DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration 1560 E. Jefferson Ave. Detroit, MI 48207	1/29-2/9,21,22,23/01 FEI NUMBER
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Mr. Scott Canute, Vice President of Pharmaceutical Manufacturing	
FIRM NAME Eli Lilly & Company	STREET ADDRESS Lilly Corporate Center
CITY, STATE AND ZIP CODE Indianapolis, IN 46285	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

1. As noted by the following observations the Quality Unit has failed to perform a comprehensive review of the established operations and raw data to adequately support the Olanzypine (Zyprexa®) manufacturing process described in the NDA.

Media Fill Operations & Aseptic Filling Practices

The cGMP concerns reported in the observations equally apply to the products that are aseptically filled at this facility. Other aseptically filled finished products include, (Line 5) Vancocin 10mg & 10mg oral, Dobutrex, Nebcin-20mg, 80mg, & 1.2gm, Humulin R 500 Unit, Heparin, Quinidine Gluconate, Diluent for Brevital 500mg, Diluent for Oncovin 1mg, Protamine Sulfate, Dolophine, Oncovin 1mg, 2mg, & 5mg, and Diluent for Humatrope. (Line 6) Vancocin 1gm, 1gm oral, 125mg, 250mg, & 500mg, AddVantage, Olanzapine Rapid Acting IM, Gemzar 200mg & 1gm, Humatrope 5mg, Amytal, Glucagon for Animal Sourced Bulk, Glucagon from rDNA Bulk, Velban, Oncovin 1mg, and Capastat.

2. The NDA describes the facility "uses acceptance criteria for media fill of not more than 0.1% contaminated units. As statistical confidence level of 95% is used with this maximum contamination rate to establish the maximum number of contaminated units based upon the number of units incubated per shift." However, not all media filled bottles are incubated or incubated for the required period of incubation as established by the following:

   a. Following the solution filtration process there are [redacted] samples of liquid growth medium taken. The [redacted] samples of liquid medium are discarded and not incubated in order to assure that the liquid medium is not contaminated.

   b. The media fill batch records also document that [redacted] samples of liquid medium will be sampled for microbial growth promotion testing. The volume of liquid medium is not incubated in order to assure that the medium is not contaminated. It was described that microbial growth promotion tests document that the medium has not failed the growth promotion tests within the last [redacted] years.

OF THIS PAGE	EMPLOYEE(S) SIGNATURE(S)	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[signature] [signature]	Thomas J. Aristarco Jeffrey A. Sommer Patricia A. Cochran	2/23/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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c. The media fill batch records document that medium filled vials were collected, not incubated, and are not included as part of the total number of media filled vials. The media filled vials are discarded (also referred to as [redacted] however, the reason(s) for discarding, or providing an assignable cause why the vials were discarded and not incubated is not defined. A summary of the discarded vials is as follows:

Date	Media Fill #	Total Filled [redacted]	Capper Discards	Capper Checks	Capping [redacted] Total
05/20/98	VALA5424	[redacted]	297	24	[redacted]
05/20/98	VAL5315		20	23	
11/25/98	VAL5517		9	24	
03/10/99	VAL5982		39	36	
	VAL6060				
08/13/99	VALA6253		184	48	
09/12/00	VALA6848		103	36	
01/25/01	VALA7090		1	0	

d. As described by knowledgeable individuals and confirmed by one of the media fill operators, there can be approximately [redacted] units (or more) of medium filled vials that are discarded at the end of the media fill operations. The media filled vials are not included with the lyophilization aseptic simulation process, they are not included in the incubation process, and not included as part of the total number of media filled vials.

e. During lyophilization simulation process, temperature thermocouples are placed inside [redacted] of the media filled vials. These vials are not included as part of the total number of aseptically media filled vials and due to the manual placement of the thermocouples are not included with the media filled vial incubation process.

f. The EM Program reveals that [redacted] of the normal microbial flora of the facility consist of bacteria and [redacted] consisting of yeast or mold. However, the media filled vials are not incubated within a temperature that is optimum for bacterial growth, that is 30-35° C. Rather, the media filled vials are incubated for 14 days within a

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temperature of 20-25°C, a temperature that is optimum and conducive for the propagation of yeast or mold isolates.

g. SOP #001-001693 "Use of Media Fills for Parenteral Product Aseptic Processing Validation" define departmental standards for validating the aseptic processes of sterile drug product process via media fills. The procedure also establishes that "the incubation temperature range selected must be justified by data or appropriate literature references." However, the preceding observation points out that the firm has failed to comply with the established written procedure in that there is no "data or appropriate literature references" concerning the justification for the incubation of media filled vials at 20-25° C.

h. As previously described, the "acceptance criteria for media fill of not more than 0.1% contaminated units. As statistical confidence level of 95% is used with this maximum contamination rate to establish the maximum number of contaminated units based upon the number of units incubated per shift." However, given the practices described in the preceding observations, the firm would not be able to substantiate that the contamination rate will not be exceeded in order to obtain the confidence level described in the NDA.

