CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE
STERILE DRUG PROCESS INSPECTIONS	*Upon Receipt*
	COMPLETION DATE
	9/30/93

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes 560O2A 54, 56, and 60-66 inclusive.	

FIELD REPORTING REQUIREMENTS

Forward a copy of each Establishment Inspection Report to H#-300 Attention: Division of Drug Quality Evaluation. Copies of Samples of Collection Reports and Analyst Worksheet for all samples except those which are classified "1"should also be submitted. (This material will be used in evaluating the program).

As soon as the district becomes aware of any significant adverse inspectional, analytical, or other information which could or should affect the agency's new product approval decisions with respect to a firm, the district should immediately notify HFC-120, Medical Products Quality Assurance Staff, via EMS or fax, and they will, in turn, convey the information by fax or equivalent expeditious means to the appropriate Center regulatory units.

NOTE: Districts should assure that each operation performed by direction of of this program circular is entered against the correct Product Code and Program/Assignment Code (P/AC).

Current Changes
TRANSMITTAL N#. 90-68 (03/05/90)

PART I - BACKGOUND

*This program is intended to cover the manufacture of all sterile drug products, including sterile bulk drugs, ophthalmic and ophthalmtic dosage forms, Small Volume Parenteral (SVP) products, Large Volume Parenteral (LVP) products, and any other drug products required to be sterile.

Biologicals, veterinary drug products, and bioassay drugs are excluded from coverage under this program.*

Current Change

PART II - IMPLEMENTATION

OBJECTIVES

To provide guidance for conducting inspections of manufacturers of sterile bulk and finished dosage form drug products to determine compliance with the Food, Drug, and Cosmetic Act and the Good Manufacturing Practice Regulations (GMPs), Title 21, CFR Parts 210 and 211.

To initiate appropriate action against those manufacturers found to be out of compliance.

To obtain information on key practices, to identify practices which need correction or improvement, and to evaluate current good manufacturing practices in the #sterile drugs industry.

PROGRAM #AGEMENT INSTRUCTIONS

*Inspections of sterile product manufacturing firms will be performed as either Full Inspections or Abbreviated inspections.

In the Abbreviated Inspection, coverage will be directed to key points in the major systems affecting the production of the sterile drug product. If the information collected indicates that the firm's practices are in compliance with CGMPs, the inspection may be concluded at this point.

It should be pointed out that inspectional coverage under this option is not intended to limit the investigator ' s initiative in any way. If questionable practices are observed in areas outside of the systems delineated under this option, the investigator is urged to expand the inspection to cover these areas to his/her satisfaction.

The Full Inspection Option involves an in depth inspection of key manufacturing systems and processes and their validation in order to maintain surveillance over the firm's activities.

See Part III - inspectional and Attachment A for a complete discussion of the coverage requested under these inspection options.

Current Change

This program is to be carried out when firms are inspected as part of the regular statutory inspection cycle in accordance with the current ORA workplan. If the sterile drug products to be inspected are radioactive drugs, then CP735G.002C, "Radioactive Drugs", should be followed as supplementary guidance.*

- Consider using a team approach in conducting these inspections, utilizing investigators familiar with these processes, and chemists, microbiologists, and engineers, as appropriate.

- *Investigators or team members should be well qualified in sterile product production experience and preferably have completed formal training courses in parenteral drug manufacture, sterilization methods, procedures and equipment. Microbiologists involved should have experience in sterility/pyrogen testing and some experience in sterile product inspections.*

Current Change

PART III - INSPECTIONAL

*Refer to CP 7356.002, Drug Process inspections, for general information on CGMP inspections. Refer to CP 7356.002C, "Radioactive Drugs" for supplemental instructions specific to radiopharmaceutical drug products.

Foreign inspections should be conducted using the guidance in this program, taking into account the time limitation on these inspections.

This program provides two inspectional options: an Abbreviated inspectional Option and a Full Inspectional Option. To determine which option should be used an evaluation of the following is appropriate:

1. Review and Evaluation

A full inspection should be conducted for initial inspections and may also be conducted on a surveillance basis at the District 's discretion. Although it is not anticipated that full inspections will be conducted every two years, they should be conducted at less frequent intervals, perhaps at every third or fourth inspection. Also, whenever information becomes known which would question the firm's ability to produce quality products, an appropriate in-depth inspection should be performed.

An abbreviated inspection should not be conducted for the initial inspection of a facility, nor when the firm has a past history of fluctuating into and out of compliance. The District should utilize all information at their disposal such as past history results of sample analyses, complaints, recalls, etc. to determine if coverage under the abbreviated inspectional option is appropriate for the specific firm.

a. Determine if changes have occurred by comparing current operations against the EIR for the previous full inspection. The following type of changes are typical of those that would warrant the Full Inspection Option:

   1. New potential for cross-contamination arising through change in process or product line.

   2. Use of new technology requiring new expertise, significantly new equipment or new facilities.*

Current Change

*b. Review the firm's complaint file, DPPRs, annual product reviews, etc. and determine if the pattern of complaints (or other information available to the District) as well as the firm's records of internal rejection or reworking of batches warrant expanding the inspection to the pu11 Inspection Option to look for weaknesses in the firm's processes, systems or controls.

c. If no significant changes have occurred and no violative conditions are observed, the Abbreviated Inspection Option may be adequate.

d. If significant changes have occurred, or if violative or potentially violative conditions are noted, the inspection should be expanded to the Full Inspection Option to provide appropriate coverage.

e. If an inspection needs to be expanded to the Full Inspection Option, it need be expanded only for the applicable general product or process area in question.

2. Abbreviated Inspection Option

This option involves a more limited inspection of the manufacturer to maintain surveillance over the firm's activities. An Abbreviated Inspection as described below is adequate for routine coverage and will satisfy the biennial inspection requirement. The use of this option will save inspectional and clerical resources.

a. Inspections performed under this option should cover those items delineated under the Fu11 Inspection Option with the exception that validation need not be covered for those systems and processes that have previously been covered under the Full Inspection Option.

Perform an inspection of the firm's manufacturing facility including a review of a representative number of Master and Batch Production Records (minimum of 5 batches) on products manufactured by the firm. Products that appear in the firm's inspectional history of previous problems should be included. A brief inspection of the laboratory should include a spot check of a limited number of test records (at least 10) to assure that batches are being subjected to adequate testing for conformance to specifications.*

Current Changes

*Special note should be taken of the firm's packaging and labeling controls. Any observation of inadequate controls will indicate that a Full inspectional Option should be performed. If the following type of procedures are encountered, in-depth inspectional coverage should be given to the firm's Labeling systems:

- The use of labels which are similar in size, shape, and color for different products.

- The use of cut labels which are similar in appearance without some type of 100 percent electronic verification system for the finished product.

- If the use of gang printing of cut labels is not minimized as required by current regulations.

- If the firm has had more than one mislabeling recall in the past two years.

- If the firm fills product into unlabeled containers which are later labeled under multiple private labels.

