To:
Dockets Management Branch (HFA-305)
Food and Drug Administration, 5630 Fishers Lane,
Rm. 1061, Rockville, MD 20852, USA

Regarding: Comments on Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Docket number: 2003D-0382

Dear Sirs,
The Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA) is a non-profit association consisting of some 100 members companies world-wide using or supplying Blow-Fill-Seal (BFS) processing equipment. BFS IOA organizes regular meetings to discuss relevant topics and also have close connections to the PDA organization.

It was with great pleasure that the BFS IOA noticed that many of the comments made on the Concept Paper and submitted to the FDA (letter to Mr. Friedman and Mrs. Uratani, dated March 5th 2003) were partly or fully incorporated in the current Draft Guidance. As a result, we find the Draft Guidance text (especially Appendix 2) a major improvement. However, there still exist some issues which we would like to comment via this letter.

As with the comments made on the concept paper, the BFS IOA is focusing on Appendix 2, covering Blow-Fill-Seal Technology, while not forgetting the rest of the draft guidance text when applicable to BFS aseptic processing.

If the FDA have any questions regarding our comments, we are more than happy to discuss these. Your primary contact in technical matters would be undersigned, being the International Technical Officer of the BFS IOA.

Yours faithfully,

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Appendix 2

General comments

The general impression received when reading Appendix 2 of this Draft Guidance is that the advanced aseptic processing characteristics of BFS-technology is not taken into full consideration. When it comes to particle control in the machine room and critical areas, the same demands are put on BFS processing as for traditional aseptic processing. In this respect EMEA has gone further and allows BFS machinery for aseptic production to be placed in grade C environment (corresponding to ISO 8 or Class 100,000 in operation). The vast majority of the world-wide BFS operations (some 1000 machines in pharmaceutical production, with around 400 represented in BFS IOA and around 30% of these in the US) are operating successfully under these conditions. Therefore, the BFS IOA would like to propose a full harmonization with EU GMP in this respect. The underlying reason for allowing BFS-machines to be installed in an ISO 8 environment is the difference in contamination risk between BFS- and traditional aseptic processing. We highly appreciate the FDA´s ambitions with a risk-based approach to GMP´s as mentioned in the first section of the draft guidance [1]. Indeed, the same approach is being taken in Appendix 1 of the EU-GMP [2] and is the underlying reason for stating that grade C (Class 100,000) environment is acceptable when operating aseptic BFS production, The vital issue of reducing the viable count is also reflected in the EU-GMP demand to use grade A/B gowning in this grade C environment surrounding the BFS machine.

According to BFS IOA, the contamination risk from airborne particles of any aseptic process is directly related to exposure of sterile product and microbial challenge. The basic principles behind this have been outlined in the book by Ljungqvist and Reinmüller [3]. In traditional aseptic processing with relatively frequent human involvement, viable particles are shed mainly from operators. This unpredictable shedding of viable particles is largely eliminated in BFS-processing where no operator is present during routine processing. Another major difference involves exposure of sterile product and packaging material. Generally, BFS-containers display a significantly smaller neck opening than corresponding containers made from glass (compare e.g. a glass vial and BFS-ampoule with 13 and 2 mm openings respectively). Although this is the typical case, there can never be any guarantee that the opening area is always smaller. However, the BFS process does show a significantly shorter exposure time than for traditional processes.

At rest, the BFS machine is not producing a parison and no mold carriage movements take place, thus there is no exposure whatsoever of sterile product. The only critical surfaces (the filling nozzles) rest within a stream of sterile air (in the air shower compartment).

In operation, the exposure time of cut parison is typically less than 1 second (during movement from cutting of parison to under the filling nozzles). Time of filling/sealing is naturally determined by container size, but generally the BFS process is faster to seal the product after filling than a corresponding glass line, since the sealing is made in the same position as filling, as soon as withdrawal of filling nozzles are made.

Although the cutting of parison using a so-called hot-knife is a known source of non-viable particles, the BFS technology is renowned for its ability to fill solutions with very low particle contamination (e.g. used as a benchmark of standard solutions for the calibration of particle

counters). Despite this, the BFS industry is constantly trying to improve the technology and find ways to minimize the particle generation without compromising product safety.

A comparison of data on particulates in solution can be seen in Attachment 1, which is a summary of values from five independent European BFS manufacturers, operating according to EU-GMP.

All in all, the relatively lower human intervention and short exposure time are the basic reasons for the robustness displayed by the typical BFS process, as indicated by results from a recent BFS Industry survey, made with the assistance of Ljungqvist and Reinmüller, see Attachment 2. There is also evidence in the literature supporting the superior aseptic quality of the BFS process [4] and the technology is mentioned in the USP as an advanced aseptic process capable of showing low contamination in media fills [5].

The robustness of the BFS process is reflected in the EU-GMP, stating what corresponds to Class 100 environment in the air shower and Class 100,000 in the filling room. It is stated that the environment should comply with viable and non-viable particles at rest and with viable limits only in operation. Grade A/B gowning should be used. As an effect, typical values of viable counts are significantly lower than the stated limits during normal BFS processing in grade C/Class 100,000 areas.