3. The partially stoppered vials are not kept in a Class 100 environment during the mobile cart transferring process from the Class 100 aseptic filling area through the Class 5,000 area and onward to the lyophilizers.

4. The aseptic media fill operations are video taped for review and/or comment in the event that there are issues that are observed or that occur during the aseptic filling process. The observations are as follows:

a. It was explained that if there are issues that occur during the media fill operations, the responsible departments and management staff would review and address the issues. However, the videotapes are not retained, rather they are discarded after the issues are reviewed and addressed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Patricia A. Cochran	Douglas J. Arista, CSO Jeffrey J. Sommer, IO Patricia A Cochran	2/23/01

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Eli Lilly & Company	Lilly Corporate Center
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Indianapolis, IN 46285	Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

b. While the firm performs a video taping of the aseptic filling process, a similar level of attention and review is not performed for the aseptic solution preparation or aseptic filtration process steps.

c. There is no written procedure for the video taping process, which was explained to be a common practice, of the media fill operations.

d. A knowledgeable individual explained that absent a video taping, the media fill operations could be observed by an individual who would record what is observed during the media fill operations. However, as noted in the preceding observation, there is no established written procedure to describe the practice.

5. During an aseptic filling process we observed fill room operators with face covers that did not cover all of their face such that a small part of their face could be seen and exposed to the aseptic filling operations. In addition:

a. There were [redacted] filling operators with head covers worn in a manner such that the side of their face or neck could be observed during some of the aseptic filling activities.

b. There were [redacted] individuals with head covers which were worn in a manner such that when these individuals would bend downward, or by their body movements, would create a bellows effect such that the air inside their body suit would be expelled outward into the aseptic filling area.

6. The media fill batch records do not document the names or initials of the aseptic filling operators who actually perform some of the aseptic filling steps. Rather, a senior operator or leader records the information that the specified steps were executed as required by the batch production record. For example, sets up media filling machine, dose in filling machine, operators must account for all filled vials, and began filling start time. NOTE: The previous examples are not intended to be an all-inclusive list of activities. In addition:

SIGNATURE OF THIS PAGE	SIGNATURE(S) OF INVESTIGATOR(S)	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Patricia A. Cochran	Thomas J. Arista, CSO Jeffrey A. Sommers, Patricia A. Cochran	2/23/01

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CITY, STATE AND ZIP CODE Indianapolis, IN 46285	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

a. The media fill batch records instruct that [redacted] aseptic operators must be present together at least one time in the critical zone". However, the records do not document the individuals who are in the critical zone, the locations of the individuals within the critical zone, the time, or total time the individuals are in the critical zone.

7. In the event that aseptic fill room operators leave the filling areas they are required to re-gown into the appropriate clean room attire prior to returning to the aseptic filling areas. However, there is no record to document the common practice.

8. It was described that Quality Control personnel enter the aseptic filling area to observe the routine aseptic filling processes. However, there is no written established procedure to describe the common practice.

Batch Records

9. There is no official or written procedure defining reprocessing/reworking, conditions under which reprocessing is acceptable, and testing necessary to verify the reprocessing did not affect the safety, purity, identity, and quality of the drug product. For example, the firm performed a reprocessing step (re-filtration) on the following products:

[redacted]/11/99
12/7/00
11/12/99
4/7/99
10/7/99
10/29/99
4/12/99
11/12/99
[redacted] 11/14/00

There is no allowance for reprocessing or reworking in the NDA submitted for each of these products.

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	Patricia Cobre	Thomas J. Arista, CSO Jeffrey A. Summers, Pharmacist Cobre	2/23/01

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10. Review of the [redacted] batch records submitted in the NDA revealed that a calculation sheet, used to determine batch quantities and lot size in the manufacture of VL 7597, Olanzapine For Injection 10 Mg., was verified for accuracy on 5/26/99, one day before the person made the calculations on 5/27/99 as witnessed by their respective signatures and dates on the yield calculation sheet.

11. Review of the [redacted] (stability lots) submitted in NDA [redacted] showed that the batch record did not record the lot number of the active pharmaceutical ingredient used in each batch.