If the abbreviated inspection reveals no significant objectionable conditions, and there are no other factors requiring the use of the Full Inspection Option, use of the Abbreviated Inspection Option 18 adequate.

Refer to the "Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing" for guidance on the applicability of CGMPs to bulk operations.

3. Full Inspection Option

The Full Inspection Option will be implemented when: (1) this is the initial inspection of the drug firm; (2) this is the first inspection performed following a regulatory action against the firm; or (3) the information collected under the Abbreviated Inspection indicates that the firm's practices are or may be deficient in one or more system areas. An in-depth inspection of all manufacturing, support, and documentation systems at the firm in question should be initiated. However, this in-depth inspection may be limited - at the discretion of the investigator - to only that system area that appears to be deficient.

It is not expected that inspections performed under this option will necessarily result in the preparation of regulatory action recommendations. *

*INSTRUCTIONS

The inspection will focus on the major systems that impact on the safety and effectiveness of all sterile products manufactured by the firm:

- sterilization procedures applied to the drug product; components; container/closures; product contact equipment and surfaces
- water systems
- air handling
- environmental monitoring
- handling of incoming components
- packaging and labeling
- laboratory
- lyophilization (where applicable)

2. It is suggested that one drug product be selected and followed throughout; if the firm utilizes more than one type of drug product sterilization process, one drug product representing each type of sterilization process should be selected.

When selecting a drug product for review, drugs that are the subject of DPPRs or listed in the firm's complaint files should be considered.

Drug product information to be reported:

A. Name of Selected Drug
B. Dosage Size
C. Strength
D. itch sizes
E. Number of batches per year

Describe what type of sterile drug products are manufactured by this firm:

F. SVP
6. LVP
#. Ophthalmics
I. Sterile Otics
J. Sterile Bulk
K. Other (identify)

Please indicate whether any of these products are lyophilized.

The report should include separate sections for each unique drug product and sterilization process investigated.

3. Attachment A has been provided as a reference guide for the type of information that should be evaluated in a sterile process inspection.

SAMPLE COLLECTION

Collect *documentary or physical* samples, including 'in-process samples where possible, to document any suspected adulteration and misbranding problems encountered during the inspection.

If microbiological contamination is suspected, document where possible the conditions which could contribute microbiological contamination to the product *both by collecting records and physical samples taken aseptically at points where such contamination might occur, such as from the WFI system. Products found positive on initial sterility testing should also be considered for sampling.

Physical samples should not be collected if the estimated level of microbial contamination is low.*

Collect samples for particulate matter contamination where inspectional observations indicate poor manufacturing practices have possibly contributed to the introduction of particulate matter into these products or where finished product controls are inadequate to assure rejection of such units.

Sample Size

For guidance in determining sample sizes for endotoxin and sterility evaluation, refer to the respective Drug Surveillance Request (DSR). Such sampling may be accomplished to meet District obligations under that program, as appropriate.

Reporting

*The investigator will utilize sections 590, 591, and 592 of the IOM for guidance in reporting inspectional findings.

For inspections made pursuant to specific assignments from HFD-33G, all appropriate program areas should be fully reviewed and reported for all firms inspected, regardless of EI classification.

Attachment of standard operating procedures (SOPs), specifications, or other documentation in response to a question and/or to illustrate a deficiency is acceptable provided the response/deficiency is clearly described in all accompanying narrative.*

Notify supervisors immediately if potentially serious health hazards exist.

*Current Change

PART IV - ANALYTICAL

*ANALYZING LABORATORIES

1. Routine chemical analyses : all District laboratories except W#C and MLMI.

2. Sterility Testing:

Region	Examining Laboratory
NE, MA	NYK-RL
SE	SE-RL
MW	MLMI
SW, PA	SAN-DO

3. Other microbiological examinations : WEAC, NYK-RL (FOR NYK and BUF), SJN, BLT, SE-RL, CIN (for NWK and CIN), LOS, SAN, SEA, DAL and DEN (for DAL and DEN).

   Salmonella Serotyping Lab : MLMI.

4. Chemical cross-contamination analyses by mass spectrometry (MS) : NYK-RL, DAL, SE-RL, DET, DEN, and LOS. Non-mass spectrometry laboratories should call one of their own regional MS labs and/or Division of Field Science (HFC-142) to determine the most appropriate MS lab for the determinations to be performed.

5. Chemical cross-contamination analyses by Nuclear Magnetic Resonance (NMR) spectroscopy : SE-RL, NYK-RL, PHI and DET. Non-NMR laboratories should call one of their own regional NMR labs and/or Division of Field Science (HFC-142) to determine the most appropriate NMR lab for the determinations to be performed.

6. Antibiotic Analyses:

Examining Laboratory	Drug Product
DEN-DO	Tetracyclines
	Erythromycins
NYK-RL	Penicillins
	Cephalosporins
Division of Drug Biology, Antimicrobial Drugs Branch, HFD-178*	All Other Antibiotics

7. Bioassys : Division of Research and Testing (HFD-470)

8. Particulate Matter in Injectables: MLMI (HFD-470).*

Current Change

ANALYSIS

1. Samples are to be examined for compliance with applicable specifications. Check analyses will be by the official method, or when no official method exists, by other validated procedures. See CPG 7152.01

2. The presence of cross-contamination must be confirmed by a second method. Spectroscopic methods, such as MS, NMR, UV-visible, or infrared are preferred. However, a second chromatographic method may be employed, provided the chromatographic mechanisms are different (e.g., ion-pairing vs. conventional reverse phase HPLC).

3. Sterility testing methods should be based on USP XXI and the Sterility Analytical Manual, 1981. Other microbiological examinations should be based on appropriate sections of USP XXI and BAM, 6th Edition, Chapter VII, Salmonella and current supplement

Current Change

PART V - REGULATORY/ADMINISTRATIVE S#TEGY

The therapeutic significance of the drug product and the potential adverse effect of the GMP deviation on the finished product must be considered in determining whether or not a regulatory action and/or administrative action (e.g., withholding NDA/##, G#QAP non-acceptance) is indicated.

When the nature of the deviations is considered in relation to the therapeutic significance of the product(s) and it is determined that they pose a minimal risk to the consumer, voluntary correction by management should be sought as the primary action. *However, this is not to imply that regulatory action will never be taken in such cases.* The district should require that all communications for achieving voluntary compliance by firm management be submitted in writing and contain a time schedule for completion. *The field should determine if the schedule is a reasonable time frame and should monitor their progress.*

When voluntary action is not accomplished or when the deviations observed pose a threat to the consumer, formal regulatory and/or administrative action should be recommended. When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect the consumer (i.e., when non-sterile injectables are found, injunction/recall would be the action(s) of choice). Outstanding instructions in the Regulatory Procedures Manual (RPM) should be followed.

NOTE: The lack of a violative physical sample is not a bar to pursuing regulatory and/or administrative action providing the GMP deficiencies have been well documented. Physical samples found to be in compliance likewise are not a bar to pursuing action under UP charges.

