March 8, 2001

Mr. Raymond Mlecko
Acting District Director
Food and Drug Administration
1560 East Jefferson Avenue
Detroit, Michigan 48207

RE: Eli Lilly and Company 483 Response

Dear Mr. Mlecko:

Observation No. 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 Olanzapine (Zyprexa®) manufacturing process described in the NDA.

Response to Observation No.1.

We believe that the data made available to the investigators during the inspection and the actions included in this response to the FDA Form 483 observations now demonstrate that the Quality Unit has performed a comprehensive review of the established operations and raw data. Upon completion of actions as described in this response, we believe that the established operations and raw data will support the Olanzapine (Zyprexa®) manufacturing process described in the NDA.

Please refer to the more detailed responses below and to the attachments provided for further supporting data and information.

Media Fill Operations & Aseptic Filling Practices

Observation:
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, [redacted] 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. [redacted] 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.

Observation No. 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:

Response to Observation No. 2.

Eli Lilly and Company has developed and implemented a comprehensive media fill program that demonstrates that the facility meets the requirements of a sterility assurance level of less than 0.1% contaminated units with a statistical confidence level of 95%. The foundation of this program is included in the Corporate Quality Policy (Part 17) Sterility Assurance, revision 2 [Attachment 2-1], which applies to all global parenteral filling lines. The next level of detail for the company's strategy for media fills is described in Corporate Procedure 002892 revision 004, Use of Media Fills in Aseptic Drug Product Filling Validation (Worldwide) [Attachment 2-2] which applies to all global parenteral filling lines. The third level of detail for the program is detailed in procedure 001-001693 revision 002, Use of Media Fills for Parenteral Product Aseptic Processing Validation [Attachment 2-3] which applies to Indianapolis parenteral operations. The company's strategy as outlined in these documents is to perform media fills which simulate the conditions that would normally occur during the processing of a drug product batch. Predetermined interventions such as addition of stoppers, changing of filling needles, and dose control as well as various unplanned interventions which might occur are included in the media fill. "Worst case" scenarios are created for the media fill, for example the presence of additional operators, maximum hold times, and maximum duration of filling runs. Operators are instructed to follow normal standard operating procedures during the filling of media, including normal sampling, discards, capper checks, manual weight checks (dose control), and [redacted] The fact that operators follow the same standard operating procedures during media fills as they do during normal production runs means that no special training or practices are necessary for media fills, fulfilling the requirement that media fills simulate normal production runs as closely as possible. There is one important difference during the performance of media fills. Vials with obvious integrity defects are removed, but the normal inspection process to remove any type of visual defect (for example, cosmetic defects) is not performed.

Corporate Procedure 002892 revision 004, Use of Media Fills in Aseptic Drug Product Filling Validation (Worldwide) [Attachment 2-2] emphasizes the strategy by stating:

> 2.d.3.7)f) " Media filled container(s) are only to be removed from the filling line when the same product container(s) would be removed during normal production."

Procedure 001-001693 revision 002, Use of Media Fills for Parenteral Product Aseptic Processing Validation [Attachment 2-3], emphasizes the strategy by stating:

> 4d. "During any of these interventions where filled containers are removed, no media filled container(s) are to be removed unless the same product container(s) would be removed during normal production."

At the completion of the media fill, the entire population of vials representative of a normal production run is incubated for 14 days at 20° to 25°C. At the completion of the incubation period, the vials are inspected using the statistically determined acceptance criteria to assure a sterility assurance level of less than 0.1% contaminated units with a confidence level of 95%.

In general, the investigators disagreed with the strategy of exactly simulating normal production operations where those operations result in discarding samples or filled vials, for example the taking of manual weight checks. Discussion with the investigators and the subsequent observations instruct us to change these practices to include the incubation of all vials filled except those that exhibit an obvious integrity defect, for example cracks or missing stoppers. This change will require the simulation of some interventions rather than the current practice of actually performing the interventions. For example, a manual weight check could be simulated by reaching in with forceps and performing the motions of pretending to remove a vial from the line rather than the normal production process and current media fill process of reaching in with forceps and removing the vial from the line and subsequently discarding it.

Regarding the incubation conditions, in all media fills, vials are incubated for the required period of 14 days at 20°-25°C. Growth promotion studies performed with every media fill support these incubation conditions. We believe that this incubation schedule is supported by a number of FDA and USP documents and opinions as detailed in our response to observations 2(f) & 2(g).
During the inspection, it became clear that our practices for media fills differed from the expectations of the investigators. The untitled document dated February 8, 2001 [Attachment 2-4] was provided to the investigators on February 8, 2001 to document and clarify our thought processes and positions at that time.

In our responses to the FDA Form 483 observations, Eli Lilly and Company commits to change the strategy of the media fill program to include the incubation of all vials except those that exhibit an obvious integrity defect, for example cracks or missing stoppers. Additionally, the incubation conditions will be changed to 7 days at 20°-25°C followed by 7 days at 30°-35°C. After incubation, the population of vials which would represent a normal production run will be inspected using the current statistically determined acceptance limits. After incubation, the population of vials which represents vials that would be discarded during normal production runs will be inspected and any evidence of growth will

be investigated with a review by Quality Control to determine the identity of the organism, possible source of contamination, and impact to the operation.

Disposition of the media fill by Quality Control will be based on the statistical acceptance criteria applied to the population of vials which would be representative of a normal production run, with consideration given to the outcome of the investigation into any positive vials from the population of vials which represents vials that would normally be discarded.

The following corporate and site procedures have been changed: 002892 revision 005, Use of Media Fills in Aseptic Drug Product Filling Validation (Worldwide) [Attachment 2-5] and 001-001693 revision 004, Use of Media Fills for Parenteral Product Aseptic Processing Validation [Attachment 2-6]. Media fills for [redacted] and [redacted] will be completed in [redacted] using the new procedures. All future media fills at the site will be completed using the new procedures.

Details of these changes are provided below in the following responses to FDA 483 observations.

Observation No. 2a.
Following the solution filtration process there are three [redacted]ml samples of liquid growth medium taken. The [redacted]ml samples of liquid medium are discarded and not incubated in order to assure that the liquid medium is not contaminated.

Response to Observation No. 2a.

The [redacted] ml samples are removed to simulate manual sampling interventions that occur during normal processing. During drug product processing, these samples, which do not have to be sterile, are collected as part of in-process control testing (e.g., potency). The media fill protocol will be modified to incubate these samples. [Attachment 2a-1]

Observation No. 2b.
The media fill batch records also document that [redacted]ml 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.

Response to Observation No. 2b.

Growth promotion testing will be performed at the end of the media fill using vials from the media fill study. Corporate procedure 002892 revision 005, Use of Media Fills in Aseptic Drug Product Filling Validation (Worldwide) and area procedure 001-001693, revision 004, Use of Media Fills for Parenteral Product Aseptic Processing Validation, have been modified [Attachment 2-5 and 2-6].

Observation No. 2c.

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	[redacted]	20	23	[redacted]
11/25/98	VAL5517	[redacted]	9	24	[redacted]
03/10/99	VAL5982	[redacted]	39	36	[redacted]
	VAL6060				
08/13/99	VALA6253	[redacted]	184	48	[redacted]
09/12/00	VALA6848	[redacted]	103	36	[redacted]
01/25/01	VALA7090	[redacted]	1	0	[redacted]

Response to Observation No. 2c

Lilly does not selectively discard media fill vials to alter the media fill outcome. For each media fill, thorough media accountability is performed.

