 mm particles/m3 | Mean 5 mm particles/m3 |
| 1 - Grade A Air Shower | 519 | 0 |
| 2 - MR Central Rear | 26,546 | 254 |
| 3 - Machine Left Rear | 23,425 | 155 |
| 4 - Machine Right Rear | 20,063 | 261 |
| 5 - Parison Left | 20,826 | 42 |
| 6 - Parison Right | 7,754 | 134 |
| 7 - MR Left Front | 4,929 | 106 |
| 8 - MR Right Front | 15,600 | 49 |

The Kleen Kut™, a mechanism (patent pending) marketed by ALP, operates at ambient temperature eliminating the creation of smoke particles during the cut-off process.

To provide a preliminary assessment of the effectiveness of this modification of the parison cutting process, the original non-viable particle survey study was repeated with the Kleen Kut™ parison cut-off mechanism replacing the electrically heated cut-off knife. The results from the study are summarized in Tables 5-6.

The results demonstrate a marked reduction in non-viable particles in the machine room environment consequent upon use of the Kleen Kut™ mechanism. For example, 0.5 µm mean particle levels in the machine room were reduced by more than 99%, while mean levels in the grade A air shower were correspondingly reduced around 50%. The improvement in machine room environment brought about by the Kleen Kut™ mechanism is evidenced through meeting grade B dynamic condition specifications as opposed to not meeting grade C dynamic condition specifications for the electrically heated cut-off knife.

Implementation of the Kleen-Kut™ cut-off mechanism, under the conditions of these studies, represents a significant improvement in BFS Machine operating capabilities. Furthermore the Kleen-Kut™ parison cut-off mechanism clearly offers users of BFS technology the opportunity to enhance the manufacturing environment without facility modification, equipment modification, or considerable financial investment.

**References:**


1 The Rules & Guidance for Pharmaceutical Manufacture & Distribution 1997

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8 M. Haerer and U. Lichenstein, "White/dark Execution of the Bottlepack Machine with a Background Presentation of the White/Dark Technology," *BFS News*, March Edition, pp. 20-25 (1997).