*The following list represents examples of deficient practices which the Center believes could warrant regulatory and/or administrative action:

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals ; or a reasonable potential for contamination by same, with demonstrated avenues of contamination such as contact with unclean equipment or through airborne contamination.

2. Failure to assure that each batch conforms to established specifications, such as NDA, USP, customer specifications, and label claims.

3. Distribution of product which does not conform to established, specifications.*

*4. Use of test methodology which is not adequate or validated.

5. Deliberate blending for the purpose of diluting and hiding pyrogenic, microbiological or other noxious contamination, or where blending of a non-standard batch with one meeting specifications results in one blended batch meeting minimum specifications.

6. Failure to assure that each batch is of uniform character and quality (homogeneous).

7. Conducting packaging and labeling operations in such a manner as to introduce a significant risk of mislabeling, for example, the use of cut labels which are similar in appearance without some type of 100 percents electronic verification system for the finished product.

8. Failure to keep adequate records, including:

- Date(s) of manufacture
- QUantity manufactured
- Lot number
- Test results and dates
- Labeliing records and specimen of label used
- signature of person(s) responsible for accomplishing significant steps including:

(1) determining yield
(2) examining labeled containers for correctness of label
(3) testing for conformance to specifications
(4) blending, if required
(5) assuring conformance with established manufacturing procedure
(6) reviewing production and testing records and authorizing release for distribution

9. Failure to record distribution by lot number in a manner which would permit prompt recall.

10. Failure to have any information which would establish stability for the intended period of use.*

PART VI - REFERENCES, ATPACHMENTS, AND PROGRAM CONTACTS

REFERENCES OR AIDS

A. Inspection Operations Manual, Chapter 5, Part 542.58 - Sterile Products.

B. Proposed CGMP's For Large Volume Parenterals published in the Federal Register, June 1, 1976.

C. United States Pharmacopeia, latest revision and its supplements.

D. *"Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices," December, 1987.*

E. Inspectors Technical Guide, Number 1, 1/9/13, "Sterilizing Symbols (D, z,

F. "Understanding and Utilizing Values", Akers, Attia and Avis, "Pharmaceutical Technology", May 1978, pages 31-35.

G. *Inspectors Technical Guide, Number 5, 6/9/72, "Ethylene Oxide a Sterilizations, I. Calculation of Initial Gas Concentration".

H. *Principles and Methods of Sterilization in Health Sciences, Charles C. Thomas Co., (1969), p. 508.*

I. *Inspectors Technical Guide, Number 6, 4/28/72, "Leak-Testing Sealed Ampuls of Parenteral Solutions"*

J. *"Parenteral Preparations", Avis, Chapter 36, pp. 498-524 in Remington's Pharmaceutical Sciences; Edit. Martin; Mack Publishing Co., (1965).*

K. *Inspectors Technical Guide, Number 24, 7/30/76, "Air Velocity Meters".*

L. *Inspectors Technical Guide, Number 25, 9/1/76, "Ethylene Oxide Sterilizations, II. Graphical Aid to Determine Gas Concentration".*

M. *Inspectors Technical Guide, Number 32, 1/12/79, "Pyrogens, Still a Danger".*

N. Inspectors Technical Guide, Number 36, 10/21/80, "Reverse Osmosis".

0. *Inspectors Technical Guide, Number 41, 10/18/85, "Expiration Dating and Stability Testing for Human Drug Products".*

P. *Inspectors Technical Guide, Number 43, 4/18/86,."Lyophilization of Parenterals".*

Q. Federal Standard 209, #current revision,*

R. Remington's Pharmaceutical Sciences, *Current Edition*

S. *"Guideline on Sterile Drug Products Produced by Aseptic Processing, # June 1987.*

T. *"Guideline on General Principles of Process Validation," May 1987.*

U. *Regulatory Procedures Manual, Part 8.*

V. "Guideline to Inspection of Bulk Pharmaceutical Chemical Manufacturing, Revised November 1987.

ATTACHMENTS

A - Reference points to be covered as appropriate to the type of inspection being performed, and the type of product and/or manufacturing system being evaluated.

B - To be completed for each type of Biological Indicator and/or Product.

CONTACTS

*The area code for commercial calls to all headquarters contacts is 301.

* A. ORA

1. Jay S. Allen
Investigations Operations Branch/DFI/ORO (HFC-133) Telephone : FTS 443-3340

2. Methods Inquiry

Division of Field Science/ORO (HFC-140), #lephone: FTS 443-*3007*

B. CDER

*Manufacturing Surveillance Branch (HFD-336)
Division of Drug Quality Evaluation
Telephone: 8-295-8107*

Current Change

PART VII - CENTER RESPONSIBILITIES

The Division of Drug Quality Evaluation (HFD-330) will evaluate all reports. Results 0f these evaluations will be shared with the field, ORA, and interested headquarters units.

Current Change

GUIDE TO EVALUATION OF STERILE PROCESS INSPECTIONS

The following reference questions are provided for evaluation of specific drug products, manufacturing systems, and quality control procedures.

The points have been numbered for easier reference in the EIR narrative.

COMPONENT STORAGE AND PREPARATION

1. Does the firm have adequate written procedures describing the receipt, handling, that are represented to be sterile and/or pyrogen free? (per 21 CFR 211.80 - 211.94; 211.184)

2. Have these procedures been followed for the selected drug product?

3. Are any colorants used (none are permitted)?

4. Does the firm have written control procedures that adequately describe the receipt, storage, sampling, issuance, and reconciliation of labeling and packaging materials? (per 21 CFR 211.122 - 130; 211.134 and 211.137).

5. Does the firm use cut or roll labels?

6. Are the labels similar in color, shape, size and format for different products or potencies?

7. Does the firm use any type of electronic label verification system (bar codes, machine vision systems, etc.)? Describe

8. Is the label verification on receipt, on line, or both?

9. Is any printing done on line of label text, lot number, expiration date, etc.?

10. Does the firm use dedicated packaging lines?

11. Are the samples of labels used for acceptance (proofing) of labels from vendors based on a statistical plan? Describe sampling plan.

12. Are labels printed by the firm or by an outside vendor?

13. Have these procedures been completely and accurately followed for the subject drug product?

EVALUATION SYSTEMS

14. Does the firm have an SOP on vendor audits?

15. Has the firm audited the (a) component, (b) container, (c) closure, and (d) label vendors? Report the dates of last audits.

16. Does the firm have written procedures for the production and process control of drug products? (per 21 CFR 211.100, - 211.115; 211.186; 211.188; 211.192)

17. Have these production and process control records been approved by the firm's quality control unit and by designated organizational units?

18. Have these process control records been completely and accurately prepared for the subject drug product?

19. Briefly describe the firm's procedures for changing any of the standard operating procedure documents described above.

20. Does the firm have written procedures for the review and approval of all drug production and control records before release of the batch for distribution? (21 CFR 211.192)

21. Were these procedures followed in the review of the selected drug product?

22. What are the firm's procedures for the investigation to be made following any unexplained discrepancy found in batch production records, or the failure of a batch or any of its components to meet specifications? (21 CFR 211.192)

23. Were these procedures followed accurately and thoroughly concerning any batch discrepancies/failures of the selected drug?