Air Handling System & Operations

12. There are a number of concerns with the airflow pattern (smoke) studies that were performed for the various manufacturing areas. The concerns are as follows:

    a. The smoke studies did not completely demonstrate that the air is moving away from the open product vials, work surfaces, or during personnel manual interventions, and demonstrate that the air moving in the direction away from the work surfaces within these aseptic filling areas.

    b. Similarly as above, the smoke studies did not completely demonstrate that the movement of the individual(s) who performed some of the manual operations during the filtration process does not produce air turbulances that can have a negative impact on the aseptic connections.

    c. The smoke studies failed to include a complete evaluation of the unidirectional flow of air during the manual transfer operations of the partially stoppered vials as the vials are transferred into the mobile transfer carts, which are used to transfer the aseptically filled vials to the lyophilizers.

    d. In addition, the smoke studies did not include simulations with transfer trays containing partially stoppered vials during the transferring process into the lyophilizer.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE(S) Patricia A. Cochran, Jeffrey A. Sommer, Thomas J. Arista, CSO	DATE(S) 2/23/01
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e. As noted in #9b above, the smoke studies failed to include an evaluation near the area (i.e., filtration and tank stemming area) that does not have a physical barrier (e.g., plastic barrier/curtain) in order to assure that the unidirectional flow of air is not compromised during dynamic operations.

f. The preceding observations point out that the smoke studies do not adequately demonstrate that there is an appropriate flow of air and control conditions in order to assure that the opened or partially stoppered vials are not compromised during the aseptic filling process.

13. During the recent airflow pattern (smoke) tests, the document used for the application of the visual smoke testing measurements was a guideline #2.019 (dated 13DEC00) rather than the established written procedures described in #SOP 011252 "Air Flow Pattern Test" (dated 2/15/99).

14. SOP # 001067 "Non-viable Particulate Monitoring of Aseptic Manufacturing Areas" describe that "samples should be taken within [redacted] to [redacted] from the work surface on filling lines." While the SOP specifically describes the sampling height, the SOP is silent with respect to providing a similar level of instructions concerning the placement of the sampling probe either adjacent to or near the aseptic filling heads.

15. The solution preparation area (room [redacted] consist of two air classifications i.e., Class A3 and A4 (Class 10,000 and Class 100,000, respectively). The observations are as follows:

a. There are no lines of demarcation or a manner with which to delineate between the A3 and A4 classifications.

b. There are no physical barriers in place (e.g., plastic curtain, or wall) in order to partition the two different air classifications within the solution preparation room.

c. The pressure differentials between the two different room air classifications are not monitored in order to assure that the A4 conditions do not compromised the A3 area.

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d. Non-viable particle measurements are not routinely taken during dynamic operations in order to assure that the A3 conditions are not compromised during routine production operations.

16. The Differential Pressure System (DPS) that is used to monitor the differential air pressures within the manufacturing areas provide audio and visual alarms if there is a increase or decrease of the specified differential air pressures. There are established specified periods of time, or duration of time e.g., [redacted] seconds, before the DPS initiates an alarm. However, there is no written document to describe the rationale that was used to establish the time intervals. In addition:

a. The devices that are used to monitor air pressure are calibrated with varied standards, e.g., reference standards, calibration standards, or working standards that have units of measure with varied levels of accuracy or margins of error. However, there has been no evaluation performed on the multiple standards' level of accuracy, or margin of error, in order to assure that the DP Systems provides accurate differential air pressure alarms.

17. SOP #001-001754 "Air Pressure Differential Monitoring" instructs that individual critical alarm report summary will be reviewed and signed by the building engineer and by a Quality Control representative. However, Quality Control does not review or provide a signature as established by the SOP. In addition:

a. Not all of the Critical Alarm Reports describe the investigation, provide an assignable cause for the alarm, or describe the corrective actions that are performed, conclusions and final recommendations.

b. The aforementioned procedure provides detailed instructions concerning the responses to critical alarms. However, as the preceding observation (16a), points out the responsible departments and individuals have failed to follow the established written procedure. 17a

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	Patricia A. Cichra	Thomas F. Arista, CSO Jeffrey A. Sommers Patricia A. Cichra	2/23/01

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18. SOP #001-001757 "Process Control System Security" is used as a global document to describe the guidelines for maintaining the security of the process control systems and related documents for Parenteral Products Operations. However, the written procedure does not adequately describe all of the steps and controls that are performed for the DP System's security and computer access. In addition:

    a. There is no written procedure to describe the process that is used to assign, maintain passwords and access levels to the control system.

19. Procedures #YA133, YA138 and YA215, "In-Place Leak Test Inspection of In-Line HEPA Filters, In Place Leak Test of Sterilization / Depyrogenation [redacted] HEPA Filters and Replacing HEPA Filters and In Place Leak Test Inspection of In-Line HEPA Filters", respectively, establish a 5% maximum repair coverage of the HEPA filters. However, there are no records to document the repair size of the HEPA filters in order to assure that the individual repair or cumulative repairs do not exceed the specified 5% maximum.

20. Concerning the HEPA filters in the depyrogenation [redacted] The HEPA filters in the hot zone are not integrity tested on a periodic base in order to assure that the HEPA filters are not compromised. In addition:

    a. It was described that the HEPA filters within the hot zone cannot be integrity tested at ambient temperatures. However, there has been no evaluation performed in order to verify that integrity testing at ambient temperatures is not possible for the HEPA filter.

    b. There is no data to support that the HEPA filters within the hot zone can not be integrity tested at ambient temperature.

    c. There is no established written procedure that describes an evaluation process in order to verify and confirm the integrity of the HEPA filters in the depyrogenation tunnel's hot zone.