We sincerely hope that the FDA take this risk-assessment based approach into consideration and introduce a fully FDA / EU-GMP harmonized standpoint in their final Guidance document for BFS manufacturing. In both the FDA draft guidance and EU-GMP the Class 100,000 or grade C limit for viable particles are 100 CFU/m^3. EU-GMP states grade A/B gowning to minimize contribution to viable counts during potential operator presence.

Specific comments

Line 1717: "Blow-Fill-Seal (BFS) technology is an automated..."

The advanced status of the BFS process is indicated in e.g. USP <1116>

We propose: "Blow-Fill-Seal (BFS) technology is an advanced aseptic automated..."

Line 1720: "...packaging ophthalmics and, less frequently, injectables."

On a world-wide basis, BFS is today widely used also for respiratory and IV-products.

We propose: "...packaging ophthalmics, respiratory care, IV fluids and injectables."

Line 1732/1735: "Move the parison under the blow-fill needle (mandrel)" / "Remove the mandrel"

This is not common BFS terminology.

We propose: "Move the parison under the blow-fill nozzle (mandrel)" / "Remove the nozzle (mandrel)"

Line 1749: We propose to rewrite this section as follows:

The classified environment surrounding BFS machinery should generally meet Class 100,000 (ISO 8) standards. HEPA-filtered or sterile air provided by membrane filters should be used during steps when sterile product or materials are exposed (e.g. parison formation, container molding or filling steps). Air in the critical area should meet Class 100 (ISO 5) and the environments should comply with viable and non-viable limits at rest and with viable limits only in operation.

Line 1771: "..integrity of the cooling or boiling system (e.g. mold plates, gaskets)..

The terminology used in this sentence is not normally used in the BFS industry. Indeed, we are somewhat puzzled by the term "boiling system" and wonder what this mean? In addition, the word "mold plates" are not normally used. If mold surface is meant, we fail to see how this surface, only in contact with the exterior surface of the container could possibly contaminate the sterile drug product.

We propose: "..integrity of the cooling/heating system / utilities in close proximity to the mold connections should be carefully monitored and maintained."

Line 1796: "Microbial air quality is particularly important"

Referring to the discussion in the general comments of this letter, we fail to see why microbial air quality should be "particularly important" compared to traditional aseptic processing. Suggested to cross out this sentence.

References

[1] FDA draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, p 4, line 127, August (2003)

[2] EC guide to Good Manufacturing Practice, Revision to Annex 1 – Manufacture of Sterile Products, Sept. (2003)

[3] Ljungqvist, B., Reinmuller, B., Cleanroom design: Minimising contamination through proper design, Interpharm Press (1997)

[4] Bradley, A., Probert, S., Sinclair, C. S., Tallentire, A., Airborne Microbial Challenges of Blow-Fill-Seal Equipment: A Case Study, *J. of Parenteral Sci. and Tech.*, 45(4), 187 (1991)

[5] USP 26, <1116>, (2003)

Attachment 1 to:

The Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA) comments on Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Docket number: 2003D-0382

Particles in solutions produced by Blow-Fill-Seal (BFS) processing

From a quick survey among BFS users, we have been able to get a picture of the normal levels of particles seen in various solutions produced by BFS processing.

Five companies producing both aseptic and terminally sterilized SVP products have sent in data on particulate contamination analyzed according to Eur. Ph. or USP methods. The data is for 10 and 25 mikron particles with pharmacopoeia limits being 6000 and 600 particles/container, respectively.

The typical values seen are very consistent among the companies:

1) 10 µm particles: 10 – 60 / container (mean values)
2) 25 µm particles: 3 – 10 / container (mean values)

Although this is by no means any scientific investigation, we do hope to perform a more thorough particulate contamination study within the BFS IOA and would like to present this data at a later occasion. The figures above do, however, indicate that typical values of particles in solution generally are orders of magnitude lower than the limits stated in the pharmacopoeias and that the non-viable particle generation from the parison cutting normally do not lead to increased levels of particulates in the finished product.

Indeed, BFS processing is well known for its excellent ability to produce low particulate contamination products, whether using class 100,000 or 10,000 clean rooms.

Attachment 2

The Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA) comments on Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Docket number: 2003D-0382

EXCERPTS OF ONGOING BLOW-FILL-SEAL SURVEY

Compiled by
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Introduction

The validation of aseptic processes using advanced processing techniques such as blow-fill-seal technology continues to be an area of interest to pharmaceutical industry and regulatory authorities.

To illustrate current industry practices with regard to aseptic processing using BFS technology, a survey is conducted by the Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA). The questionnaire is based on an industry survey made earlier this year among conventional aseptic producers. This survey was conducted by the PQRI (Product Quality and Research Institute) and the questions in this survey follow very closely those in the PQRI document. Questionnaires have been sent to BFS users of aseptic processing worldwide.

With responses still being collected; until today, 10 responses representing 72 filling lines were received, representing European, Australian, Asian and American manufacturers.

Excerpts from the responses have been performed and the answers are compiled in the following.