24. Does the firm have written laboratory control mechanisms, including change control procedures, which describe conformance to established specifications and standards for the selected drug product? (21 CFR 211.160-167)

25. Were all specified in-process and end product tests performed on the selected drug product?

26. Were all specifications met?

Current Change

MAJOR SYSTEMS AND PROCESSES

Monitoring of Environment

27. Is the air supplied to critical areas (exposed product/filling areas) filtered through HEPA filters under positive pressure?

28. Is the air flow in critical areas laminar when delivered to the point of use? At what velocity? Is velocity determined at the critical area or at the filter face?

29. How is the air filtered that is supplied to controlled areas (where unsterilized product, in-process materials, and container/closures are prepared)?

30. What are the firm's air quality classifications for:
    a. exposed product areas
    b. filling area
    c. surrounding plant areas

31. Is room classification system based upon Federal Standard 209d or other?

32. Are HEPA filters efficiency tested?

33. How often are HEPA filters integrity tested? What test method is used?

34. How often are air flow velocities checked for each HEPA filter?

35. Does the firm have a written monitoring program for classified areas that included a scientifically sound sampling schedule that describes sampling locations, their relation to the working level, and frequency? Describe the basis for the sampling program. (21 CFR 211.160)

36. Are both viable and non-viable particulate samplings performed in all classified areas during production?

37. Report the frequency of viable sampling using "active" sampling methods for:
    a. exposed product areas
    b. filling areas
    c. surrounding areas

38. Report the limits used, length of sampling period, and if sampling is done during production or at rest.

39. Report the type of viable sampling equipment use (STA, Centrifugal sampler, etc.)

40. Does the firm have data on the ability of these samplers to recover organisms without deleterious effect on survivability such as through impact or dessication of organisms or media?

41. Report the actual volume of air sampled per location.

42. Are settling plates used? Describe the length of exposure period; sampling frequency; location (including proximity to critical operations); microbial limits.

43. Are recovered microorganisms routinely identified? To what level (genus, species)?

44. Are the culture media used in the viable monitoring program shown to be capable of detecting molds and yeasts as well as bacteria by means of growth promotion tests? Is anaerobic monitoring performed?

45. What media are used?

46. Are deactivators (e.g., penicillinase) use for antibiotics or other bacteriocidal/bacteriostatic substances? Has the firm shown that these are effective?
(Are records available? Are calculations correct?)

47. What incubation periods are used and at what temperature?

48. How often is non-viable particulate sampling performed in classified areas:
a. exposed product areas
b. filling areas
c. surrounding areas

49. What sampling device is used? What volume of air is sampled?

50. How many samples are collected per location? Are results averaged?

51. When was sampling equipment last calibrated?

52. Were environmental sampling results within specifications during the manufacture of the batches of the selected drug product? (Describe any deviations and firm's response.)

53. How often is monitoring performed on filling room personnel?

54. What are the firm's alert and action limits for personnel monitoring?

55. What type of monitoring is done?

56. Does the firm have written procedures for the monitoring of product contact surfaces?

57. What type of contact surface monitoring devices are used (RODAC, swabs, etc.)?

58. Any changes in the air handling or environmental monitoring systems since the last EI? Were changes evaluated by management regarding the need for re-validation?

FACILITY CLEANING/DISINFKTION

59. Are there written procedures describing the cleanup, sanitization/sterilization of drug production equipment and utensils?

60. Were these written procedures describing the cleanup, sanitization/sterilization of drug production equipment and utensils?

MANUFACTURING FACILITIES

Gowning

61. Briefly describe the firm's procedures for initial gowning and re-gowning after breaks.

FREEZE-DRYING (LYOPHILIZATION)

62. If lyophilization is performed by an outside firm, report the firm's name and address.

If lyophilization is performed in-house, report the following:

63. Manufacturer of lyophilizer.

64. Percentage of firm's products which are lyophilized:

65. Describe the heating and cooling systems used in the lyophilizer; the vacuum system; what gas is used to break the vacuum and whether it is sterile; and the temperature controlling system.

66. Briefly describe preparation of the sterile product for drying, including procedures for protecting the product from contamination while loading into the lyophilizer.

67. How is stopper seating vials performed?

68. If performed automatically, is it under vacuum, or if not under vacuum, what gas is used and how is it sterilized?

69. If vials are stoppered outside of chamber, describe how lyophilized product is protected from contamination during this procedure.

70. Is the lyophilizer steam sterilizable?

71. Describe chamber clean-up procedures between batches of the same product and between different products (including sterilant/cleaning agent used and exposure cycle),

72. How are inert gas or air supply lines cleaned? Sterilized?

Lyophilization Validation

73. Is the aseptic handling of lyophilized products validated by:
    (a) media fill process
    (b) other (describe)

74. If media fills are used, are the fills performed uniquely to evaluate the lyophilization process, or as part of a validation of the aseptic filling process?

75. Are the same acceptance criteria (allowable contamination rate) used as for liquid filling? If not, what criteria are used?

76. What number of units are filled for lyophilized product?

77. During validation, what level of vacuum is pulled on the lyophilization chamber?

78. Do media fill vials remain in the lyophilization chamber under vacuum as long as production vials?

79. Is the media frozen?

80. Is environmental monitoring performed during loading of the lyophilizer both during - production as well as during validation?

81. Does the firm have data on growth promotion of the media after the above procedures?

82. Is environmental monitoring performed during unloading of the chamber during production as well as during validation?

83. What is used to break vacuum (nitrogen, air, other gas)?

84. Has the firm validated the lyophilization cycle (e.g., time, rate of heat input, temperatures, eutectic melting point) for each product? (Review validation records for selected drug product and at least three other drug products with different physical

and chemical characteristics.)

85. Review at least three lyophilization production records for the products referenced above., are the cycle parameters and observed results within the validated cycles?

86. What are the firm's criteria for acceptable vs. unacceptable runs, including general appearance, moisture, etc.?

UTILITY SYSTEMS

WFI

87. What is the source water for the plant?

88. Briefly describe the treatment applied to the source water before it is considered acceptable for use in manufacture.

89. What type of water is used for
    a. bulk product compounding
    b. non-product contact surfaces
    c. washing of container-closures
    d. final rinse of container-closures
    e. final rinse of product contact surfaces
    f. water used for production of sterile product

90. What process is used to produce Water for Injection (WFI)/sterile WFI?

91. If distilled water is prepared, briefly describe the production, delivery and storage system and temperatures.

92. Briefly describe pyrogen/microbial control in the WFI system,

93. Does the firm have written procedures detailing the specifications and monitoring program for all types of water used in the plant?

94. Review process water sampling results for at least two months preceding and one month following the manufacture of batches of the selected drug product. Were specifications met? (If not, describe any deficiencies and the firm's response.)

95. Have there been any changes in the process water system since the last EI? Have these changes been evaluated for the need for re-validation of the water system?