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		Thomas J. Arista, ASO Patricia A. Cochran Jeffrey J. Sommers	2/23/01

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DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

21. The Air Handling Unit (AHU) As-Build drawings document specific pre-filter for the air that supplies the various rooms and ultimately the HEPA filters. However, there is no record to document that the pre-filters that are in the AHUs are the required [redacted] efficiency rated pre-filters and [redacted] filters.

22. There is no record to document that the AHU diagrams or As-build drawings have been reviewed and approved the responsible departments, e.g., Engineering, Production, and the Quality Unit.

    a. The Quality Unit has failed to put in place procedures to coordinate and control updates to these structural diagrams when modifications are made to the AHU(s).

23. The [redacted] was initially qualified in 1993. Since then there have been multiple additions or modifications in 1996 and 1998. Modifications or changes include, installing the DPS & a CSV system, exchange of an in-house fan, and addition of the [redacted] computer monitoring system. However, there is no written document that describes the current configurations of the air handler unit. In addition:

    a. While the individual changes have been reviewed during the change control process, a comprehensive review of all the collective changes has not been performed in order to assure that the initial 1993 I/OQ remains to be valid and to assure that AHU does not require requalification or revalidation.

24. There are [redacted] blueprint type diagrams (dated 1989) illustrating the water system that were discovered in a worktable that is next to one of the AHUs. The diagrams are not controlled in order to assure that maintenance or other personnel do not use the diagrams as a reference document. In addition:

    a. There are [redacted] blueprint type diagrams that illustrate the room control temperature and static pressure [redacted] that were attached to one of the AHUs. Similarly as above, the 1/19/89 diagrams are not controlled in order to assure that maintenance or other personnel do not use the diagrams as a reference document.

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	Patricia A. Cochran	Thomas J. Arista, ESQ Patricia A. Cochran	Jeffrey A. Simmons	2/23/01

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b. There are [redacted] laminated documents (dated 1/12/93) permanently attached to the AHUs monitoring panel. The documents list the air handling units [redacted] temperature and supply air set points. However, these documents have not been reviewed and approved by the Quality Unit and they are not part of an established written procedure.

c. The [redacted] air handling unit (AHU) list winter and summer set points, however, the AHU for [redacted] does not include or address the supply air set point, return air CFM or fan static pressure.

25. There is a magnehelic gauge inside the monitoring panel that is next to the AHU(s). It was explained that in the event that the [redacted] monitor fails (the unit that monitors or measures the airflow) the airflow reading would be read from the magnehelic gauge. However, the magnehelic gauges have not been calibrated to a reference standard in order to assure that the measurements are accurate.

26. There are [redacted] synthetic media pads (blue color pre-filters) that are installed with the laminar airflow cabinets that are used within the manufacturing areas that include the airflow cabinets that are used to supply Class 100 conditions for the aseptic filling operations. However, these filters are not described in any of the installation diagrams or in any of the support qualification documents for the laminar airflow cabinets. In addition:

a. The firm has established written procedures to describe steam sterilization of all materials that are used in the aseptic filling area. Some of the materials that are used in the aseptic filling rooms, equipment, or small utensils that are not able to be steam sterilized are appropriately cleaned and sanitized. However, the blue color pre-filters are not cleaned or sanitized prior to installation or periodically cleaned.

27. Viewing Aseptic Fill Line [redacted] from an observation window in a glass vial wash room we observed a HEPA filter metal grill that is in Aseptic Fill Line [redacted] The metal grill appeared to have formations of what appeared to be rust.

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Equipment & Operations

28. The firm's procedure (or any associated document) for the transfer of "Ready To Use" stoppers sterilization does not contain provisions for requirements of transfer conditions. The firm's current practice is to perform this transfer step for this type of stopper under Class 100 Laminar Flow conditions in the production area.

29. No procedure exists for the firm's set up of stoppering machines used during production of aseptically filled products. The firm only has a training document to describe the set up of these machines with no ready access to these instructions by operators when performing this task in the production area.

30. The data for the firm's microbiological seal integrity test study does not identify the number of vials inspected for microbial growth after incubation. The test report only indicates the number of vials prepared for testing under normal torque application and at levels above/below the target torque but does not show the number of vials in the test results section of the report or any associated records. The report does not quantify the number of vials placed in storage at 25°C for container/closure integrity testing at the [redacted] month mark.

31. There is no established written procedure to describe the set-up of the capper. For example, installing bottles, star wheels and sealing fixtures, adjust height and guide rails, check the adjusted sealing pressure, which require checking for [redacted] dimple on the stopper".