It is important to note that those vials referenced in Observation 2c as Filling [redacted] and Capper [redacted] represent vials that would be normally discarded during routine production runs. The Filling [redacted] also includes the vial equivalent of media obtained from bleeding the fill lines. This media is never actually filled into vials as it is collected into a tray located under the filling heads. The vial equivalent of media is based on the weight of media collected in the pan and the dose weight for the vial.

As an example, the following table summarizes vial accountability on [redacted] over the last [redacted] years. It shows that the media fill program accounts for [redacted] of media on average. This calculation is based on accountability of both incubated and non-incubated vials. All non-incubated vials represent vials and the vial equivalent of media that would always be discarded during routine production.

Table 2c. Line 6 Vial Accountability

VAL #	Date Filled	Theoretical Yield	Filling [redacted] (A)	Capper [redacted] (B)	Vials Incubated (C)	Total (A + B + C)	% Account.
5315	4/98	[redacted]	846	49	[redacted]	[redacted]	100.8
5424	4/98	[redacted]	412	321	[redacted]	[redacted]	99.4
5517	10/98	[redacted]	628	245	[redacted]	[redacted]	99.7
6060	1/99	[redacted]	641	334	[redacted]	[redacted]	99.8
6253	7/99	[redacted]	4073	681	[redacted]	[redacted]	99.1
6610	3/00	[redacted]	596	955	[redacted]	[redacted]	99.8
6848	8/00	[redacted]	3204	242	[redacted]	[redacted]	100.0
7090	12/00	[redacted]	861	692	[redacted]	[redacted]	100.3
							X = 99.9

As described in the general response to Observation 2, the media fill protocol has been changed so that these vials will be incubated.

Observation No. 2d.
As described by knowledgeable individuals and confirmed by [redacted] 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.

Response to Observation No. 2d

This observation describes vials that are manually discarded during production runs following the procedures and training for aseptic filling operations.

As described in the general response to Observation 2, the media fill protocol has been changed so that all filled vials will be incubated.

Observation No. 2e.
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.

Response to Observation No. 2e

The vials in which temperature thermocouples are placed are discarded during normal production runs following the procedures and training for aseptic filling operations. As described in the general response, the media fill protocol has been changed so that all filled vials except those that have obvious integrity defects will be incubated.

NOTE: The following observations (2f. and 2g.) have a combined response.

Observation No. 2f.
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 temperature of 20-25°C, a temperature that is optimum and conducive for the propagation of yeast or mold isolates.

Observation No. 2g.
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.

Response to Observation No. 2f. and 2g.

Eli Lilly and Company has data and literature references to justify the incubation of media filled vials at 20°-25°C.

The following literature references, which were provided to the investigators during the inspection in the aforementioned untitled document dated February 8, 2001 [Attachment 2-4] support this process:

1. A publication in the PDA Letter, June 1996 Vol. XXXII, No. 6, page 3, in which Linda English, FDA Baltimore District states; "In applying this principle, it is FDA's general policy in regard to compliance with CGMP to accept incubation at 20-25°C for a minimum of 14 days without having to collect data to support this incubation schedule. It is similarly acceptable for firms who prefer a two-temperature incubation schedule to incubate at 20-25°C for a minimum of seven days followed immediately by incubation at a higher temperature range not to exceed 35°C for a total minimum incubation time of 14 days. Other schedules would be expected to be supported by appropriate data." [Attachment 2f-1].

2. Quality Control Reports, "The Gold Sheet", Vol. 32, No. 9, September 1998, page 10, in which the transcript of CBER reviewer John Levchuk's position at that time on media fill incubation states; "Incubation schedule: Biologics may have slightly different perspective on this than drugs, I'm not sure. But just from our point of view, if you use an incubation schedule of 20-25° for 14 days, we are not going to fuss at you to do any validation to make sure it is going to pick up contaminates that might exist in your filling suite." [Attachment 2f-2]

Current practice of incubation at 20°-25°C is supported by the growth promotion study completed with each media fill. The growth promotion study utilizes typical building flora, including bacteria, and growth is demonstrated within 7 days at the 20°-25°C incubation temperature. We believe this clearly justifies our current incubation program. These documents were provided to the investigator during the inspection as well as in [Attachment 2-4] which was given to the inspector upon his departure.

Although the above references support our incubation schedule, incubation conditions for all future media fills will be conducted at 7 days 20°-25°C followed by 7 days at 30°-35°C.

Observation No. 2h.
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.

Response to Observation No. 2h.

Eli Lilly and Company has changed the applicable procedures for media fills as described above.

All future media fills in the Indianapolis Parenteral site will be done using the new procedures. Eli Lilly and Company asserts that the media fill program in place at the time of the inspection and the revised media fill program are both adequate to assure the acceptance criteria of less than 0.1% contaminated units with a 95% confidence level is substantiated for marketed product.

Observation No. 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.

Response to Observation No. 3.

The current practice of using unsealed carts to transfer product from the filling lines to the freeze dryers and back has been shown to adequately protect product during the transfer process. Procedure 001-001877, revision 001, Freeze Dryer Transfer Carts [Attachment 3-1], specifies that the carts are sanitized following the completion of use on each lot. Environmental monitoring of representative carts is conducted according procedures 001-001710, revision 003, Viable Monitoring of Aseptic Manufacturing Areas [Attachment 3-2] and 001-001712, revision 006, Viable Monitoring of Aseptic Manufacturing Areas Sampling Locations and Data Sheets for LTC South, IC171 and IC172 [Attachment 3-3]. There were no actions or alerts associated with this monitoring during all of 2000. The unsealed carts have been adequately tested in the media fill program.

We have identified improvements that are being made to these transfer carts that will further ensure the transferred vials remain within Class 100 conditions. The sealing properties of the carts are being enhanced by the addition of mechanical latches and gasket material. Testing is being conducted, subsequent to modification to the carts to assure the integrity of the seal.

In addition, an environmental process qualification will be conducted to gather viable and non-viable data to demonstrate Class 100 conditions are maintained within the sealed carts.

Change proposal QK-1992-CCN, Sealed Freeze Dryer Carts [Attachment 3-4], has been written and approved to document the modification to the carts and environmental monitoring results of the cart change. All carts will be modified on or before [redacted]

NOTE: The following observations (4a., 4b., 4c. and 4d.) have a combined response.

Observation No. 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.

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.

Response to Observation No. 4a., 4b., 4c. and 4d.
The video taping of media fill process will be discontinued and observers will be used to document media fill practices including the aseptic solution preparation and aseptic filtration processing steps. The area media fill procedure [Attachment 2-6] has been modified to describe the role of observers and related documentation.

NOTE: The following observations (5a. and 5b.) have a combined response.

Observation No. 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.

Response to Observation No. 5a. & 5b.

We have ordered replacement hood covers of superior design to assist the operators in consistently achieving sufficient coverage as per their training. The replacement of the hoods will be complete in [redacted].

Additionally, retraining will be completed by [redacted].

Observation No. 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:

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.

Response to Observation No. 6 and 6a.

During normal production operations, an effort is made to minimize the number of activities/interventions by our operators in aseptic areas. The existing media fill practice of having one person in the aseptic filling room verify with initials that the media fill requirement "[redacted] aseptic operators are present together at least one time in the critical zone" is consistent with this philosophy.

The media fill protocol [Attachment 2a-1] has been revised to include details such as those mentioned in the observation.

Observation No. 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.

Response to Observation No. 7.