DEPYROGENATION

96. What type of depyrogenation procedures are used? If dry heat is used, report the cycle time/temperature.

97. Is WFI Washing used?

98. If a caustic wash is used, what agent is used?

99. Is ultrafiltration used?

100. Describe any other methods used.

101. Which of the above procedures are used on:
    a. Raw materials
    b. Drug product containers
    c. Drug product container closures
    d. Sterile product contact surfaces
    e. Manufacturing equipment
    f. Drug product

102. What method is used for determining endotoxins? Rabbit or LAL?

103. Have all depyrogenation procedures been validated to demonstrate a minimum of a three-log reduction in endotoxin content? Does the firm have data on recovery of the original endotoxin challenge amount?

104. Have any depyrogenation procedures been changed/added/deleted since the last EI? Have such events been evaluated for re-validation?

105. If pyrogen testing is performed by a facility other than the manufacturer, report the name and address of the facility.

CONTAINER & CLOSURE INTEGRITY

Particulates

106. Evaluate the adequacy of the firm's procedures and criteria used to inspect units for particles.

107. What is the duration of duty of operators doing visual examinations?

108. What is the firm's general rejection rate for particulate matter, and type(s) of particulates which predominate?

109. Report results of investigations into sources/types of particulates (other than visual examination.)

110. In evaluating the adequacy of the firm's particulate matter quality control procedures, make a visual examination of a representative number (at least 100) of units that have passed the firm's inspection. Report the number of units examined; passed; failed. (This examination can be performed on warehouse stock. What is the firm's normal level of rejects for particulates (%)?)

111. If the firm uses an automated method, provide the name and sensitivity levels of the equipment.

112. What are the firm's alert, action, and reject levels for particulate contamination?

113. Briefly describe the firm's procedure when each of these levels is exceeded (attach SOP if appropriate).

114. What is the frequency of testing for particulates?

115. If particulate levels ar determined by a facility other than the manufacturer, report the name and address of the facility.

116. Has there been a change in particulate contamination testing since the last EI (e.g., equipment)? Has the change been evaluated for re-validation?

STERILIZATION SYSTEMS

General

117. What types of parenteral drug products are manufactured by this firm?

    a. solutions
    b. suspensions
    c. lyophilized
    d. powder fills

118. Are form, fill and seal packages used for any of these products?

119. Which of the above products are manufactured aseptically?

120. Are any products which can be produced using terminal sterilization produced aseptically? (If so, describe the firm's rationale for producing them aseptically.)

121. Do all of the firm's aseptically filled products contain a preservative; would they pass a USP preservative efficacy test?

122. If the information requested is unavailable at the site of the inspection, determine the name and address of the firm where the information can be gathered.

If the firm does not have a record of a particular parameter, or will not reveal it, a notation to that effect should be made.

NOTE: If biological indicators are used during production and/or validation cycles, complete Attachment A for each type of indicator used.

123. Contract Sterilizers: If the firm being inspected is a contract sterilizer, choose one drug component/container- closure system and follow it through one complete sterilization cycle. Complete as many items as applicable, especially under GENERAL INFORMATION and the type of sterilization procedure used on the drug component/container closure system. Refer to Compliance Policy Guide 7150.16 for Agency policy concerning the status and responsibilities of contract sterilizers.

Steam Sterilization

124. Report the steam sterilizer (autoclave) manufacturer.

125. What is the internal volume of the autoclave?

126. What is the sterilant (e.g., steam, air over pressure, superheated water)?

127. If jacketed, what pressure/temperature is maintained in the jacket as opposed to the chamber?

128. What type of vent filters are used and how often are they integrity tested?

129. Are vent filters hydrophobic? Are the vent filter housings heated to prevent condensation?

130. Is cycle control manual or programmed?

131. What type of monitoring and controlling sensors are used (e.g., mercury-in glass thermometer, thermocouple, RTD, pressure gauge)?

132. How are these sensors calibrated? Are the standards NIST traceable (where appropriate)?

133. If the autoclave is equipped with a steam spreader, describe it (more than one steam entry line would be considered in this category).

134. If more than one autoclave is used by the firm, what is the system's capacity for steam production in relation to all autoclaves being in operation at the same time?

135. What are the sterilization cycle parameters? (Compare Master Process Record/SOP specifications against processing records completed for the selected drug product.)

136. What are the firm's specifications and observed parameters for:

a. Time
b. Temperature
c. Pressure (psi, in. Hg)
d. Pressure Come Down Rate (specify pressure and time)

136. Where is the cycle controller sensor located?

137. How are each of the above parameters monitored (specify when not monitored)?

138. Is the "cold spot" in each load monitored during each autoclave cycle?

139. Report other characteristics (e.g., air quality, water quality, alarms, etc.).

140. Have any changes in the steam sterilization system occurred since the last EI? Have these changes been evaluated for the need for re-validation?

Steam Sterilization Validation

141. Does the firm have written procedures for validation that include:

(1) installation qualification of equipment
(2) operational qualification of equipment
(3) performance qualification with product
(4) description of circumstances requiring re-validation of the system and procedures to do so

142. Does validation documentation include:
(1) empty chamber heat distribution studies:
(a) number of runs?
(b) was cold spot determined?
(c) report firm's allowable variation and actual variation found

(2) heat penetration studies performed:
(a) for each type of loading pattern/for each container size utilized?.
(b) number of runs per pattern?
(c) was the "cold spot" determined for each pattern?

(3) what type of temperature measurement system was used? Does it provide a separate printed reading for each thermocouple?

(4) what type of thermocouples were used, and were they calibrated before and after each run?

(5) was an ice-point reference standard used for calibration?

(6) was the high temperature reference standard NBS traceable?

(7) If biological indicators were used during validation runs:
(a) type of indicator
(b) source of indicator
(c) organism used
(1) concentration
(2) D Value.

(d) were BIs used in an "end point" or "count reductions" mode?
(1) If any positive BIs were found (when not expected), what was the firm's response? Include records and response in exhibits to EIR

143. In the event a heat distribution or penetration variance was disclosed during the studies, how did the firm correct or allow for it?

144. Has the firm determined lag times for all container sizes, product viscosities, etc. and adjusted their cycles accordingly?

Dry Heat Sterilization (separate from depyrogenation)

145. If dry heat sterilization is performed by an outside firm, report the name and address.

146. If dry heat sterilization is performed in-house, complete the following:

   a. Sterilizer manufacturer
   b. Size (internal dimensions)
   c. Location of the heat source

147. Is sterilizer equipped with a fan or is heat distributed by convection only?

148. Is the cooling air HEPA filtered?

149. How often are the HEPA filters integrity tested?

150. Is the cycle control manual or automatic?

151. What type of monitoring and controlling sensors are used (e.g., mercury-in-glass thermometer, thermocouple, RTD, pressure gauge)? How often are they calibrated?