BFS IOA 2003 Aseptic Processing Survey; Excerpts

General Filling Line Information

1. **Filling Line:**

   For each BFS Filling Line at your facility, fill out a row on the spreadsheet for each media fill run. Fill out using sequential line numbers (1,2,3, etc.) or another appropriate descriptor to describe the individual line (actual line numbers used in your facility are *not* required). (Example: If you performed 4 media fills in the past 12 –14 months on a single filling line fill out a line on the spreadsheet for each media fill – see example).

Ten companies with a total of 72 filling lines have performed 205 media fills over the past 12 – 14 months.

2. Line Speed:

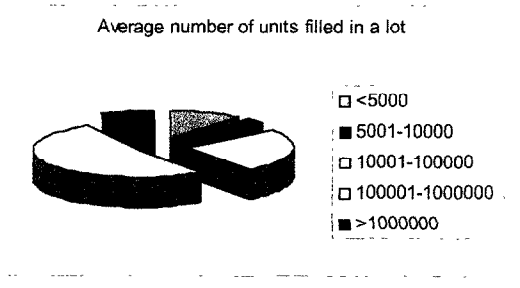
Indicate average # of units filled/hours

<2000	20.8 %
2001-5000	50.0 %
5001-10000	18.1 %
10001-50000	11.1 %

4. Batch Size:

Average number of units filled in a lot.

<5000	11.1 %
5001-10000	2.8 %
10001-100000	26.4 %
100001-1000000	51.4 %
>1 000000	8.3 %



6. Min Volume:

State minimum fill volume run on the line (specify in ml per container)

	Min volume
<1 ml	31.9 %
1-5 ml	19.4 %
6-10 ml	27.8 %
11-100ml	16.7 %
>100 ml	4.2 %

7. Max Volume:

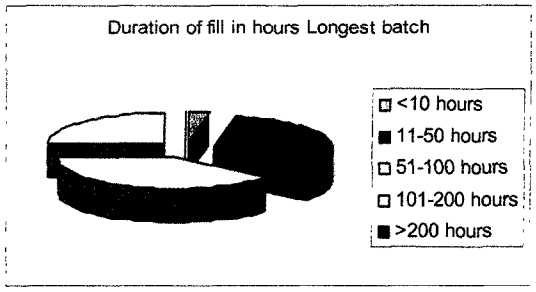
State maximum fill volume run on the line (specify in ml per container)

	Max volume
<1 ml	9.7 %
1-5 ml	18.1 %
6-10 ml	20.8 %
11-100ml	40.3 %
>100 ml	11.1 %

8. Duration of Fill:

State duration of the longest aseptic processing operation (lot) in hours (includes time at which aseptic transfers and filling begins, to the final unit filled).

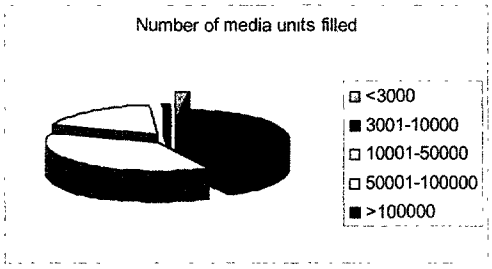
<10 hours	2.8 %
11-50 hours	33.3 %
51-100 hours	38.9 %
101-200 hours	25.0 %
>200 hours	0 %



Media Fill Specific Information

9. Batch Size: Number of media units filled.

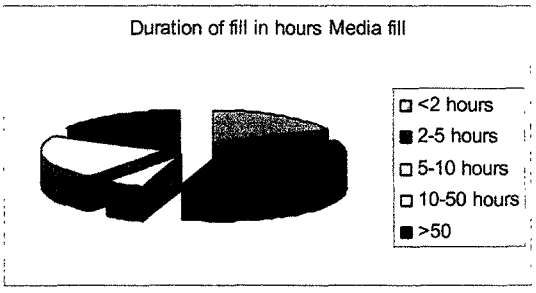
<3000	2.0 %
3001-10 000	40.5 %
10 001-50 000	38.0 %
50 001-100 000	18.5 %
>100 000	1.0 %



11. Duration of Fill:

State duration of the media fill in hours.

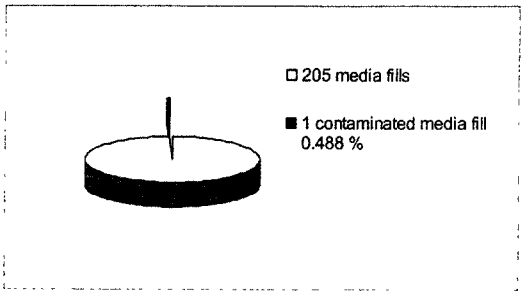
<2 hours	18.5 %
2-5 hours	36.1 %
5-10 hours	3.9 %
10-50 hours	23.9 %
>50 hours	17.6 %



16. # of units contaminated:

One media fill contaminated by 1 contaminated unit.

Total number of media fills 205
Number of contaminated media fills 1
0.488 %



Conclusion

The excerpts from the ongoing survey illustrate the current status of blow-fill-seal technology when used for aseptic processing of sterile drugs.

The BFS IOA together with Ljungqvist/Reinmüller would be happy to present the complete study results when all data has been compiled.