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October 10, 2003

Division of Dockets Management (HFA 305)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2003D-0382

Dear Sir or Madam:

The purpose of this letter is to comment on the Food and Drug Administration document entitled *Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing."* As a general comment, I would like to commend the agency for the amount of work that unquestionably went into the revision of the 1987 Guidelines on the same topic. The proposed draft clearly reflects a substantial effort to provide well-intended guidance to the industry in many areas that were vague or left out of the 1987 Guideline. Despite the fact that the review team went out of their way to justify the proposed changes in light of the basic cGMP regulations, the agency will most likely receive formalized responses from trade and professional associations that focus on the impact and the associated hardship the proposed draft will have on the "convenience" of their membership more so than safety issues the agency is, by rights, more sensitive to. Even without the justification and direct references to the cGMP regulations, various areas addressed in the draft, such as media fills, equipment qualification and environmental control programs tend to guide the industry to a better understanding of the processes performed. In my opinion, this "gain control" spirit is missing in the section regarding sterile filtration. This aspect of the proposed guideline needs to be addressed, since even if better controlled, aseptic processing steps subsequent to sterile filtration cannot improve the sterility assurance of the product solution once sterile filtered. In anticipation that the agency will most likely receive very little input on this topic from other sources and considering that sterile filtration is my area of expertise, I concentrated my comments on this topic.

Much like the rest of the document, the section that covers sterile filtration presents a number of valuable concepts that may be better understood by the industry if rearranged in a more consequential manner, as I suggest in the attached redlined rewrite. In addition, my main concern continues to be that as presented by the agency, sterile filtration will again be taken for granted, since some aspects needed to bring this crucial processing step under the control of filter users continue to be treated as lightly, if not worse, than they were in 1987. If not modified, the message of the proposed draft will very likely continue to be read by the industry as it has been for several decades, namely, "Don't worry, let the filter manufacturer tell you how good their filters are..."

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Without a push by the agency for a better understanding of any process, the industry has always taken the easier way out. Case in point: moist heat sterilization. Prior to the advent of Validation in the 1970's, most pharmaceutical companies settled for following the generic cycle instructions provided by autoclave manufacturers. The then "new" requirement for autoclave users to become involved in the validation of autoclave cycles created increased awareness of moist heat sterilization and later many other processes. Unquestionably, this had an immediate positive impact on the sterility assurance of terminally processed parenterals, and, ultimately, overall product quality. In sharp contrast to the progress made in moist heat sterilization, filter users have yet to become aware of potential limitations of sterile filtration, and failure by users to "gain control" over this crucial process step has no doubt been the cause of loss of product from unexplained sterility problems and likely even allowed non-sterile injectable products to inadvertently slip into the distribution channels. If the relaxed attitude towards sterile filtration is perpetuated, filter users will not gain control of the process nor will they perform meaningful validations. Why should they, if for practical purposes the validation of sterile filtration continues to be optional? And revalidation of sterile filtration is not even mentioned, no matter how sensible the task seems to the agency and the industry alike for most other operations and far more permanent installations such as autoclaves.

A sound set of regulations should assist the industry in producing pharmaceutical products of better quality, but this may not be the case if filter users strictly follow the proposed guidelines for sterile filtration. The regulations in other countries are no that much better in this area, but sadly enough, other countries look at the regulations of our great nation for guidance. Thus, in order to make the guideline more meaningful, I offer a few additional suggestions in the attached redlined text. A rationale for some of those suggestions follows below.

Specific comments:

1. Section IV D (starting on line 262) talks about the importance of purity and microbial quality of compressed gases. Additional guidance is warranted.

Rationale: The draft recognizes the importance of "sterile" compressed gases for such purposes and suggests the use of membrane filters, but it provides no guidance on how the expected filter performance can be validated. It would be very difficult to end up with a sterile product if the compressed nitrogen to pressurize or dry, let us say, a 1000-liter sterile holding tank is allowed to have the microbial allowance made for critical areas.

2. Line 969 states: "...rated porosity of 0.2 micron or smaller." This should be changed to "...a numerical retention rating of 0.2 micrometers or smaller."