Sterilization Cycle Parameters

152. What are the sterilization cycle parameters (compare Master Process Record/SOP - specifications against processing records completed for the selected drug product)

153. What are the firm's specifications and observed parameters for time and temperature? 154. Where is the cycle controller sensor located?

155. How are each of the above parameters monitored (specify when not monitored)?

156. Report other characteristics (e.g., air quality, alarms, etc.).

If biological indicators are used during regular production cycles, complete Attachment B.

157. Have any changes in the dry heat sterilization system occurred since the last EI? Have these changes been evaluated for the need for re-validation?

158. Does the firm have written procedures for validation that include:

(a) installation qualification of equipment
(b) operational qualification of equipment
(c) performance qualification with product
(d) description of circumstances requiring re-validation of the system and . procedures to do so

159. Does validation documentation include:

(1) empty chamber heat distribution studies:
    (a) number of runs
    (b) was cold spot determined
    (c) report firm's allowable variation and actual variation found

(2) heat penetration studies performed:

    (a) For each type of loading pattern/container size to be utilized
    (b) number of runs per pattern
    (c) was the "cold spot" determined for each pattern

(3) what type of temperature measurement system was used?

(4) were thermocouples calibrated before and after each run?

(5) was an ice-point reference standard used for calibration?

(6) was the high temperature reference standard NIST traceable?

(7) If biological indicators were used during validation runs:
    (a) type of indicator
    (b) source of indicator
    (c) organism used
        (1) concentration
        (2) D Value
    (d) were BIs used in an "end point" or "count reduction" mode? (1) If any positive BIs were found (when not expected), what was the firm's response?

160. In the event a heat distribution or penetration variance was disclosed during the studies, how did the firm correct or allow for it?

161. Has the firm determined lag times for all container sizes and adjusted their cycles accordingly?

Chemical Sterilization/Disinfection/Sanitization

162. What product (container/closure; manufacturing equipment) is sterilized by this method?

163. What is the sterilant, sterilant concentration and exposure time?

164. After sterilant exposure, does the item receive a final rinse and/or allowed to air dry?

165. Report the specifications for the final rinse water and/or air quality.

166. Briefly describe how the sterilized item is protected from re-contamination before use.

167. Are there written procedures detailing all chemical sterilization processes?

168. Were these procedures followed with reference to their employment in the manufacture of the selected drug product?

Chemical Sterilization Validation

169. Describe the firm's validation of all chemical sterilization processes utilized, including completeness of documentation, the type of microbial challenges employed, and results.

170. Have any chemical sterilization processes changed since the last EI? Have these changes been evaluated for the need for re-validation?

Ethylene Oxide Gas Sterilization (EtO)

171. If EtO sterilization is performed by an outside firm, report the name and address.

172. If EtO sterilization is performed in-house, report the sterilizer (autoclave) manufacturer.

173. What is the internal volume of the EtO sterilization?

174. What is the ratio of EtO to the carrier (%)(e.g., 12% EtO/88% Freon; 10% EtO/90% CO, etc.)?

175. Is a Certificate of Analysis received with the gas or analyzed by the user (specify which)?

176. Identify equipment/container/closure/other that is EtO sterilized as part of manufacture of selected drug product.

177. What is the sterilization cycle? (Compare Master Process Record/SOP specifications against processing records completed for the selected drug product.)

178. Is there preconditioning (specify external or in chamber, or both, at start of cycle)?

179. What are the firm's Master specifications and observed parameters for time, relative humidity and temperature?

180. Are biological indicators included in prehumidification cycle?

Cycle Parameters

181. What are the Master specifications and observed parameters for the following:
    a. Vacuum (mm Hg, in. H2O)
    b. Air Venting other than by vacuum (prior to or during gas charging)
    c. Temperature
    d. Operating Pressure
    e. Relative Humidity (%)
       - at start of cycle
       - during cycle
    f. Preheating (heat exchanger) or holding temperature of gas when injected into chamber
    g. Gas concentration in chamber (mg/Liter)
    h. Use of a circulation fan
    i. Exposure to sterilant (hrs.)
    j. Use of Multiple Evacuation #cles (# of cycles)
    k. Come-Down or Evacuation Rate

182. How are each of the above parameters monitored? (specify when not monitored)

183. Specify method used to control addition of EtO to chamber (e.g., chamber pressure, EtO concentration analysis, EtO weight measurement, other).

184. Specify method of moisture addition during cycle.

185. If more than one EtO sterilizer is used by the firm, or there are multiple EtO sterilization points within one EtO sterilization system, what is the system's capacity for maintaining established EtO levels when all chambers/sterilization points are operating at the same time?

186. Explain length of supply line from bulk source, inside diameter, number of equipment serviced by supply line.

187. Are EtO concentration levels monitored in aeration and sterilization work areas? Specify levels.

Report information requested in Attachment B for biological indicators used.

Residue Levels

188. Report procedures used to assure EtO residue removal (specify time, tamp., etc.)(e.g., hold in forced aeration area, hold in warehouse-ambient, etc.):

189. Report firm's specifications and conformance for residue levels, if any.

190. What are the firm's specifications and observed levels of ethylene oxide (ppm), ethylene glycol (ppm) and ethylene chlorohydrin (ppm)?

191. Are the residue levels established according to any standard?

192. Obtain copy of dissipation curves (specify when not available).

193. If residue levels on the products are determined by a facility other than the manufacturer, report the name and address of the facility.

194. Have there been any changes in the EtO sterilization system since the last EI? Have these changes been evaluated for the need for re-validation?

Ethylene Oxide Validation

195. Does the firm have written procedures for validation that include:
(a) installation qualification of equipment
(b) operational qualification of equipment
(c) performance qualification with items to be sterilized (d) description of circumstances requiring re-validation of the system and procedures to do so.

196. Does validation documentation include:
(1) empty chamber temperature distribution studies
(a) number of studies performed
(b) number of probes used and their location
(c) report firm's allowable variation and actual variation found

(2) empty chamber EtO concentration distribution studies
(a) number of studies performed
(b) number and location of probes utilized
(c) report firm's allowable variation and actual variation found

(3) empty chamber Relative Humidity Measurement studies
(a) number of studies performed
(b) number and location of probes utilized
(c) report firm's allowable variation and actual variation found

(4) Heat/EtO penetration studies performed:
(a) for each type of loading pattern to be utilized
(b) number of runs per pattern
(c) was the "cold spot" determined for each loading configuration

(5) What type of temperature/EtO/RH measurement systems were used?

(6) Is this equipment calibrated according to an established schedule, and traceable to an NIST standard where practible?

(7) Were measurement systems calibrated before and after each study?

(8) If biological indicators were used during validation run:
(a) type of indicator used
(b) source of indicator
(c) organism used
(1) concentration
(2) D value

(d) was load placement based upon heat/EtO penetration data?

(9) were BIs used in an "end point" or "count reduction" mode?
(1) if any positive BIs were found when not expected, what was the firm's response?

(10) if BIs were not used to determine sterilization effectiveness, what methods were used?

Radiation Sterilization

197. Identify the equipment/container/closure/other that is radiation sterilized as part of the manufacture of the selected drug product.