The practice of re-gowning into appropriate clean room attire, upon each entry to the aseptic filling areas is described in the following procedures which were provided to the investigators during the inspection:

Procedure 001-001768, revision 002, Gowning Procedure For Entrance Into Aseptic Manufacturing Areas (IC171, IC172, and GL269). [Attachment 7-1]

In chapter 1.c., scrubs (garments worn under the sterile gown) are to be put on prior to each entry.
In chapter 2, bagged gowning items (gown, boots, goggles, gloves and mask) have to be used to enter into the aseptic block.
In chapter 3, it is described that sterile gowns, goggles have to be placed in recycle containers when exiting the aseptic area.

As described by procedure 001-001768, revision 2, people flow is unidirectional since garments are removed when exiting, new garments must be used to re-enter the aseptic manufacturing areas.

Furthermore, Corporate Procedure 002893, revision 003, Dress Code And Hygiene Requirements For Work in Bulk Sterile, Sterile Drug Product and Sterile Clinical Trial Preparation Operations (Worldwide) [Attachment 7-2], chapter 2.b.2) c) requires "Sterilized protective garments must be provided each time a person enters an aseptic area and must not be re-used when the area is exited and re-entered.

The above procedures were shared with the investigators during the inspection.

To enhance documentation of gowning and de-gowning practices, procedure 001-001698, revision 006, Aseptic Personnel Monitoring and Qualifications for Parenteral Products Operations, [Attachment 7-3] has been revised to require operators when leaving the aseptic core to document, on an ASEPTIC AREA EXIT LOG, that they have removed and discarded their gown garments. In procedure 001-001768 revision 004, Gowning Procedure for Entrance Into Aseptic Manufacturing Areas (IC171, IC172 and GL269) [Attachment 7-4], a sentence will be added to clarify what is implied: Sterile gown may not be reused, new sterilized gowning items are required for each entry in aseptic manufacturing areas. These procedures become effective [redacted] NOTE: Training will be completed prior to all procedure effective dates throughout this response.

Observation No. 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.

Response to Observation No. 8.

As stated in the Quality Control Representative "Job Description" [Attachment 8-1], the Parenteral Quality Control Representative has the responsibility to provide support to Parenteral Products Production in building [redacted] at [redacted], for maintaining quality systems and GMP compliance. It specifically states that "a portion of the QC Rep.'s time is spent in the production environment lending direct and immediate support to the manufacturing and filling operations. Time spent on the production floor is devoted to coaching on the quality systems, increasing technical expertise in the manufacturing/filling process, problem solving and in-process document audits and first line judge for deviation resolution in-process". Procedure 001-001140, revision 003, Responsibilities of the Quality Control Unit [Attachment 8-2], and associated training course PO22047-03, Responsibilities of the Quality Control Unit [Attachment 8-3], have been enhanced to include detailed Quality Control inspection requirements that are performed on a daily basis.

Batch Records

Observation No. 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], lot [redacted], 10/11/99
[redacted], lot [redacted], 12/7/00
[redacted] lot [redacted] 11/12/99
[redacted] lot [redacted] 4/7/99
[redacted] lot [redacted] 10/7/99
[redacted] lot [redacted] 10/29/99
[redacted] lot [redacted] 4/12/99
[redacted], lot [redacted] 11/12/99
[redacted] 4MS39, 11/14/00

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

Response to Observation No. 9.

Historically, Lilly has considered that the repetition of a step in the normal sequence of operations is a step in the normal sequence of operations is not reprocessing. Thus, Lilly has not considered refiltration of a bulk drug solution to be reprocessing as described in FDA's *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products* (February 1987), section II.E.2.[Attachment 9-1], if the refiltration occurs immediately following the initial filtration and prior to moving to the next step. Lilly's practice has been to document the deviation which resulted in the potential

loss of sterility assurance and subsequent refiltration in a deviation report. This practice was based on Lilly's understanding that this was in compliance with the cGMP's registration requirements and with current industry standards.

After publication of FDA's *Guidance for Industry:* Changes to an Approved NDA or ANDA (November 1999), Lilly evaluated current practices against the requirements stated in the new guidance. During this evaluation, it was noted that section VII.C.1.d of the guidance states that "Filtration process changes that provide for a change from single to dual product sterilizing filters in series, *or for repeated filtration of a bulk*" should be reported in a Changes Being Effected in 30 Days supplement.

On December 7, 1999, a representative of Lilly contacted Dr. Nancy Sager, Associate Director, Office of Pharmaceutical Science, CDER, to clarify whether this section applied to permanently changing the process to include refiltration of every lot or if it applied to non-routine refiltration resulting from manufacturing deviations with a potential loss of sterility assurance. [redacted] with Dr. Sager. Dr. Sager confirmed Lilly's belief that this section of the guidance applied to permanent process changes. Furthermore, she stated that non-routine repeating of a step (i.e., repeat operation) would fall under cGMPs and that refiltering examples such as those mentioned were covered under the cGMPs.

Based on this information, Lilly determined that our current practices for refiltration are in compliance with FDA guidance and guidelines and that allowance in our NDAs for this specific use of refiltration is not needed.

A copy of the note to file documenting this conversation was provided to the investigators and is included as [Attachment 9-2].

Repeat operations such as re-filtration are documented by a manufacturing deviation report, which are reviewed and approved by Quality Control. Written procedures require the notification of Technical Service and creation of a batch record insert that describes the additional testing necessary as part of the refiltration operation.

Procedure 001-002012, revision 001, Rework, Reprocessing and Repeat Operations for Parenteral Drug Products [Attachment 9-3], has been created to describe that repeat operations will be documented by a manufacturing deviation report and batch record insert. The batch record insert will describe if any additional testing is required.

Observation No. 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.

Response to Observation No. 10.

The calculation sheet observation has been documented as a manufacturing deviation (DEV-11887) [Attachment 10-1] on February 7, 2001. As shown by the date printed on the calculation sheets, the sheets were generated and the calculations performed on May 20 and May 24, 1999. These sheets were verified on May 26, 1999 as shown by the signature of the verifier. On May 27, 1999, the calculator realized he had not signed the calculation sheets and did so, using the date of signature (according to procedure) rather than the date of calculation creating the apparent out of sequence event. This is considered to be an isolated error. This deviation was shared with the investigators during the course of the inspection.

Observation No. 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.

Response to Observation No. 11.

The omission of the active pharmaceutical ingredient lot number has been documented as a manufacturing deviation report (DEV-11948) [Attachment 11-1], on [redacted]. An entry line for recording the lot number of the active pharmaceutical ingredient was inadvertently omitted when the manufacturing tickets for these development lots were created. This deviation was shared with the investigators during the course of the inspection. Included is the supporting documentation from the batch record [Attachment 11-2] to show which active pharmaceutical ingredient was used in each batch. Subsequent to these [redacted] lots, all batch records did include the entry line for the active pharmaceutical ingredient lot numbers.

Air Handling System & Operations

NOTE: The following observations (12, 12a, 12b, 12c, 12d, 12e and 12f have a combined response.

Observation No. 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 turbulence 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.

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.

Response to Observation 12, 12a, 12b, 12c, 12d, 12e, and 12f.

Eli Lilly and Company has designed a comprehensive qualification, validation and maintenance program of the air handling systems serving sterile manufacturing operations. The Corporate requirements for these activities are documented in:

Corporate Policy (Part 17) revision 2, Sterility Assurance [Attachment 2-1]

Corporate Procedure 002890, revision 003, Maintenance of HEPA Filters in Bulk Sterile, Sterile Drug Product, and Sterile Clinical Trial Preparations Operations (Worldwide) [Attachment 12-1]

Corporate Procedure 002885 revision 004, Classification and Monitoring Requirements for Operating Areas in Bulk Sterile Drug Product, and Sterile Clinical Trial Preparation Operations (Worldwide) [Attachment 12-2].

