

PDA Commentary on:

"Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products," Federal Register December 3, 1993

Explanatory Note:

In late 1992 and 1993, FDA's Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (DVM) conducted a series of workshops on the data requirements for NDAs, ANDAs, Supplements and other applications for sterile drugs, including those subject to terminal processes and aseptic filling. True to forecasts, the requirements were published as a "guideline" on December 3, 1993 [Docket No. 93D-0312] for 30 day comment, extended to 60 days. The guideline was republished in November 1994, with minor typographical revisions, as part of FDA's "Guidance to Industry Series."

PDA's comments were prepared by a task force of member scientists and regulatory experts, and submitted to FDA on January 31, 1994. FDA considered the guidance as effective when published.

PDA staff contact: James C. Lyda, x121
July 1996

January 31, 1994

Dockets Management Branch (HFA-305)
US Food and Drug Administration
Room 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Re:
Docket No. 93D-0312
Response to "Guideline for Submitting Documentation for
Sterilization Process Validation in Applications for Human
and Veterinary Drug Products," Federal Register December
3, 1993

Dear Sir/Madam:

Enclosed please find the Parenteral Drug Association (PDA) response to the above notice. For almost 50 years, PDA has served the pharmaceutical industry in the areas of sterile manufacturing technology and quality assurance. This subject is highly important to the association's members, and we welcome the opportunity for comment.

We urge FDA to consider and respond to these comments before finalizing the guideline.

Sincerely,

Edmund M. Fry
Executive Vice President

PARENTERAL DRUG ASSOCIATION, INC.
January 31, 1994

Commentary to the US Food & Drug Administration
"Guideline for Submitting Documentation
for Sterilization Process Validation
In Applications for Human and Veterinary Drug Products"
[Docket No.93D-0312] December 3, 1993

Introduction

Parenteral Drug Association, Inc. (PDA) is a scientific and technical association whose members share professional interest in the development, formulation, manufacture and regulation of pharmaceuticals and health care products. PDA was founded 47 years ago with a focus on sterile dosage forms. Since then PDA has issued numerous technical publications covering manufacturing, validation, and quality assurance systems that are recognized worldwide. PDA's 5,000 members reside in over 40 countries, and represent all disciplines and facets of the pharmaceutical and health care industries including dosage form and bulk production, equipment manufacturers, academia, suppliers of materials and services, and regulatory authorities.

The subject guideline falls directly in PDA's primary area of interest and expertise. PDA has long served as a forum for dialog regarding the technical issues covered by the guideline. FDA has always been a part of that dialog since the regulatory environment impacts strongly on sterile pharmaceutical production.

This response was prepared by a task force of PDA individual members (see Attachment 1) who represent a broad cross-section of the human and veterinary pharmaceutical industry. The task force solicited comments from PDA's worldwide membership, and those comments provide the basis for this response.

PDA appreciates the opportunity to comment to FDA on this important policy development. We urge FDA consideration and response to these comments before the guideline is finalized.

General Comments

PDA notes the guideline contains frequent statements that it represents recommendations, not requirements, for information to be submitted with an application or supplement.¹ We urge FDA to continue to view the guideline in such light. Many of our members recognize the value of guidance regarding the information FDA expects to review.

To our knowledge sterilization is the only drug manufacturing process for which firms are required or expected to submit process validation documentation in the marketing application. The guideline requires that very detailed and extensive information regarding manufacturing and sterilization processes be provided with the applications. In this respect the guideline represents a very different, and potentially problematic, approach to application filing requirements compared to other dosage forms or processes.

PDA is concerned that submission of detailed process information and operational procedures in the application will result in the applicant being legally bound to adhere to procedures that are provided with the application, as is currently FDA practice for other information in applications. We fear this will lead to requirements for FDA pre-approval for even minor process changes.

Costs of Pre-Approval for Minor Process Changes

PDA objects to a requirement for pre-approval supplements when making minor process changes for the following reasons:

1. Longer Supplement Review Time/Loss of Process Improvement Flexibility : Pharmaceutical firms require flexibility to allow for *timely* process improvements and *timely* resolutions of process problems. FDA review and approval times have not provided the needed flexibility. It is not unusual for FDA review of a supplement to take 12-24 months. Pre-approval of changes in processes and systems, as currently described by the guideline, will doubtless overburden the Agency and result in further extending the review time of supplements. By requiring submission and pre-approval of scientifically validated changes to all sterile process systems, FDA is limiting

In this document PDA uses the term marketing application, or application, as descriptive of the different types of applications and supplements covered by the guideline, e.g. NDA, NADA, ANDA, AADA, etc.

the manufacturer's flexibility to resolve equipment and processing problems and improve processing systems which result in product improvement.