198. Report the following:
a. Sterilizer manufacturer
b. Radiation type (e.g., beta, gamma)
c. Radiation Source (e.g., cobalt 60)
d. Dosimeter type and supplier
e. Placement of dosimeters within the load

199. If radiation sterilization is performed by an outside firm, report the name and address.

200. Method for Certifying Dosimeter (e.g., traceability to a NIST (National Institute of Standards and Technology) primary reference, etc.).

201. If sterilization is performed in-house, what are the radiation cycle parameters? (Compare reference to the selected drug product.)

202. What are the firm's specifications and observed levels for the following:
a. Exposure time
(1) by batch, report time
(2) by continuous process, report conveyor speed time

b. Dose rate (Mrad/hr.)
c. Uniformity of dose rate (±%)
d. Total dose (Mrad)
Acceptable maximum
Acceptable minimum

e. Temperature

203. How does the firm adjust exposure time for source decay and when does this occur?

204. How often does the firm do a dose mapping of the chamber?
205. How is each of the above parameters monitored (specify when not monitored)?

206. Are dosimeters and/or BIs used in routine sterilization runs? Are they used in determining whether a sterilization run may be released? If so, attach release specifications.

207. Have there been any changes in the radiation sterilization system since the last EI? If so, have these changes been evaluated for the need for re-validation?

Radiation Sterilization Validation

208. Dose Setting: has a minimum sterilizing dose been established for each material?

What method is used to establish the sterilizing dose? (e.g., AAMI Bl, 82, etc. Any dose-setting method used must take into account the quantity and resistance of the natural bioburden of the material being sterilized.)

Has a sterility assurance level (SAL) been established for the material?

209. Product Loading Pattern: has a loading pattern been established for each material to be sterilized? The specification for each loading pattern should describe the number and position of material units within the irradiation chamber.

210. Dose Distribution Mapping: has the dose distribution within the material been determined in the irradiator, using either actual material or a simulated material that approximates the density of the actual material?

With irradiators that offer a variety of conveyor paths, dose mapping of the material must be performed for each conveyor path to be used.

Have the zones of minimum and maximum dosages been determined (for each conveyor path utilized)?

211. Cycle Timer Setting: has a cycle timer setting been established for each material that will yield the minimum required sterilization dose?

212. If biological indicators were used during the validation runs:
- a. type of indicator used
- b. source of indicator
- c. organism used
  - (1) concentration
  - (2) D value

213. How was dosimeter placement correlated with BI placement in the validation loading patterns?

Aseptic Sterilization Systems

Dry Powder Filling

214. Briefly describe the processes used for preparing the sterile drug powder (i.e., sterile filtration, crystallization, spray drying, EtO gassing, etc.

215. Is the production facility dedicated to the product? If not, determine the potential for cross contamination with other products manufactured by the firm.

216. Are any penicillin products produced in the same facility as non-penicillin products?

217. Briefly describe the environmental monitoring performed by the firm in critical areas during actual production. (e.g., how are Class 100 conditions maintained? Where are the sampling sites? Is non-viable particulate monitoring performed?

218. Review monitoring data for several representative months of production. Were results within specifications? If not, what was the firm's response? How many months were reviewed?

219. Does the firm have written procedures describing the filling of sterile dry powders?

Dry Fill Validation

220. How has the firm validated the filling operation for product homogeneity?

221. Is the sterile filling procedure validated by media fill procedure, placebo fill procedure, or other (describe)?

222. Briefly describe media fill procedures or placebo fill procedure (including frequency; whether performed as its own batch or piggy-backed onto a production batch; number of vials routinely filled; etc.).

223. Review results of medial fills/placebo fills performed since last EI (or a minimum of 3 runs, whichever is greater). Are results within specifications? How many fills were reviewed?

224. What are the firm's specifications and procedures following an out-of-limit media fill/placebo fill result?

Placebo Fill:

225. What placebo material is used?

226. How is the placebo material sterilized?

227. Does the firm utilize the same acceptance criteria for placebo fills as for media fills? If not, and higher alert and action levels are permitted for the placebo fills, determine rationale.

228. How long and at what temperature(s) are placebo filled units incubated?

Filtration Sterilization

I. Sterilizing Filters

229. Provide the following information on all sterilizing filters used by the firm:
    a. Type
    b. Manufacturer
    c. Media
    d. Nominal porosity
    e. Operating pressure
    f. Flow rates

230. Is the filter assembly pressure tested before and after use?

231. How does the pressure used for testing correlate with the pressure used in production?

232. What type of integrity testing is performed?

233. What in the firm's procedure when the filter fails post-filtration testing?

234. How many filter failures has the firm had in past year?

235. What investigation was performed following filter failures?

236. Does the firm use a single sterilizing filter or multiple (redundant) filters?

237. Has the firm or the filter supplier performed the bacterial challenge test on each lot of filter media? Summarize testing procedure (or attach documentation).

238. How are filters/filter assemblies sterilized? Is the sterilization process validated? (attach SOP)

239. Are filters resterilized and reused? Is this procedure validated? (attach SOP)

240. Are filters changed during manufacture of the batch? Has this change frequency been validated? (attach SOP)

Filter Validation

241. Has the firm or an outside supplier performed physical and chemical challenge testing of each filter and product combination in the manufacturing process to validate filter-product compatibility? (If these tests were performed by an outside firm, report the name and address). Summerize study results or attach documentation.

242. Did the test conditions duplicate, as nearly as possible, the actual conditions of production?

243. Following validation of a specific filter for a given process and product, does the firm extrapolate the validation findings to related products having similar attributes and processing conditions? If so, is the justification for such extrapolation documented? Is filter performance data correlated with filter integrity testing data as part of the justification?

244. Microbial challenge:

    a. is a "worst case" organism used?

    b. do challenge tests cover:

        i. flow conditions, pressures, volumes

        ii. fluid characteristics, including pH, ionic strength, surface tension. Is there a limit of centipoise for solutions to be filtered. Has the firm determined the effect of elevated viscosity over extended time periods, if applicable?

        iii. time, Does validation cover "worst case" conditions? For example, the firm is doing a continuous form/fill/seal operation and using the filter over an extended period of time.

II. Aseptic Filling

245. Briefly describe the aseptic filling processes from preparation of bulk liquid product to filling and sealing of final dosage form, including the environmental monitoring performed in critical areas during actual production (e.g., how are Class 100 conditions maintained., where are the sampling sites; is bioburden testing performed on the bulk product?)

246. Review monitoring data for several representative months of production, including the period during which batches of the selected drug product were prepared. Were results within specifications? If not, what was the firm's resense?

247. Does the firm have written procedures describing aseptic filling of liquid drug, products?

Aseptic Filling Validation

248. Is the aseptic filling procedure validated by media fill procedure or other (describe)?

249. If media fills were used, report the procedures followed and the results, including: number of runs performed; how many vials were filled per run; sizes of vials and fill volume; media used, incubat' periods, temperatures and results ; allowable contamination rate.., and what firm's response was to results that failed established limits.