Additional Guidance is provided in Quality Technical Guideline 2.019 revision 1.0, Visual Smoke Testing and Velocity Measurements to Evaluate Airflow Patterns [Attachment 12-3].

Eli Lilly and Company documents smoke tests on a written protocol and on video tape. Quality Control has considered these two methods of documentation to be complementary – for example, if the video tape did not clearly show the air pattern for a portion of the test due to lighting, camera angle, etc., then the observation of the person performing the test on the written protocol would be considered as acceptable documentation for the study.

We are changing our applicable procedures to provide more specific details (e.g. movement of personnel who perform manual operations, evaluation near the area that does not have physical barrier) around the methodology of conducting and video taping the smoke test to assure more complete documentation.

In the future, when dispositioning a smoke study, the video tape will need to demonstrate that the study was complete and that acceptance criteria are supported by the video tape.

The Quality Control Unit has re-reviewed the data associated with these existing smoke studies and made recommendations for those that should be re-performed to assure completeness of documentation. The smoke studies will be re-performed and completed by [redacted]

In addition, the following smoke studies will be reperformed: filtration operation (filtration and tank stemming), manual transfer operation of the partially stoppered vials as the vials are transferred into the mobile transfer carts and transferred into the lyophilizer. These smoke studies will be performed and completed by [redacted]

Observation No. 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).

Response to Observation No. 13.

During recent airflow pattern smoke testing, the Quality Technical Guideline 2.019 (QTG 2.019), revision 1.0, Visual Smoke Testing and Velocity Measurements to Evaluate Airflow Patterns [Attachment 12-3], was used in conjunction with procedure 011252, revision 003, Air Flow Pattern Test [Attachment 13-1], to define the requirements for the studies. At the time that the studies were performed, procedure 011252 had not yet been updated to reflect the content of QTG 2.019, which was approved 12-13-00. QTG 2.019 was prepared to describe the Corporate Quality Unit's best current knowledge of airflow pattern

testing, in accordance with procedure 015990, revision 004, Quality Technical Guidelines Preparation, Review and Approval, Distribution and Maintenance [Attachment 13-2]. The acceptance criteria contained in QTG 2.019 were used to summarize results of airflow pattern testing to provide more detail to the summary required by Attachment A of Procedure 011252.

Procedure 011252, Air Flow Pattern Test, has since been updated and approved to include content from QTG 2.019. The updated version is procedure 001-001699, revision 004, Airflow Pattern Testing [Attachment 13-3].

The updated procedure reflects the same requirements as QTG 2.019 revision 1.0 [Attachment 12-3] Appropriate personnel will be trained on procedure 001-001699. Procedure 001-001699 revision 002 is effective March 8, 2001.

Observation No. 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.

Response to Observation No. 14.

Procedure 001-001717, revision 003, Non-Viable Particulate Monitoring of Aseptic Manufacturing Areas, [Attachment 14-1], was made effective on February 7, 2001 to change the wording to "Samples are to be taken not more than one foot from work site on filling lines" which includes sites either adjacent to or near the aseptic filling heads. This information was made available to the investigators during the course of the inspection. In addition, fixed-point monitoring in A1 areas will be implemented during the mid-summer shutdown.

NOTE: The following observations (15a., 15b. and 15c.) have a combined response.

Observation No. 15.
The solution preparation area (room [redacted]) consist of [redacted] air classifications i.e., Class [redacted] and [redacted] (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 [redacted] and [redacted] 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 [redacted] conditions do not compromised the [redacted] area.

Response to Observation No. 15a., 15b. and 15c.

The solution preparation area (room [redacted] air classification will be modified to be class [redacted].

A change control has been written, CC 512 [Attachment 15a-1], that outlines the implementation requirements for the air classification change. In addition an Environmental Qualification for the solution preparation area, DHC Solution Manufacturing Controlled Area Room [redacted] PM Performance Qualification [Attachment 15a-2], will be performed. The change control will be executed by [redacted]

Observation No. 15d.

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

Response to Observation No. 15d.

We would like to provide clarification to the above observation point. We have reviewed the historical data for the manufacturing bays and the data demonstrate that non-viable particle measurements are taken during routine production hours. Please see attached historical data for confirmation [Attachment 15d-1 & 15d-2].

Observation No. 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.

Response to Observation No. 16.

The Differential Pressure System (DPS) is used to monitor differential air pressures within the controlled manufacturing area. The system was qualified in 1996 to replace a Manual Differential Operating System. As part of the qualification of the DPS System, an evaluation, ICT2517, Building [redacted] Differential Pressure Testing to Determine Impact of Forced Differential Pressure Inversions on Parenteral Processing Areas[Attachment 16-1] was conducted to determine the impact of forced differential pressure inversions. The ICT was available at the time of the inspection but due to shortage of time, was not reviewed.

The study confirmed that environmental conditions were maintained during a [redacted] minute pressure inversion. Our current time delay alarm configuration of [redacted].

[redacted] seconds are within our demonstrated level of control by a significant safety margin.

In order to enhance our documentation of the DPS System, we will evaluate DPS during the periodic evaluation of the HVAC System. Thus, parameters such as alarms and alarm time delays will be reviewed as part of the evaluation.

Observation No 16a
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.

Response to Observation No. 16a.

The control system software for monitoring differential pressure alarms includes a [redacted] inch of water column offset. This offset accounts for the cumulative error of the measuring devices, the error in the calibrating devices and the error associated with the NIST traceable standard for the differential pressure system.

We have performed an evaluation to confirm that the specified offset, [redacted] of water column, in the software accounts for "worst-case" calibration, reference standard and measurement errors [Attachment 16a-1].

We have concluded from our evaluation that our current calibration, measurement method and alarm software provide a 95% confidence interval that our system is in control and capable of alarming all inversions and pressure equilibration between rooms.

Although our data demonstrates that no change is necessary to our alarm control software, we have identified an opportunity to improve our field calibration device accuracy. Based on the fact that the [redacted] device accuracy is the largest contributor to total cumulative error, Parenteral Site Engineering will initiate an evaluation of alternative calibration methods and devices by [redacted]

NOTE: The following observations (17, 17a. and 17b.) have a combined response.

Observation No. 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 (17a), points out the responsible departments and individuals have failed to follow the established written procedure.

Response to Observation No. 17, 17a. & 17b.

During the inspection, critical alarm reports were reviewed for the Differential Pressure system. In one example, an incident created [redacted] critical alarm reports spaced approximately [redacted] minutes apart. Upon investigation, it was determined that these [redacted] alarms were related to one incident. One report was written on the first alarm report and the subsequent alarm reports were attached to the investigation. This investigation including assignable cause and corrective action was reviewed and approved by Quality Control.

As a result of the discussion during the inspection, procedure 001-001754, revision 006, Air Pressure Differential Monitoring [Attachment 17-1], has been enhanced to provide guidance that individual alarm reports are to be completed for each individual alarm that occurs. It further states that alarm reports are not to be grouped for documentation purposes. This approved procedure was provided to the investigators during the inspection.

NOTE: The following observations (18 and 18a.) have a combined response.

Observation No. 18.

SOP #001-0001757 "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.

Response to Observation No. 18 and18a.