Rationale: Technically, porosity cannot be measured in micrometers. If the expression were changed to "...rated pore size..." the statement would be in conflict with the (correct) observation that the numerical rating assigned by the filter manufacturers is "...a figment of their imagination..." as stated by Ed Fry in "FDA Update on Aseptic Processing Guideline", J. Parenteral Sci, Technol. 41 (2) 56 (1987). It is not the "rating" but the actual "integrity" (a combination of true pore size and absence of defects) of the filter that assures the desired retention characteristics. The numerical rating was discouraged in 1987 and should have no place in 2003 regulations either. A better approach would be to define retention performance by using a model organism, e.g., *B. diminuta*, as discussed

on lines 974+. However, it must be recognized that the suitability of *B. diminuta* is challenged in several articles, "commercially driven," as they may be:

- S. Sundaram, J. Eisenhuth, G. Howard Jr., and H. Brandwein, "Retention of Water-Borne Bacteria by Membrane Filters Part I, Bacterial Challenge Tests on 0.2 and 0.22 Micron Rated Filters", PDA J. Pharm. Sci. Technol. **55** (2): 65 (2001).
- S. Sundaram, S. Mallick, J. Eisenhuth, G. Howard Jr., and H. Brandwein, "Retention of Water-Borne Bacteria by Membrane Filters Part II, SEM and FAME Characterization of Bacterial Species Recovered Downstream of 0.2 / 0.22 Micron Rated Filters", PDA J. Pharm. Sci. Technol. **55** (2): 87 (2001).
- S. Sundaram, J. Eisenhuth, G. Howard Jr., and H. Brandwein, "Retention of Water-Borne Bacteria by Membrane Filters Part III, Bacterial Challenge Tests on 0.1 Micron Rated Filters", PDA J. Pharm. Sci. Technol. **55** (2): 114 (2001).

Perhaps time has come for the agency to investigate the choice of a microbial model independently, much like over 30 years ago the switch from *S. marcescens* to *B. diminuta* as a marker organism for sterile filtration was prompted by FDA research.

3. Line 984: "A challenge concentration of at least 10^7 organisms per cm^2 ..." is specified, but emphasis should also be made on the expected "zero" passage.

Rationale: Self evident.

4. Lines 985 to 987: "A commercial lot's actual influent bioburden should not include microorganisms of a size or concentration that would present a challenge beyond that considered by the validation study." This statement should be changed to read "A commercial lot's actual influent bioburden should not include microorganisms of a size smaller than and/or a total concentration that would present a challenge beyond a factor of 10^x (where "x" is a safety margin that should be suggested by the agency) of the level covered by the retention validation study."

Rationale: As proposed in the draft, this statement presents a serious and unacceptable health risk to the general public since it makes no allowance for a safety margin. "Luckily," the statement is in conflict with common sense and other (safer) statements made within the document, e.g., Section X C on Pre-filtration Bioburden, which "...should be minimal..." (line 1316). Albeit the lack of a numerical specification, this is far more suitable guidance. Much like the safety margin in terminal sterilization, the ratio between the validated retention capability of the filter and the actual bioburden of a batch of product can be interpreted as a safety margin for the sterile filtration process. As stated in the draft, the Agency endorses the outcome of sterile filtration to be, in essence, a 50-50 toss-up. The autoclave equivalent on line 1100 would be "...A sterility assurance level of 10^0 is adequate..." instead of suggesting the traditional 10^6 safety margin. The level of 10^7 per cm^2 can cautiously be compared to the 10^{12} overkill, also good for a safety margin of 10^6 only if there are no more than 10^6 microbes of a D-value of 1 minute in the original bioburden. Such equivalents between regular sterilization and sterile filtration need to be understood by the agency and filter users before regulations like this one can be considered sound and reasonable.

5. Lines 1001+: The draft lists the various parameters that affect the retention capability of sterile filters. A more consequential rearrangement of these very important concepts is suggested in the attached (redlined) revision. It is also important to point out that if validated as (appropriately) requested, i.e., "over-kill" bioburden level, product as a carrier vehicle and simulation of the process parameters, practically all of the variables

become fixed parameters, leaving only the “integrity” of the filter as the key parameter against which the retention performance can be correlated. Hence, the importance of filter integrity, but this aspect does not receive the attention necessary to provide sound guidance to the filter user. Vague requirements such as the statements in lines 1017 to 1025 regarding the validity of the scale-up from challenge test level to the production setting should be more specific. Also please refer to comment 7 below.

6. Lines 1010+ state: "When the more complex filter validation studies go beyond the capabilities of the filter user..." Please see redlined text, but this sentence should, by rights, be completed with "...the firm shall not be granted a license to produce sterile products by aseptic processing."

Rationale: The use of independent third party laboratories might be justifiable, but allowing filter manufacturers to be “judge and jury” of their own products goes against all rules of common sense and the general spirit of “validation” as set forth throughout GMP regulations and FDA Guidelines. Even PDA TR No. 26 suggests the filter user take responsibility for in-product retention validation. Ideally, much like 25 years ago the industry learned how to work around previously “non-existing” cold-spots in autoclaves, the industry should learn how to cope with the filtration equivalent thereof. Filter users need to be encouraged to become more involved in the validation and gain control of this important process step, not offered an easy way out. This 1987 mistake should not be perpetuated even in light of the request that “...it is the responsibility of the filter user to review...” (line1012), since the fact is that most filter users end up basing their review on potentially biased information provided to them by filter manufacturers. How can the FDA have confidence in a process that by the filter user's own admission needed to be explained to the agency by the filter supplier? (See Millipore advertisement campaign “testimonials” on back covers of Pharmaceutical Technology, a sad but evidently real reflection of the industries “control” over this important tool).