In addition, it is our understanding that these supplements would address the CMC section of the application, and thus be exempt from user fees. As such these supplements will take a lower priority for Agency review. The net effect will be unnecessary delays by firms in making process improvements and will even discourage firms from making improvements.

2. Field Investigator Review/Duplication of Effort: The information to be submitted in an application, per this guideline, has historically been reviewed by field investigators during inspections. Changes in study design, methodology, SOP's etc. (see below) were previously made at the discretion of the manufacturer after appropriate internal evaluation and internal review. These changes were available for the investigator's review during inspections.

PDA has every reason to believe field investigator review during inspections will continue. Despite FDA's intent to work cooperatively between the field and headquarters, it seems FDA is inviting a duplication of effort which will result in inefficient use of industry and government resources. There will be regulatory confusion from such field/HQ duplication. The industry and FDA have witnessed the results of such duplication and confusion in recent years. FDA should not continue a review system that leads to inconsistencies in policy.

The industry has many years of experience in the design, conduct and assessment of validation studies for sterile processes. In our view, the provisions of this guideline will not result in increased safety or quality of sterile pharmaceuticals. We are aware of no industry-wide adverse data or evidence justifying the amount of detail requested, and the resulting inflexibility from inclusion of this information in the application. However, it is appropriate that the detailed information specified in the guideline be available on site since this information provides justification for a manufacturer's current processes and operations.

Processes Where Manufacturer Flexibility is Needed

In the opinion of PDA the following portions of the guideline are examples of sections which should not be considered legally binding. Firms should maintain the flexibility to make changes after appropriate revalidation studies and internal reviews.

Section II A 3:

The Autoclave Process...(re: Manufacturer and Model)

Section II A 4:

Autoclave Loading Patterns

Section II A 6:

Requalification of Production Autoclaves

Section II B 2:

Thermal Monitors

Section II C 1:

Identification and Characterization of Bioburden Organisms

Section II C 2:

Specifications for Bioburden

Section II C 3:

Identification, Resistance, and Stability of Biological Indicators

Section II D:

Microbiological Monitoring of the Environment

Section II E 4:

The Sensitivity of the Test

Section II H:

Evidence of Formal, Written Procedures

Section IV A 2:

Location of Equipment

Section IV B 1:

Drug Product Solution Filtration

Section IV B 2:

Specifications Concerning Holding Periods

Section IV D:

Procedures and Specifications for Media Fills

Section IV E:

Actions Concerning Product When Media Fills Fail

Section IV F:

Microbiological Monitoring of the Environment

Section IV G:

Container-Closure and Package Integrity

(see "Specific Comments" for examples of recommended text)

changes.

Advantages of Field Inspection Review of Sterile Process Validation Data

As previously mentioned, PDA supports the availability for FDA review of the sterilization process validation information described in the guideline. However, it is PDA's opinion that providing this information in the application is redundant to the review conducted during the pre-approval inspection (PAI) and routine GMP inspections. PDA believes that the inspection is the ideal mechanism for reviewing this information for a number of reasons:

- The information required is extensive and detailed, and by its nature leads to reviewer questions. These questions can best be answered by company experts during an inspection.
- Much of the information is GMP in nature, involves manufacturing processes related to *numerous products*, and is not related to the safety and efficacy of a *specific product*. Since the review involves the evaluation of a firm's manufacturing capability and control systems (i.e. aseptic processing) it can best be accomplished on site by field investigators familiar with manufacturing processes.
- In addition, the stated purpose of the FDA review is to perform a scientific evaluation of studies. Any specific information and data that are requested are intended to provide assurances to the FDA that the firm has adequate procedures in place and that sufficient data are available to establish adequate sterility assurance levels. FDA objectives may be better served by evaluating the adequacy of a firm's overall systems and program, rather than to evaluate specific validation data as part of the application review. In PDA's opinion, detailed audits of process data should be part of the field inspection approach in evaluating the adequacy of the firm's program. We believe that a second review of this information when associated with a specific application is redundant to the review during the PAI or regular inspection, and is not an effective use of FDA's limited resources.

Conclusion

In conclusion, PDA recommends that the information on sterilization process validation described in the guideline be available at the site of the pharmaceutical firm for FDA review during the pre-approval inspection or routine GMP inspection. In order for both FDA and the pharmaceutical industry to avoid the use of resources on redundant activities PDA recommends that this detailed information not be required as part of the marketing application, allowing firms the continued flexibility in making timely process improvements after appropriate validation studies and internal review.