A standard methodology for assigning and maintaining access levels and passwords for the DP system is followed within the site. Requests for access are received by the Control System Administrator. The System Administrator reviews the request for justification and, if acceptable, grants access and provides the required training. The System Administrator forwards the approved personnel's information to the Site Documentation Controller who maintains the list of persons with access and training. This process is followed and ensures that we have maintained control of system security. We do commit to improving our procedural control of this current process for system security.

The procedure 001-001757, revision 004, Process Control System Security [Attachment 18a-1], has been modified and approved to address DP System Security and Computer Access. The procedure is approved and effective on March 6, 2001.

Observation No. 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.

Response to Observation No. 19.

To improve the documentation of our practices, the procedures YA133#, version 009, In Place Leak Test Inspection of In-Line HEPA Filters, YA138#, version 010, In Place Leak Test of Sterilization/Depyrogenation [redacted] HEPA Filters, and YA215#, version 002, Replacing HEPA Filters and In Place Leak Test Inspection of In-Line HEPA Filters [Attachments 19-1, 19-2 and 19-3 respectively] have been updated to require documentation of the size of the leak repair. These procedures will instruct personnel to perform a cumulative mathematical addition of the size of each repair to assure that the established 5% maximum coverage is not exceeded. These procedures were effective February 23, 2001.

Observation No. 20.
Concerning the HEPA filters in the depyrogenation tunnels. 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

Response to Observation No. 20

The HEPA filters in the hot zone are not integrity tested on a periodic basis due to flash point (fire concerns) and the probability of subsequent test material particle

generation as the HEPA filters are heated to operating temperatures. Our current acceptable testing media, [redacted], has a flash point of [redacted]C while our tunnels operate at [redacted]. There has been a concern that residual material remaining in the filter after ambient temperature testing could be hazardous when the filters are heated.

During the inspection, the untitled document dated February 9, 2001 and the document titled "Current Technology: High Temperature HEPA Filters" were provided to the investigators on February 9, 2001 to document and clarify our evaluation and positions at that time [Attachment 20-1].

The industry standard is that the best possible measure of filter performance to ensure class 100 conditions at high temperatures (325° - 350°C) is periodic airborne particulate counts. Procedure 001-001703, revision 003, Particle Monitoring of [redacted]unnel [Attachment 20a-1], describes the [redacted]testing that is performed to determine that a class 100 environment is maintained. The results of this comprehensive [redacted]test routinely demonstrate that class 100 conditions exist in our depyrogenation tunnels.

Eli Lilly and Company commits to further evaluate integrity testing techniques that could be safely applied at ambient temperature to initial installation of HEPA filters in the heating zones of depyrogenation tunnels. This evaluation has begun and will be completed in [redacted]

Observation No. 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.

Response to Observation No. 21.

Procedure YA243#, version 001, Air Handling Unit Prefilter and [redacted] Replacement [Attachment 21-1], has been revised to included a specification checklist for the [redacted] efficiency rated filters and the [redacted] filters. The preventive maintenance (PM) procedure will document the installation of the defined filters.

NOTE: The following observations (22 and 22a) have a combined response.

Observation No. 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).

Response to Observation No. 22 and 22a.

Procedure 001-001112, revision 003, Change Control For Equipment, Systems And Facilities For Drug Products [Attachment 22-1], is specifically designed to manage change to facilities, systems and equipment. [redacted] different implementation checklists are used to determine the scope of impact. One of the checklists is dedicated to assessing potential impact on drawings and marking actual revisions on affected drawings. These marked up drawings must be signed by the originator of the change and a Quality Control Representative or Engineer prior to implementing the change. If drawings are impacted, the change control document can not be completed until the GMP drawings have been revised in accordance with the marked-up drawings. These steps are reviewed and approved by Quality Control through the change control process. Although the actual GMP drawings do not contain the signature of Quality Control personnel, the GMP drawings do reference the applicable number of the change control, which is reviewed and approved by Quality Control. To further clarify and enhance this process, procedure 001-001972, revision 002, Maintenance of Critical Drawings [Attachment 22-2], has been created and approved to instruct responsible individuals, including QC, to review and approve Critical Drawings on the GMP drawing itself.

This process was shared with the investigation team during the inspection. Additionally, a draft copy of the enhanced procedure was made available to the inspection team. The approved procedure is attached [Attachment 22-2] and will be effective [redacted]

Observation No. 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.

Response to Observation No. 23 and 23a.

The approval of each change control establishes that the system is operating in a validated state. We recognize that an overall review of system performance would be a valuable tool. This review would include but not be limited to items

such as functional description, current configuration, changes, deviations, and maintenance history. To achieve this, procedure 001-001746, revision 001, Process Automation Computer System Periodic Review for Parenteral Plant Operations, will be revised to include requirements for periodic review of systems and equipment. The first of these reviews will be performed on air handling units [redacted] and [redacted] and any indicated actions will be completed by [redacted] Revised procedure 001-001746, revision 002, Process Automation Computer Systems Periodic Review for Parenteral Products Operations is attached [Attachment 23-1].

NOTE: Responses to Observations 24, 24a, 24b and 24c have a combined response.

Observation No. 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] and [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.

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.

Response to Observation No. 24, 24a, 24b and 24c
The document(s) found inside work desks, attached to AHU or inside AHU Control Panel have all been removed. Personnel that are responsible for equipment installation, maintenance and upgrade(s) will be trained on a new procedure 001-001972, revision 002, Maintenance of Critical Drawings [Attachment 22-2], to assure Critical Drawings are maintained current and are controlled by [redacted] This procedure requires that drawings are reviewed and approved by the Quality Unit.

The[redacted] laminated documents listing temperature and supply air set points have been discarded. An assessment within the facility is being completed and non-approved documents are either discarded or controlled according to procedure.

Observation No. 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 magenehelic gauge. However, the magnegelic gauges have not been calibrated to a reference standard in order to assure that the measurements are accurate.

Response to Observation No. 25.

The magnehelic gauges, when discovered during the inspection, were immediately placed on HOLD by the Quality Unit. They will be removed during plant down-time. In addition, we have reviewed our air handling systems to ensure we have eliminated all non-calibrated measuring devices.

Observation No. 26.

There are[redacted] synthetic media pads (blue color pre-filters) that are installed with the[redacted] 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:

Response to Observation No. 26.

The Parenteral Operation Engineering Department reviewed the historical qualification of Building[redacted]. We were able to confirm that the[redacted] synthetic media pad(s) (blue pre-filters) were described in the original qualification packages for Building 105 [Attachment 26-1]. (Attachment 26-1 consists of[redacted] Flow Modules Qualification Sheet – Section 2, Prefilters and[redacted] Flow Units Line[redacted] Trayloader and Protocol No. ENGR-0015 – Section 4.4 and[redacted] Prefilter.)

Observation No. 26.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.

Response to Observation No. 26a.

The blue pre-filters will be eliminated if feasible.

We will confirm through change proposals, QK-1925-CCN, Replace Prefilters on [redacted] Hoods with [redacted] [Attachment 26a-1] and QK-1926 CCN, Replace Prefilters on [redacted] Hoods with [redacted] [Attachment 26a-2], that the elimination of the pre-filter(s) will have no negative impact on the flow velocity of the [redacted] Unit. The confirmation testing for line [redacted] and [redacted] will be conducted in [redacted]

If the pre-filter(s) can not be eliminated, the filters will be replaced with a new sanitizable pre-filter. In addition, the pre-filters will have an established Preventive Maintenance Program to assure the filters are sanitized and changed at periodic intervals.