250. Does the firm provide for periodic monitoring or revalidation of filling lines using media fill procedures?

251. If media fills are used, briefly describe procedure (including frequency; whether performed as its own batch or piggy-backed onto a production run; number of vials routinely filled., allowable contamination rate).

252. Review results of media fills performed since last EI (or a minimum of 3 runs, whichever is greater); are results within specifications?

253. What are the firm's specifications and procedures following an out-of-limit media fill result?

254. Are media fills performed on all shifts?

255. Are all personnel included in the media fill program?

256. What system does the firm have for assuring all personnel are included?

257. If end-line filters are used in actual manufacture, are they also used during media fills?

258. What size vial or ampule is used for media fills?

261. Is more than one medium used?

262. Will the number of samples used in a media fill vary from line to line? (If yes, please explain)

263. Are growth promotion studies performed on each type of medium used?

264. Are growth promotion studies conducted every time a media fill is done?

265. When are the growth promotion studies performed (before/after filling; after incubation; etc.)?

266. Is the source of the growth promotion test USP XXI or other (if other, describe, including organisms used)

267. What temperatures and incubation times are used to incubate media fill samples?

268. Are microorganisms from positive vials identified according to genus?

269. Are such microorganisms correlated to those found during environmental monitoring?

Parametric Release: Parametric release of terminally heat sterilized drug products (in lieu of end product sterility testing) is only permitted pursuant to an approved (supplemental) New Drug Application. A copy of the NDA portion containing the approved parametric release specifications should be requested from the Division of Manufacturing and Product Quality, Sterile Products Branch (HFD-322) prior to initiating inspection.

Refer to Compliance Policy Guide 7132a.l3 for information on this sterility release procedure. Questions or problems should be directed to:

Sterile Products Branch, HFD-322
Tkrry Munsen, Branch Chief
8/295-8095.

LABORATORY

Stability and Expiration Dating

270. What is the expiration dating on the subject product?

271. Do the stability studies performed on the selected product include preservative effectiveness testing?

272. What is the source of Analytic Method?

Sterility Testing

273. If sterility testing is performed by an outside laboratory, report the name and address.

274. Has the firm audited the contract laboratory procedures and test results? What is the date of the last audit?

275. If sterility testing is performed in-house, what are the qualifications off personnel responsible for sterility testing?

276. Does the firm have adequate written procedures for the sampling and testing of products for sterility, potency, pyrogens, particulate matter, and other appropriate tests?

277. Review sampling and testing records for three lots of the selected drug product: were all required tests performed appropriately, and were results within specifications?*

278. Review sterility testing results summary data accumulated since the last EIR, or the last six months, whichever is greater. What is the firm's overall failure rate upon:

    a. initial testing
    b. first retest
    c. second retest

279. How much time routinely elapses between sterilization of a product and when sterility test samples are put on test? What are the holding conditions of lot samples waiting to be tested?

280. What is the average number of lots sterility tested per month?

281. Describe the firm's procedures for evaluating batches that fail the initial sterility test. How are "false positives" determined? If the cause of a sterility failure cannot be determined as arising from the production environment or laboratory error, what decision is made by the firm concerning the release of the lot in question? (attach retest protocol)

282. Are the "false positive" rates similiar for aseptically filled products and terminally sterilized products? If the rate for aseptically filled products is markedly higher than for terminally sterilized products that are manipulated in a similiar manner during sterility testing, then this rate indicates truely contaminated rather than "false positive", and an in-depth review should be made of the sterilization process.

Pyrogen Testing

283. If the firm is using LAL for pyrogen testing, has the procedure been validated for all products on which it is used?

Environment

284. What air quality is provided in the laboratory environment?

285. What air quality is specified for sterility testing areas? Is laminar air flow provided?

286. What type of environmental monitoring is performed in the laboratory (e.g., type and location of sampling; sampling equipment; frequency)?

287. Compare the firm's written environmental specifications for the laboratory with sampling data for the previous three months. Are results within specifications? If not, what action was taken by the firm with reference to: (a) environmental specifications; (b) product undergoing testing at the time of the out-of-spec results?

CALIBRATION

288. Have all testing, measuring, monitoring equipment (thermometer, thermocouple systems, pressure gauges, pH meter, etc.) used in production and in laboratory testing been calibrated?

289. Is equipment periodically checked for accuracy and recalibrated?

290. Are there written procedures covering the calibration and periodic checking and recalibration of production and laboratory equipment, including set intervals and specifications?

Computers

291. Report if the firm is using an automated process control system. Report if source code documentation is available at the firm.

BIOLOGICAL INDICATOR USAGE
USE SEPARATE PAGE #R EACH TYPE OF INDIC##R AND/ORPRODUCT

1. What type of indicator is used (e.g., inoculated carrier, inoculated product, inoculated simulated product, etc.).?

2. Is the source of the indicator commercial (report brand name and manufacturer) or prepared in-house? (Identify supplier of organism, describe means of propagation and storage, and method of preparation.)

3. What organism is used (specify Genus, species)?

4. What i# the challenge level of the biological indicator prior to exposure to sterilant?

5. Does firm verify viable spore count on each lot BIs?

6. Does the firm or the indicator labeling claim to meet USP performance criteria for steam or EtO biological indicators?

7. Does the firm perform USP testing on each lot of BIs received?

8. What is the approximate D-value of the biological indicator?

9. How many indicators are used per sterilizer load?

10. Describe the firm's procedure used to assay the indicators after exposure (i.e., USP, NASA, etc.). (Specify growth media used, optimal and actual incubation time and temperature.)

11. How are the indicators packaged for sterilization?

12. Are these biological indicators located in the most difficult.-to-sterilize product sites (explain)?

13. Draw a diagram of the distribution of biological indicators in the loading pattern(s) for the selected drug product.

14. What i# the elapsed time (hrs.) between removing indicators from the sterilizer and testing? Are there time limits established for this period? What happens if they are exceeded?

15. What is the average number of sterilizer loads processed per month?

16. How many sterilizer loads with positive indicator test results are there per year?

17. What i# the disposition of lots with positive bioindicator tests results (release, relabel, resterilize, destroy, etc.)?

18. Describe biological indicator storage conditions:

a. Type of room, cabinet, etc. (if stored in freezer or refrigerator, state if frost-free)
b. Temperature
c. Relative humidity (if known)
d. Proximity of storage area to sterilizer(s)

19. If biological indicators are used to monitor EtO processes, also describe:

a. The storage history of the particular lot used in processing selected drug product (including dates of lot expiration lot received, lot sampled, etc.)

b. How long has this particular lot been held by the manufacturer?

c. If there a potential for the biological indicators to be exposed to EtO in the environment before use? (If yes, explain)

20. If the biological indicator testing is performed by a facility other than the primary manufacturer, report the name and address of the facility.

21. Does the firm use chemical process monitor(s) to indicate cycle exposure or to measure one or more cycle parameters? (Report type, brand name and how used.)