32. SOP "001-00243 "Operation of Capping Machine" provide instructions for the operation of the capping equipment that is used to place the aluminum seal onto stoppered vials. In addition, the SOP instructs that the operators are to perform checks for seal quality and stopper appearance i.e., physical examination of the seal and dimpled stopper checks (as appropriate). However, the procedure does not define or address what the physical examination consists of or describe what "as appropriate" is in reference to. In addition:

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FIRM NAME Eli Lilly & Company	STREET ADDRESS Lilly Corporate Center
CITY, STATE AND ZIP CODE Indianapolis, IN 46285	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

a. There are aluminum seal checks that are performed that include observing for [redacted] or [redacted] seal, damaged flip top of seal, severely dented seal and any other gross abnormality. However, there are no representative samples illustrating the aforementioned quality attributes in order to provide defined visual standards for the inspection process, which would include providing standards for the employee's visual training process.

b. One of the equipment operators also added that the visual checks would include a check for [redacted] scratches and discoloration of the plastic flip top. However, these quality attributes are not included in the established written procedure.

c. Concerning the term "gross abnormality" as it relates to the visual inspection process, no additional information or examples could be provided to address what constitutes gross abnormality.

33. Similar to some of the concerns noted in the preceding observation, SOP #006103 "Inspection and Statistical Evaluation of Parenteral Products" provides various classification of [redacted] that include critical defects for containers, products, stoppers, seals, and cosmetic [redacted] for containers and seals. However, there are no representative samples to illustrate the critical or cosmetic defects in order to provide defined visual standards for the inspection process. In addition:

   a. The training module that was used for inspectors who perform the visual inspection list that the training included acceptable and unacceptable units. However, as noted above there are no representative standards to illustrate the critical or cosmetic defects.

34. The firm uses a [redacted] Torque Tester to determine that the finished product vials, rubber stoppers, and aluminum closures meet the predefined torque specifications. However, there have been no qualifications performed on the equipment in order to assure that the equipment operates as required.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) SIGNATURE AND TITLE(S)	DATE
	Jeffrey A. Sommers, Patricia A. Cochran	Tarmo J. Aristo, CSO, Jeffrey A. Sommers, Patricia A. Cochran	2/23/01

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FOOD AND DRUG ADMINISTRATION

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED TO: Mr. Scott Canute, Vice President of Pharmaceutical Manufacturing	
FIRM NAME Eli Lilly & Company	STREET ADDRESS Lilly Corporate Center
CITY, STATE AND ZIP CODE Indianapolis, IN 46285	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

Personnel Flow & Personnel Activities

35. There is no established written procedure to describe restrictions to prevent cross contamination of other aseptic filling lines and/or products when employees have lyophilized powder on their aseptic gown attire. On 2/9/01 we observed an employee unloading lyophizer number [redacted]. A glass vial of [redacted] lot [redacted] was dropped and lyoliphized powder was observed on two different shelves. We observed the employee dragging his arms through the powder as he continued to unload the lyophizer. When the employee left the lyo unloading area he walks through other aseptic areas in order to return to the de-gowning area. Management stated employees are not restricted from entering the aseptic filling lines.

36. SOP #001-001768 "Gowning Procedure for Entrance into Aseptic Manu Areas ([redacted] describes the gowning procedure performed by personnel prior to entering the manufacturing areas. However, the procedure is silent with respect to the current practices that are performed within the existing configuration of Room [redacted] and does not address the personnel flow from the [redacted]

37. Room [redacted] is used by personnel that are required to change from their street clothes and shoes into the requisite blue or white color work "scrub" suits. However, the design and physical location of the gowning room does not provide adequate space in order to assure that the gowned personnel do not come into contact with personnel that have their street shoes and street cloths on.

38. As described by the management staff, when personnel are gowned with the requisite blue color "scrub" suit, they are required to continue onward to the [redacted] floor pre-gowning room in order to change into the gowning attire that is used in the aseptic filling rooms. However, there is no assurance that the individuals do not come into contact with other employees while at the common entryway into manufacturing areas, the stairwell that is used by all employees in the manufacturing area, or with employees that are not required to have facial or hair covers.

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	[signature]	Thomas J. Arista, CSO Jeffrey A. Sommers, Patricia A. Cetnar	2/23/01

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39. The preceding SOP and SOP #001-0011685 "General Garment and Hygiene Require PPO for Bldg [redacted] describe that "Beard / mustache coverings must be worn ensuring that all facial hair is completely covered." However, [redacted] individuals walking in the corridor, which is adjacent to the manufacturing areas, and [redacted] individual were observed without the requisite beard cover.

40. The yellow color shoe covers are required to be don by personnel prior to entering into the manufacturing area pre-gowning room. The yellow color shoe covers assist in controlling the ingress of microbial contamination into the pre-gowning room. However, the yellow shoe covers are slipped on within the same area and floor that other factory personnel walk across.

Environmental Monitoring

41. The following observations concern the 12/19/83 Protocol for Heat Profile of Incubators for the walk-in 30-35° C incubator, room [redacted]

    a. There is no record to document that the protocol was reviewed and approved by the responsible department (Production Process Validation Department) or the Quality Unit.

    b. There is no record to describe the rationale for the thermocouple placement / locations or record to describe the reason for using the number of thermocouples that were used.

    c. The protocol describes that there is a potentiometer chart with the records. However, the chart could not be located.