Observation No. 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.

Response to Observation No. 27.

The HEPA filter grate was replaced on February 8, 2001. Work Order No. 832912 [Attachment 27-1] and Maintenance Action Plan AP10080 [Attachment 27-2] verify the action taken. These documents supporting the corrective action were provided to the investigators during the course of the inspection. Quality Control representatives will be alerted to this incident and reminded to look for similar occurrences.

Equipment & Operations

Observation No. 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 [redacted] Flow conditions in the production area.

Response to Observation No. 28.

The area procedure has been revised to describe the current practice of transfer of "Ready to Use" stoppers under Class 100 Laminar Flow. Procedure 001-000293, revision 011, Preparation of Vial Stoppers [Attachment 28-1], was approved March 6, 2001.

Observation No. 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.

Response to Observation No. 29

The Stopper Set-up process is described by procedure 001-000236, revision 007, [redacted] Filling Machine Operation. Operators are trained and certified according to training course CP26417 [Attachment 29-1] corresponds with procedure 001-000236. A review of the current procedure and training program determined that the procedure could be enhanced with the inclusion of the detailed information from the training course. The revised procedure 001-000236, revision 008, [redacted] Filling and Stoppering Machine Operation , Bldg. [redacted] [Attachment 29-2], will be effective by [redacted]. Procedures are available in the area for ready access by operators.

Observation No. 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.

Response to Observation No. 30

The [redacted] record documents that [redacted] vials were placed in storage at 25°C. All vials prepared for testing are evaluated. The protocol CC1001-01, Validation of Container Closure Systems for Indianapolis Parenterals [Attachment 30-1] has been revised to improve vial accountability.

NOTE: The following observations (31, 32, 32a, 32b and 32c have a combined response

Observation No. 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] or dimple on the stopper".

Observation No. 32.

SOP "001-00243 "Operation of Capping Machine" provides 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:

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.

Response to Observations 31, 32, 32a, 32b and 32c

The procedure 001-000243, revision 009, Operation of Capping Machines [Attachment 31-1], has been revised to detail the set-up of the capping machine and to include a description for seal defects.

In addition, the leader-led training program that is associated with procedure 001-000243 will be enhanced to define the physical examination attributes that are used to determine acceptable and unacceptable units (e.g., samples and photographs). The procedure and training program will be effective by [redacted]

Observation No. 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 [redacted]

Response to Observation No. 33 and 33a.

The training program CP26508, DHC Identification of [redacted] in Sorting [Attachment 33-1], has been revised to include leader led instruction that provides examples of acceptable and unacceptable units (samples and photographs) followed by on the job training watching an experienced, qualified trainer.

Observation No. 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.

Response to Observation No. 34.

Each [redacted] Torque Tester used in the parenteral manufacturing capping area requires a calibration to be performed per procedure on a [redacted] month interval to assure specifications are continually met. The torque tester(s) are not placed in the manufacturing capping area unless they have a calibration performed that demonstrates the instruments meet specification. We will further enhance the process by implementing a protocol to confirm that the installation and operational requirements are documented for the torque testers used in the Parenteral Manufacturing Operation by [redacted]

Personnel Flow & Personnel Activities

Observation No. 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.

Response to Observation No. 35.

To clarify the points of discussion during the inspection, by current practice freeze dry operators are not restricted from delivering the freeze dry carts to the capping line; the operators do not enter aseptic filling lines.

The personnel flows within the aseptic block were reviewed. Procedure 001-000164, revision 011, General Aseptic Procedures and Rules for People, Equipment, and Material Flow in Aseptic Areas and Areas Leading to Aseptic Areas[Attachment 35-1] has been revised to instruct personnel to directly leave the aseptic block after performing freeze drier unloading, capping operations of freeze dried product, and powder-filling operations. These personnel are instructed not to participate in other production activities without changing their aseptic gown.

Procedure 001-001698 revision 006, Aseptic Personnel Monitoring and Qualifications for Parenteral Products Operations [Attachment 7-3], has

been revised to instruct personnel to record on the ASEPTIC AREA EXIT LOG each time they are leaving the aseptic core and what activity they have performed. Employees will be trained on the new versions with an implementation date of [redacted]

NOTE: The following observations (36, 37 and 38) will have a combined response

Observation No. 36
SOP #001-001768 "Gowning Procedure for Entrance into Aseptic Manu Areas (IC171, IC172, & GL269)" 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 [redacted]

Observation No. 37
Room #002 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 clothes on.

Observation No. 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.

Response to Observation No. 36, 37 and 38

During the inspection, the investigators were provided with details on the new building extension and the subsequent improved flows that will result from the building addition which will be completed by [redacted].

An extension of the locker room is under construction to allow a two-stage gowning process and unidirectional flow. Gowned personnel leaving the new locker rooms will access directly into a clean corridor from the clean locker side. Procedure 001-001685, revision 006, General Garment and Hygiene Requirements for Parenteral Operations in Building [redacted] [Attachment 36-1], is under revision to describe these changes.

In the interim, the people flow of administrative and support staff has been re-routed. The entrance into the administrative wing of Bldg. [redacted] will be upstream of the locker rooms used by the production personnel.

Procedures for entrance into the manufacturing facility will be modified. Immediately after donning scrubs, the operators will be required to wear protective over garments to protect their scrubs. These over garments will be removed at the aseptic gown room prior to beginning the aseptic gowning process.

The stairwell will be classified at the same level of cleanliness as the corridor adjacent to the manufacturing areas.

These improvements will be effective by mid [redacted]

Observation No. 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.

Response to Observation No. 39.

The individuals noted in the observation were immediately approached by management and corrective action was taken.

In the corridor adjacent to the manufacturing areas, beard/mustache coverings are required per procedure 001-001685, revision 006, General Garment and Hygiene Requirements for Parenteral Operations in Building [redacted] [Attachment 36-1]. A re-training of personnel on the gowning requirements will be completed by [redacted]

Observation No. 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.

Response to Observation No. 40.

The design of the gowning stations, where shoe covers are put on, has been reevaluated across the building. All the stations will be re-designed by using a physical barrier, e.g., fixed bench or line to separate the cleaner side, from the less clean side. Personnel wearing shoe covers or dedicated shoes to enter in a cleaner area will no longer cross on the floor that other personnel walk across. The shoe cover stations will be modified by [redacted]

Environmental Monitoring

NOTE: The following observations (41a., 41b. and 41c.) have a combined response.

Observation No. 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.

Response to Observation No. 41a, 41b & 41c.

This incubator has been requalified. The protocol for VALA7285, Protocol Summary for Static and Dynamic Temperature Distribution Studies of B105/2 30-35°C Environmental Monitoring Incubator [Attachment 41a-1] was written and approved on February 16, 2001. The protocol was executed on February 18-19, 2001 and the final package was approved by responsible departments (Product Process Validation Department and Environmental Monitoring) and Quality Control on February 21, 2001. This protocol describes the rationale for the thermocouple placement/locations and describes the reasoning for the number of thermocouples that were used. This validation package also includes the potentiometer chart. A copy of the executed protocol, charts and data are included.

A summary of the requalification was provided to the investigators during the inspection.

All other incubators will be reviewed by [redacted] and requalification will be performed if indicated.

Observation No. 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:

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 describe the rationale for the thermocouple placement/locations or record to describe the reason for using the number of thermocouples that were used.

Response to Observation No. 42a and 42b.