7. Line 1024 states: "A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies." This is appropriate, but the currently accepted practice of “diffusion” integrity testing production filters at 80% of the minimum bubble-point value established in the challenge studies, as promoted by the filter manufacturers, is technically unacceptable. A detailed discussion of this error can be found in H. G. Schroeder, “Rationalization and Valid Scale-Up of Integrity Test Parameters for Sterilizing Grade Filters,” PDA J. Pharm. Sci. Technol. 55 (2): 134 (2001). A “certificate of compliance” often issued by “judge and jury” of their own filter product line is also a poor substitute for a sound integrity test.

8. Line 1027 endorses the use of sterilizing grade filters in series. While this has indeed become common practice, it also creates a false sense of security. In an oral presentation at the December 2001 PDA meeting, Dr. Sundaram presented compelling evidence that redundant filtration is not a fool-proof safeguard against passage of organisms able to penetrate filters recognized as sterilizing grade by a B. diminuta challenge test. Improperly validated filters in series are as unsafe as two consecutive un-validated autoclave cycles. (This concept was moved into the “validation” portion of the section with a caveat to test both filters for integrity if two are required to assure sterility.)

Last, but not least, the definition on line 2038: "Sterilizing grade filter- A filter that, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent." No room for error? Such a statement gives filter users a false sense of

security that is sure to lead them into trouble. Even the reliability of autoclave cycles is validated to within a finite probability of survival, and an equivalent probabilistic limitation must be recognized for sterile filtration as well. The statement is particularly surprising in view of the fact that the FDA is (pain)fully aware of sterility failures that have occurred in the field as a consequence of filter failures, such as described in the above cited article by Ed Fry while he was working for the agency. At best, the concept of absoluteness is "commercial" rather than scientifically sound. Even articles written by the very filter manufacturers in support of their own product line shows clearly that under currently accepted filter integrity test practices it is mathematically impossible to count on "total" retention when a filter is challenged to the prescribed 10^7 cfu/cm² (e.g., Pall, D.B., and E. Kirnbauer, "Bacteria Removal Prediction in Membrane Filters", 52nd Colloid and Surface Science Symposium, University of Tennessee, Knoxville, TN, 12 June 1978, reprints available from the Pall Corporation as STR PUF 13, Pall Corporation 1990).

Please note that these comments are limited to the area of sterile filtration, and only address issues covered in the proposed draft. In addition to the pivotal importance of bacteria retention capability, other aspects (e.g., compatibility, extractables, etc.) of sterile filters need to be considered, but such are not addressed in the document at all. Evidently, such aspects are not considered pertinent by the agency from a regulatory point of view. The reader is correctly referred to PDA Technical Report No. 26 for additional information and guidance on such issues, but it needs to be pointed out that the roster of the Sterile Filtration Task Force was practically dominated by filter suppliers. The resulting "consensus" is not necessarily in the best interest of the advancement of general knowledge in the field of filtration, since filter manufacturers prefer for users (and the agency, for that matter) not to know "too much" about sterile filtration.

One final comment: Some members of our community who are actively involved in the field of sterile filtration may take exception to the choice of references cited. A broader and more appropriate reference base can be found in PDA Technical Report No. 26.

Independently and respectfully submitted,



Hans G. Schroeder, Ph.D.,
Senior Consultant

cc: Mr. Richard Friedman, CDER (HFD-320)

Suggestions for the section on "Filtration Efficiency"