42. Concerning room [redacted] walk-in 20-25° C incubator that is used to incubate the media filled vials, the qualification document illustrates the location of the shelves that line the walk-in incubator. However, a different configuration of shelves than the shelf configuration described in the qualification documents was observed. In addition:

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	[signatures]	Thomas J. Arista, CSO, Jeffrey H. Sommers, Patricia A. Cochran	2/23/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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a. There are [redacted] mobile carts adjacent to the left side of the walk-in incubator shelves, with [redacted] mobile chart containing media filled vials for batch #VALA7170. The temperature distribution study did not include the addition of mobile carts and their respective locations with the qualification of the walk-in incubator.

b. Similar to the 1983 Protocol in the preceding observation, there is no record to described the rationale for the thermocouple placement / locations or record to describe the reason for using the number of thermocouples that were used.

43. The Environmental Monitoring (EM) Program does not include the use of microbial growth media that is optimum for the propagation of yeast or mold contaminates.

44. The firm's microbial alert and action limits established for the [redacted] to [redacted] manufacturing areas are not based on historical data taken from the EM Program.

45. Non-viable particle measurements are taken with the use of a [redacted] Particle Counter. The particle measurements are recorded onto a 3.5" floppy disk and the data is manually transferred to the firm's [redacted] computer data base system. The observations are as follows:

a. There has been no formal evaluation performed in order to assure that the measurements that are printed as the permanent record is an accurate reflection of the data that is obtained via the 3.5" floppy disc from the [redacted] Particle Counter.

b. As explained by one of the knowledgeable individuals, when the capacity of the 3.5" floppy disc is filled, the original electronic data is not retained as a permanent record. Rather, the data on the floppy disc is overwritten and/or deleted in order to obtain the new non-viable particle counts from the various manufacturing areas that include the aseptic filling areas.

c. There is no established written procedure to describe the reuse of the 3.5" floppy discs.

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d. There are [redacted] 3.5" floppy discs containing EM or laboratory data that are stored in a plastic disc case and floppy disc that are left on various laboratory work desks. When asked, it was confirmed that there is no written procedure to describe the security and control of the data on the floppy discs.

46. During a review of the media fill video and aseptic filling process operators were observed opening and closing the [redacted] zones, by the door bottom and side edges. However, these areas are not sampled for the presence or absence of microbial contaminates during the EM sampling process. In addition:

a. Similarly, we observed aseptic filling room personnel using a telephone that is used to communicate with other departments. However, the telephone was not sampled during the EM sampling process.

b. The records do not document the actual tool or utensil that is sampled during the EM Program.

47. SOP #0027777-018 "Viable Monitoring of Aseptic Manufacturing Areas" describes the frequency of monitoring, sampling methods, recording and analysis of data. As described by an EM Operator, in the event that there is an increase of activity in area within the aseptic manufacturing area, the EM operator has the discretion of obtaining samples the high activity area. However, this is not described in the established written procedure.

48. The aseptic fill operators are allowed to perform the Quality Control EM sampling, that is, self-sampling or self-monitoring prior to exiting the aseptic filling area. This practice is performed approximately [redacted] of the time. The self-sampling is not observed by a Quality Control representative or verified by a second individual in order to assure that the EM sampling is performed as required.

49. The 1999 and 2000 Deviation Audit Reports do not document the reasons why the following listed events occurred. The Deviation Audit Reports revealed numerous occasions when personnel failed to:

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a. perform the "self-monitoring" during the EM sampling;
b. perform some of the [redacted] EM sampling;
c. enter the EM plate count data into the [redacted] Computer System;
d. locate some of the EM incubated samples; or,
e. locate some of the blue color analytical task sheets.

Microbiology & Laboratory Equipment

50. There are a number of observations concerning the [redacted] Sterility Test Isolators Validation and Qualification documents. The observations are as follows:

a. The initial 1991 Sterilization Validation Protocol lists acceptance criteria that includes, "spore challenges to the sterilized isolators must all be rendered negative. However, there were multiple validation runs that failed and [redacted] validation runs were "for informational purposes only".

b. [redacted] of the validation runs submitted in the 1991 Validation documents were considered to be non-acceptable for various reasons that included performing sterilization development studies.

c. The 1991 Sterilization Validation Protocol does not describe or list performing developmental sterilization runs.

d. The 1991 initial validation records document that there were multiple validation runs performed. However, [redacted] of the approved validation runs had to be repeated because the runs exceeded the minimal time parameter.

e. The [redacted] repeated validation runs failed to include diagrams that illustrate the Biological Indicator (BI) and Bioburden sample locations, which is required and described in the validation protocol procedure.

f. There is no established written procedure to describe the validation operation parameters that were used during the 1991 validation runs.