This incubator has been requalified. The validation protocol for VALA7284, Protocol for Static and Dynamic Temperature Distribution Studies of B105/2 20-25° C Media Fill Incubator [Attachment 42a-1] was written and approved on February 15, 2001. The protocol was executed on February 15-17, 2001 and approved by responsible departments (Product Process Validation Department and Quality Control) on February 21, 2001. The mobile carts were in place in the central area of the incubator throughout both static and dynamic mapping. Photographs and diagrams were part of the pre-approved protocol and these documents describe locations of the shelves and the thermocouple locations on the mobile carts as well as throughout the chamber. This protocol describes the rationale for the thermocouple placement/locations and describes the reasoning for the number of thermocouples that were used.

A summary of this requalification was provided to the investigators during the inspection.

All other incubators will be reviewed by [redacted] and requalification will be performed if indicated.

Observation No. 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.

Response to Observation No. 43

Tryptic Soy Agar (Soybean-Casein Digest Agar) has been used as the primary agar for environmental monitoring purposes based on its ability to support the growth of a large variety of microorganisms. USP 24 Chapter <1116> section "Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program" indicates that the use of Tryptic Soy Agar (Soybean-Casein Digest Agar) in environmental control programs is suitable in most cases. We test batches of Tryptic Soy Agar (Soybean-Casein Digest Agar) used for environmental monitoring purposes for growth promotion by procedure 001-001702 revision 002, Receipt and Testing of Media for Environmental Monitoring and Water Lab [Attachment 43-1]. This is consistent with USP <71> and includes both a mold and a yeast (Apergillus niger and Candida albicans).

A protocol VALA7330, Media Comparison Study [Attachment 43-2], has been written in order to test more thoroughly that the current media being used adequately supports the growth of yeast and mold. This protocol will be executed and completed by [redacted] and will serve as documentation for all environmental monitoring programs in Indianapolis.

Observation No. 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.

Response to Observation No. 44.

A statistical analysis (VALA7331) [Attachment 44-1] will be performed on historical data using both viable and non-viable results. The environmental monitoring results generated for at least [redacted] year (to capture seasonal variations) will be used to establish new levels. Data will be analyzed for both alert and action levels. New alert and action limits will be implemented by [redacted]

NOTE: The following observations (45a, 45b, 45c and 45d.) have a combined response.

Observation No. 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.

d. There are 14 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.

Response to Observation No. 45a, 45b, 45c and 45d

The use of the 3.5" floppy discs to record data from the [redacted] Particle Counter will be discontinued as of [redacted] The following procedures have been revised:

- 001-001717, revision 004, Non-Viable Particulate Monitoring of Aseptic Manufacturing Areas [Attachment 45a-1]
- 001-001719, revision 005, Non-Viable Particulate Sampling Site Maps and Datasheets of Aseptic Manufacturing Areas for LTC [redacted] and [redacted] [Attachment 45a-2]
- 001-001727, revision 003, Operation of [redacted] Particle Counters [Attachment 45a-3]
- 001-001742, revision 002, Non-Viable Particulate Monitoring of Controlled Manufactured Areas [Attachment 45a-4]
- 001-001744, revision 005, Non-Viable Particulate Sampling Site Maps and Worksheets of the Controlled Areas for LTC South IC171 and IC172 [Attachment 45a-5]

Additionally a review and any indicated actions regarding the use of floppy disks to record data in Parenteral Operations will be completed by [redacted]

NOTE: The following observations (46, 46a, 46b. and 47) have a combined response.

Observation No. 46.

During a review of the media fill video and aseptic filling process operators were observed opening and closing the lexan plastic doors, that lead into the aseptic filling 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.

Observation No. 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 not described in the established written procedure.

Response to Observation No. 46, 46a, 46b & 47.

For routine environmental monitoring, the sampling site on a [redacted] door or panel is chosen by the Environmental Monitoring technician based on where the operator touches it. This could include the bottom and/or sides of the [redacted] doors, depending on where it is touched most by the operator. It is the intent of the Environmental Monitoring program that this site be chosen based on operator activity such that the most representative sample is retrieved. Since this will vary depending on the operator, a specific sampling site on the [redacted] door or panel is not recommended.

To address observation 46a, 46b and 47, Procedure 001-001712 revision 006, Viable Monitoring of Aseptic Manufacturing Areas Sampling Locations and Data Sheets for LTC [redacted] and [redacted] [Attachment 3-3], which includes all of the EM datasheets, and Procedure 001-001710 revision 003, Viable Monitoring of Aseptic Manufacturing Areas [Attachment 3-2], which describes the frequency of monitoring, sampling methods and analysis of data, were revised and approved on February 16th, 2001. All EM technicians were retrained on these procedures by February 28th, 2001, which was the effective date.
These procedures were revised in order to:

1. Modify the statement: "Sample vertical surfaces (LFH, doors, walls) at work height, [redacted] to [redacted] inches above the floor or in heavy traffic areas" to "Sample vertical surfaces (LFH, doors, walls) at work height, [redacted] to [redacted] inches above the floor or in heavy traffic or high activity areas (e.g., areas of [redacted] that could be bumped or touched such as the bottom and side edges of [redacted] doors)".
2. Add the statement "sample any unusual situations or occurrences (e.g. excessive phone use) when observed."
3. Include a requirement that the actual tool sampled is documented on the datasheets. A line has been added by the word "tool" on every datasheet so that the technician will be required to document the actual tool sampled.
4. Include a requirement that if the EM technician identifies an increase of activity in an area, he/she is to document on the datasheet that the increase in activity was observed. In addition, the datasheets have also been revised in order to include a specific section to document that the extra samples were obtained in this area as a direct result of the increase in activity. This section is designed not only to document that the samples were taken, but also to require that the EM technician proactively look for an increase in activity.

The revised procedures were provided to the investigators during the inspection.

In addition to these procedure changes, the appropriate procedures will be changed to add a sampling site for the phone in every aseptic area, effective no later than [redacted]

Observation No. 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.

Response to Observation No. 48.

All aseptic operators are trained to perform personnel monitoring by completing the self study training on procedure 001-001698, Aseptic Personnel Monitoring and Qualifications for Parenteral Products Operations, and the leader led training, CP18011, Aseptic Personnel Monitoring and Qualification. Procedure 001-001698, revision 006, Aseptic Personnel Monitoring and Qualifications for Parenteral Products Operations [Attachment 7-3], requires that all personnel monitoring is performed either by Environmental Monitoring (EM), in the presence of EM, or in cases where EM is unavailable, with a documented second person observation. These three choices of personnel monitoring are listed in the order presented above such that EM is given optimal chance of performing or observing the monitoring. This procedure will be effective [redacted]

This procedure was provided to the investigators during the inspection.

NOTE: The following observations (49a., 49b., 49c., 49d. and 49e.) have a combined response.

Observation No. 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:

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.

Response to Observation No. 49.a-e.

The procedure 001-001694 revision 005, Environmental Monitoring Data Review Process [Attachment 49-1], will be revised to add a requirement to document the reasons for missed personnel monitoring, missed EM monitoring, missing data in [redacted] or missing samples/paperwork. This procedure will be effective [redacted]

Microbiology & Laboratory Equipment

NOTE: The following observations (50, 50a, 50b, 50c, 50d, 50e and 50f) will have a combined response

Observation No. 50.
There are a number of observations concerning the [redacted] Sterility Test Isolators Validation and Qualification documents.

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 validations 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.