Draft — Not for Implementation

Contains Nonbinding Recommendations

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08/22/03

B. Filtration Efficacy

Filtration is a common method of sterilizing drug product solutions. Ideally, an appropriate sterilizing grade filter is one that reproducibly removes all microorganisms from the process stream, producing a sterile effluent. Such filters usually have a numerical retention rating of 0.2 micrometers or smaller. Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst-case production conditions regarding the size of microorganisms in the material to be filtered and integrity test results of the filters used for the study. The microorganisms should be small enough to both challenge the filter and simulate the smallest microorganism that may occur in production. The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly grown, harvested and used, can be satisfactory in this regard because it is one of the smallest bacteria. Bioburden of unsterilized bulk solutions should be determined on a "x" basis (the agency should have a suggestion as to batch per batch, weekly, monthly...) to trend the characteristics of potentially contaminating organisms. In certain cases, when justified as equivalent as or better than use of *Brevundimonas diminuta*, it may be appropriate to conduct bacterial retention studies with a bioburden isolate. The number of microorganisms in the challenge is important because a filter can contain a number of pores larger than the nominal rating, which have the potential to allow passage of microorganisms. The probability of such passage is considered to increase as the number of organisms (bioburden) in the material to be filtered increases (?Refs. 10, 11, 12). A challenge concentration of at least 10^7 organisms per cm^2 of effective filtration area of *B. diminuta* should generally be used, and no passage should be observed for the filter to be considered sterilizing. A commercial lot's actual influent bioburden should not include microorganisms of a size smaller and/or a total concentration that would present a challenge beyond a factor of 10^x (where "x" is a safety margin that should be suggested by the agency) of the level, covered by the retention validation study. While the retention capability should be assessed against physical integrity test results of a single filter, the use of two sterilizing-grade filters in series is recommended in order to enhance the margin of safety of the filtration step; this is a common practice. If redundant filtration is found to be necessary to achieve sterility, both filter units should meet validated integrity criteria.

The filter related factors that affect the retention performance obviously include the filter itself, the compatibility of the filter materials and components with the product to be filtered and most importantly the state of integrity of the filter as documented by a suitable physical integrity test. Forward flow and bubble point tests, when appropriately employed, are two integrity tests that can be used. A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies.

(Note: Concepts not deleted, just reorganized...) Product related factors that can affect filter performance, include the viscosity

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of the material to be filtered, the pH, the osmolarity and other physicochemical properties of the product filtered. Therefore, direct inoculation of the challenge organism into the, formulation provides the most appropriate assessment of the effect of the product on the retention performance of the filter and as well as the impact of the formulation on the challenge organism. However, directly inoculating *B. diminuta* into products with inherent bactericidal activity or into oil-based formulations can lead to erroneous conclusions.

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Processing related factors that can affect the filter performance include the applied, pressure differential, flow rates, use time, temperature, and the effects of hydraulic shock. When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted using the worst-case conditions, such as maximum filter use time and pressure (Ref. 12). When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed using an appropriate alternate method. For example, the drug product could be filtered in a manner in which the worst-case combination of process specifications and conditions are simulated. This step could be followed by filtration of the challenge organism for a significant period of time, under the same conditions, using an appropriately modified product (e.g., lacking an antimicrobial preservative or other antimicrobial component) as the vehicle. Any divergence from a simulation using the actual product and processing conditions should be justified.

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Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation tests go beyond the capabilities of the filter user, tests may be conducted by independent third party laboratories. However, it is the responsibility of the filter user to review the validation data on the efficacy of the filter in producing a sterile effluent. The data should be applicable to the user's products and conditions of use because filter performance may differ significantly for various conditions and products.

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After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filter replacements (membrane or cartridge) used in production runs will perform in the same manner. Normally, integrity testing of the filter is performed prior to processing, after the filter apparatus has been assembled and sterilized. It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration. Sterilizing filters should be routinely discarded after processing of a single batch.

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Suggestions for the section on “Filtration Efficiency” (Redline “accepted”)

Draft — Not for Implementation
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B. Filtration Efficacy

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The filter related factors that affect the retention performance obviously include the filter itself, the compatibility of the filter materials and components with the product to be filtered and most importantly the state of integrity of the filter as documented by a suitable physical integrity test. *Forward flow and bubble point* tests, when appropriately employed, are two integrity tests that can be used. A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies.

Product related factors that can affect filter performance include the viscosity of the material to be filtered, the pH, the osmolarity and other physicochemical properties of the product filtered. Therefore, direct inoculation of the challenge organism into the

formulation provides the most appropriate assessment of the effect of the product on the retention performance of the filter and as well as the impact of the formulation on the challenge organism. However, directly inoculating *B. diminuta* into products with inherent bactericidal activity or into oil-based formulations can lead to erroneous conclusions.

Processing related factors that can affect the filter performance include the applied pressure differential, flow rates, use time, temperature and the effects of hydraulic shock. When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted using the worst-case conditions, such as maximum filter use time and pressure (Ref. 12). When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed using an appropriate alternate method. For example, the drug product could be filtered in a manner in which the worst-case combination of process specifications and conditions are simulated. This step could be followed by filtration of the challenge organism for a significant period of time, under the same conditions, using an appropriately modified product (e.g., lacking an antimicrobial preservative or other antimicrobial component) as the vehicle. Any divergence from a simulation using the actual product and processing conditions should be justified.

Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation tests go beyond the capabilities of the filter user, tests may be conducted by independent third party laboratories. However, it is the responsibility of the filter user to review the validation data on the efficacy of the filter in producing a sterile effluent. The data should be applicable to the user's products and conditions of use because filter performance may differ significantly for various conditions and products.

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