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		Thomas J. Acirtl Jeffrey A. Saunders Patricia A. Cochran	2/23/01

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g. The 1991 PQ documents raw data written in pencil, numerous entries with obliterated data, no initials or dates of the person who obliterated the data, and no initials or signature of the person who recorded the data.

h. There is no record to verify (e.g., photographs or videotape) the airflow profiles that were performed during the, PQ, re-qualifications, and re-validation of the Left and Right Transfer Isolators and the Workstation Isolator. (Note: The 1991 I/OQ documents that airflow patterns are identified as a critical equipment feature.)

i. A videotape was taken during the initial 1991 validation to document smoke airflow patterns within the isolator chamber. However, the videotape does not adequately describe or illustrate the smoke airflow patterns within the isolator chamber.

j. There is no record to document that the 1991 videotape was reviewed and approved by the Quality Unit.

k. The 1993 and 1994 Requalification Documents describe that a smoke test will be completed to identify the dead spots in the isolators and will present the worst case for the sterilization of the spore challenges. However, SOP #001-001361-[redacted] Operations" describes decontamination steps for areas that are more difficult to sterilize e.g., under half suit arms / sleeves or under some of the equipment. The requalification runs did not identify the aforementioned areas as dead spots or identify the areas as the more difficult areas to sterilize.

l. The 2/94 Isolator Requalification describes that air pattern profiling was performed to define dead spots for chemical sterilization. While an evaluation was performed with an empty chamber, the requalification failed to include an evaluation with test equipment, media bottles, EM sampling equipment, or equivalent physical conditions that are used during Sterility Testing in order to determine the dead spots for chemical sterilization.

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m. The 12/97 Revalidation of the Isolator provides a summary of the tests equipment, bottles of media and EM equipment. However, the validation document does not describe the quantity, the placement, or equipment load configuration of how the equipment should be placed in the isolator.

n. The 11/00 Revalidation of the [redacted] solator describes that a study was performed in December 1997 to determine the worst-case loading of the isolators during sterilization. Due to the preliminary study performed as part of the End of Year 1997 Revalidation, the Empty load type was used for this study. However, the 12/97 revalidation did not include a study for the [redacted] Isolator.

o. There is no written document to describe the rationale that establishes the acceptable number of BIs that are required to be used when performing a sterilization validation run.

p. There has been no validation performed to demonstrate that the [redacted] acid solutions that is used to wipe down the isolator and various pieces of equipment inside the isolator can effectively reduce the [redacted] under real time conditions.

q. The preceding observations and the supporting data document that the [redacted] Isolators are not appropriately validated.

51. There is no established written procedure to describe the acceptable equipment load configurations for the isolators in order to assure that the routine load configurations conform to, and do not exceed, the validated load configurations.

52. The 1999 and 2000 HEPA filter integrity tests for the Isolators document that there were "no leaks detected". However, there is no established written procedure to describe the HEPA filter integrity tests that are performed for the [redacted]

53. There is no diagrams or system description for the Pressure Test Equipment that is used to leak test the [redacted] In addition:

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DURING AN INSPECTION OF YOUR FIRM ["WE"] OBSERVED:

a. There is no record to document the qualification or validation of the Pressure Test Equipment.

54. There are a few concerns with the [redacted] Automated Workstation (AWS) that is used for sample preparation of the microorganism for analysis of fatty acid extracts via the [redacted] Microbial Identification (MIDI) System. The observations are as follows:

a. The validation protocol lists the acceptance criteria of ATCC reference cultures for [redacted] different microorganisms. However, as described in the validation summary, for [redacted] would require the use of a different media and the use of a separate automated microbial identification equipment i.e., [redacted] System, "would be required to confirm results reported by the [redacted] system." However, the additional confirmation process is not described in the validation document or described in the acceptance criteria.

b. There has been no evaluation performed to determine that the environmental monitoring contaminants or other microorganisms recovered from the manufacturing process are comparable to the [redacted] System's clinical isolate library. For example, the EM contaminants are not as robust as the ATCC control standards or clinical standards that are used to establish the [redacted] Identification Library.

c. The validation did not include a challenge with EM contaminants during the statistical evaluation in order to determine that the variance and the mean of the similarity indices (i.e., the match factor) was comparable from data generated on the [redacted] AWS as compared to manually generated data.

d. The validation data presents that the ATCC references cultures were processed on the [redacted] AWS and the ATCC reference standards were identified correctly on the [redacted] System. However, the validation did not include EM contaminants in order to determine that the [redacted] AWS can perform a similar level of processing for the non-ATCC, less-robust,

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environmentally compromised contaminants, and that the same level of correct identification can be obtained by the [redacted]

55. SOP #009138 "GMP Computer Systems and Purchased Automated Systems in Quality Control Laboratories (FDA-Regulated)" establish validation requirements for GMP computer systems. For example:

a. The firm did not reviewed the software source code which operates the [redacted] Automated Microabial Identification Sample Prep Workstation to see if it met their user requirements before installation and operation.