Specific Comments

1. Consistent with PDA's recommendation that the information be available on site, and not submitted as part of the application, the following sections of the guideline are representative examples where the word "available" should be substituted for "submitted" or "provided:"

- a.
Section II A 2
- b.
Section II A 4
- c.
Section II B 1
- d.
Section II B 4
- e.
Section IV B 1
- f.
Section IV C

In such cases where it is recommended that information be provided in the marketing application, the guideline should be reworded to state that the information would be available for FDA review during the site inspection.

2. Section II B 1: Heat Distribution and Penetration Studies (change to read "Temperature Distribution and Heat Penetration Studies".) Heat distribution is an incorrect term and implies a "capacity" function which is not normally measured in chamber temperature distribution studies. Heat penetration refers to the ability of the chamber atmosphere to heat the product.

3. Section II B 4: The batch record is an inappropriate location for this information. Such data should reside in the

firm's validation or development files, and be readily available for FDA inspectional review.

4. Section II C 2: "A description of the program for routinely monitoring bioburden (add "where appropriate") to ensure that validated and established limits are not exceeded." A properly designed overkill validation approach can justify the absence of routine monitoring of bioburden since overkill sterilization cycles are designed to provide a 10^{-6} probability of microbial survival regardless of the number and resistance of bioburden.²

For example, in the case of equipment containers, closures (inert items) where there is no substrate for microbial growth (and endotoxin development) bioburden testing would not be warranted when overkill sterilization cycles are employed. In other cases where historical data established that bioburden remained within reproducible ranges, routine bioburden testing would also not be necessary when employing overkill sterilization cycles.

5. Section II C 5: Last sentence. (should read "simulate" not "stimulate")

6. Section II D: Definition of process water, line 13. (should read "Process water includes autoclave cooling water if it has potential contact with the product.")

7. Section III: First sentence. (should read "Section II A through II G" not "I A through I G")

8. Section IV G and V A: Reference is made to the "sensitivity" of the container/closure integrity test. The term "sensitivity" should be clarified or this reference deleted.

9. Section IV G: Microbiological Monitoring of the Environment. The requirement to monitor anaerobes should be deleted. The purpose of environmental monitoring is detection of changes and trend analysis. Aerobic and facultative microorganisms will far exceed in number and provide a more sensitive indication of trends than anaerobic microorganisms. This position has been supported in the scientific literature. Munson and Sorensen of the U.S FDA took the position that routine environmental monitoring for anaerobes in an aseptic processing

Parenteral Drug Association, Inc., Technical Monograph No. 1, "Validation of Steam Sterilization Cycles", 1978.

area is usually not productive.³ Abdou maintains a similar position.⁴ Finally, in the section entitled Surveillance Procedures, PDA Technical Report No. 13 states that, "Unless sterility test data or periodic environmental monitoring data show there is a problem with special groups of microbes such as anaerobes, routine surveillance for organisms other than those expected to populate the environment should not be necessary."⁵

10. Sections V A & V C: It should be clarified that the phrase "sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container/closure system" (line 6, V A) does not imply a requirement for sterility testing at the endpoint in a stability program. On a scientific basis, the assurance of sterility over the shelf life of a sterile product is based on the integrity of the container/closure system. The closure system is validated by appropriate physical and/or microbiological challenge tests during the formulation/development stage of the product. Once validated, there is no scientific reason to perform sterility or bacterial endotoxin testing (as requested in Section V C) over the shelf life of the product, since the product must be "sterile" and "endotoxin free" at the time of release. The sterility test is not adequate to measure the adequacy of container/closure integrity. Rather, a test (Section V A) that directly measures container/closure integrity would be a suitable alternative to the sterility test. This test may be either a physical or microbiological challenge test.

11. Section V B: The guidelines suggest conducting the USP Antimicrobial Preservative Effectiveness Test (APET) at the end of the stability period. This would not be necessary in the situation where the firm has demonstrated the ability to pass the APET at a minimal concentration of preservative at which the product remained above during the expiration period.

³"Sterile Pharmaceutical Manufacturing, Applications for the 1990's," Volume 2, Interpharm Press, 1991, Chapter 5, "Environmental Monitoring: Regulatory Issues," p. 169.

Abdou, M. A. F. "Determination of airborne microorganisms in a pharmaceutical plant using standard, elective, and selective culture media," *Pharm. Tech.* 4(11):93, 1980.

Technical Report No. 13, *J. Parenter. Sci. Technol.* 44(S1):S4, 1990

Also in V B, the following should be reworded: "chemical assays to monitor the concentration of preservatives should be performed at all (change "all" to "appropriate") test intervals. For subsequent lots placed on stability, chemical assays may (Change "may" to "will") be adequate." FDA's stability guidelines state chemical assays may be used in lieu of the APET. ⁶

"Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics," FDA, February 1987, p. 12.

Attachment 1

Parenteral Drug Association, Inc. Task Force on Sterilization Process Validation

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