b. The procedure describes establishing a written security policy, maintain an access control roster, and virus protection will be installed. However, there is no written security policy, and there is no virus protection installed for the [redacted] AWS.

c. The procedure also describes that [redacted] copies of the archived data will be prepared and the [redacted] copies will be stored in separate secured locations. However, the data taken from the [redacted] AWS is not obtained as established in the procedure.

d. The [redacted] Automated Microbial Identification Sample Prep Workstation is considered GMP equipment and as such generates electronic records which are not backed-up or stored for retrieval. The Operational Qualification document states that ..."since reports are printed after each run and attached to the original laboratory data document, no data is stored long term and data security is not an issue....."Data will not be stored on the system long term since analysts will printout and attach copies of reports to their original laboratory data documents. Therefore backup and archiving of data is not necessary".

56. There is no record to document the mold characteristics or morphology that are observed during the microscopic examination for the mold contaminants that are isolated from the EM Program or from other samples or analyses that are obtained by the firm.

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	Jeffrey A. Sommers for Patricia A. Eckert	Thomas J. Arcuta, Jeffrey A. Sommers, Patricia A. Cochran	2/23/01

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57. There is an inventory logbook that contains a ATCC culture index, Seed Culture List, ATCC Lyophilized Cultures in Stock, Department Lyo's in Stock, and Nitrogen Tank Inventory list. However, there is no established written procedure to describe the inventory practices, which consists of tracking the ATCC cultures, genus & species, expiration data, lot #, and quantity on hand. In addition:

    a. Some of the ATCC cultures are stored in a liquid nitrogen tank. There has been no formal qualification or validation performed for the liquid nitrogen storage tank.

    b. It was explained that the liquid nitrogen tank's storage temperature is approximately [redacted] However, the temperature is not monitored and there is no record to document the actual temperature.

    c. There is no record to determine the level of liquid nitrogen in the tank in order to assure that there is a sufficient volume in order to maintain the requisite sub-freezing temperature.

    d. The inventory records are not reviewed by a secondary individual in order to assure that the inventory and tracking information is accurate, complete and up to date.

58. Concerning the acceptance of media that is used in the laboratory for various analyses, there is no established written procedure to describe the practice that is used to identify and label approved and non-approved media. For example, media that is approved for use will have a green color self-adhesive sticker and media that is not approved and is not to be used will have a red color self-adhesive sticker.

Additional Observations

59. There is a CAD Standards Manual that describe the various processes that are to be performed with regards to consulting firms develop CAD drawings for capital improvement projects and to ensure that drawings are constructed and delivered in the requested format. The manual describes the approvals that are required for in-house

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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produced drawings and consulting firms' drawing approvals. However, the approximately [redacted] diagrams listed in the following sections have not been approved by the responsible departments e.g., Engineering, Production and the Quality Unit:

a. Mechanical Drawings Flow Sheets & Process / Service Piping
b. Mechanical Drawings Flow Sheets & Process / Instruments
c. Mechanical Drawings HVAC Instrumentation
d. Mechanical Drawing HVAC Air Handling System.

e. Similar to a previous observation concerning the AHU diagrams, the Quality Unit has failed to put in place procedures to coordinate and control updates to these diagrams.

60. There are a number of ceiling panels above the personnel corridors that are adjacent to the manufacturing rooms that appeared to be either ajar or positioned in a manner which provide for small openings in the ceiling. There is no record to document that the ceiling panels are secured, or periodically checked, in order to assure that the panels are not left ajar or opened. The open conditions provide an avenue of ingress of viable and non-viable contamination from the ceiling plenum into the personnel corridors that lead into the manufacturing rooms. In addition:

    a. A ceiling panel in a laboratory was removed, or positioned, in a manner that allowed for the ceiling plenum to be exposed. The laboratory, adjacent to the personnel corridor, door was left in an open position.

61. There are a number of non-approved documents or instructions that are used by personnel, for example:

    a. In the event of an alarm from the DPS the operators are to acknowledge the alarm, call or contact a designated individual.

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b. There is a small orange color book titled [redacted] that contains information concerning steam dry sterilization, leak rate, freeze dry charts, temperature and freeze drying charts with handwritten notations, and a Checklist for Quality Control Approval of Manufactured Parenteral Lots.

c. There was a small videotape titled [redacted] dated 6/00 in [redacted] in the lyophilizer's control room.

d. "NOTICE!!!! The Environmental Monitoring data files are to be accessed by Environmental Monitoring Personnel ONLY! Please ask for assistance if data is needed. THANK YOU"

e. Excluding the checklist in Observation 61b, these documents do not list that they have been reviewed and approved by Quality Control or part of the officially established written procedures.

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	[signature] [signature]	Thomas J. Arista, Tiffany A. Sommers, C&O Patricia A. Cochran	2/23/01

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