Response to Observation No. 50, 50a, 50b, 50c, 50d, 50e and 50f

New sterility isolator units are currently being validated as per procedure 010203, revision 002, Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) for GMP-Regulated Equipment [Attachment 50-1]. The items cited in this observation have been considered in the Installation Qualification, Operational Qualification, Cycle Development Study and Performance Qualification for the new Isolator units and will be similarly incorporated into future requalification protocols. The new units will be validated in phases. The first units are scheduled to complete validation by [redacted] Testing will be transferred to the new isolator units when validation is complete. Protocols for the Installation and Operational Qualification for a Sterility Testing Isolator [Attachment 50-2] and the Approval of Isolator Sterilization Cycle Development and Performance Qualification Rationale document [Attachment 50-3] are attached. Key points include the following:

1. For each isolator, complete cycle development will be conducted before the execution of PQ.

2. Airflow patterns will not be deemed as a critical equipment feature. USP General Chapter <1208> on Sterility Testing – Validation of Isolator Systems [Attachment 50-4], which was effective July 2000, states "Airflow within isolators used for sterility testing is unidirectional or turbulent." Any work that is performed to determine airflow patterns will be adequately documented to meet pre-determined criteria.

3. The Cycle Development study will be written to establish and document rationales for the placement of chemical and biological indicators. The validation runs will adequately document the load conditions of the isolator units for the cycles run.

4. The rationale to determine the acceptable number of BIs to be used when performing a sterilization validation run will be documented in the Sterilization Validation protocol.

The current [redacted] Sterility Test Isolator was originally validated and put into use in 1991. The protocol used for this validation to establish that the isolator met the USP General Chapter <1216> requirement that "The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility." Over the past [redacted] years, [redacted] requalification packages were completed to support the [redacted] ability to meet the USP requirement and to provide the proper testing environment for sterility testing. Responses to specific observations are provided below:

The [redacted] isolator was first installed and validated in 1991. At that time the current IQ/OQ/PQ Procedure was not in effect. In addition, the sterility testing isolator was new technology and there were no industry standards or guidelines regarding the validation of isolators. Eli Lilly worked with the vendor to develop a program for validation. Additional information about the isolator units became available as runs were performed. The result was that cycle development steps were integrated into the operational and performance qualification execution. All of these runs (cycle development and the final 3 for each configuration) are in the same validation package. The cycles were deemed to be validated only after the cycle parameters were finally defined and three consecutive no-growth runs of each configuration were performed. Revalidation runs were properly diagramed. Our requalification program has confirmed this validated state. The sterilization cycle parameters (time, temperature, flowrate, acid consumption) are the same to-day as they were when validated in 1991.

Observation 50g
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.

Response to Observation 50g

A data documentation procedure was not effective at the time this validation package was written and executed. Data documentation has significantly improved within the quality control laboratories. The first revision of Corporate Procedure 008930, revision 003, Data Documentation, Storage and Security in Quality Control Laboratories and Purchased Material Quality Control (FDA Regulated) [Attachment 50g-1] became effective in 1992 and addressed the items cited in this finding. Items written in pencil will be reproduced as a certified exact copy to ensure the data is maintained over time. Copies will be made and retained by [redacted]

NOTE: The following observations (50h, 50i and 50j) will have a combined response

Observation 50h
There is no record to verify (e.g., photographs or videotape) the airflow profiles that were performed during the, PQ, re-qualifications, and revalidation of the Left and Right Transfer Isolators and the Workstation Isolator. (Note: The 1991 I/OQ documents that airflow patterns are identified as critical equipment feature.)

Observation 50i
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.

Observation 50j
There is no record to document that the 1991 videotape was reviewed and approved by the Quality Unit.

Response to Observations 50h, 50i, 50j

The 1991 validation and subsequent requalification package document air flow via a diagram. A videotape was made of the smoke test in 1991; however the quality of the tape was not sufficient to assess the airflow patterns. As a result, no other smoke tests in the isolators were videotaped. The trained observer's account of the airflow pattern, documented via a diagram, is considered to be the raw data for this test. The Quality Unit did review the validation document, which included the diagram of airflow observed during the smoke test and concluded that it met the acceptance criteria.

Observation 50k

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.

Response to Observation 50k

The definition of areas that are more difficult to sterilize, such as listed in the example, include some areas that were not identified in the requalification runs but were thought to be potentially difficult to sterilize and therefore deserving of extra attention during normal operations.

Observation 50l

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.

Response to Observation 50l

The 1994 Isolator Requalification was executed after annual preventative maintenance. Airflow pattern profiling was performed with chemical indicators to define dead spots for chemical sterilization to ensure effective microorganism kill. The 1992-1995 packages support that successful test runs were demonstrated in empty and full load conditions. In addition, in 1997, a study was performed to support that empty and full conditions did not impact validation results. Total kill was demonstrated in all empty and all full isolator runs. All acceptance criteria were met. Data from previous requalifications support that the combination of the [redacted] acid and the cycle would result in an effective level of kill for an empty or full load.

Observation 50m

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.

Response to Observation 50m

In the Sterilization Protocol for [redacted] Isolator Comparison of Empty vs. Full December 1997 study (Section III-B) [Attachment 50m-1], a full isolator is described. The procedure section of the protocol reads "A full isolator is defined as having the top shelf full of samples, a bottom shelf full of media and buffers,

and the bottom of the isolator full of [redacted] canisters, media and environmental monitoring equipment. For both types of loading configurations include a bottle of spray down solution, a wipedown cloth, hydrogen peroxide strips, syringes, Acrodisc filters, needles and a marking pen."

It is again important to note that this is a sterility test isolator. Assay load and type of samples vary on a daily basis; therefore, predetermined static pattern loads for testing are not feasible.

Observation 50n

The 11/00 Revalidation of the [redacted] Isolator 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.

Response to Observation 50n

The study conducted in 1997 was performed on a representative (right) isolator. The [redacted] isolator ([redacted] left and right units) was requalified with runs in both empty and full conditions in 1992-1995. These previous requalification runs provide data to support the use of a representative isolator.

Observation 50o

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.

Response to Observation 50o

The documentation of the rationale used to determine the acceptable number of BIs to be used when performing a sterilization validation run will be documented in the Sterilization Validation procedure section of future protocols.

Observation 50p

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.

Response to Observation 50p

The [redacted] acid spray down was used from the outset since the [redacted] users manual stated the use of this solution on 'all the internal surfaces' is required before isolator sterilization. A study was performed in 1994 to determine the effectiveness of the [redacted] acid solution used for pre-sterilization spray down of the isolators. This study was performed in triplicate in a biosafety cabinet, and showed that the solution was effective against B. stearothermophilus spore suspensions inoculated onto coupons. The results indicated total kill at and beyond the [redacted]-minute time interval for a fresh solution, and at and beyond [redacted]

minutes for a [redacted] day old solution. Procedure 006935, revision 003, Basics of [redacted] System Operation [Attachment 50p-1], established a solution expiration date at [redacted] days of age.

Observation 50q
The preceding observations and the supporting data document that the [redacted] Isolators are not appropriately validated.

Response to Observation 50q

The sterility test method for each product is fully validated. The isolator provides the environment in which the sterility tests are performed. The historical validation data and requalification data have consistently demonstrated that the [redacted] meets the acceptance criteria and provides an appropriate environment for sterility testing. Further data to support the validated state of the system is supplied below:

Environmental Monitoring
Daily viable environmental monitoring is performed at multiple locations throughout the isolator, including gloves, surfaces, and door gaskets. During the calendar year 2000, approximately [redacted] EM samples were taken of which only [redacted] sample showed growth. (Note: By procedure, any positive result is investigated)

Control Samples
A negative control sample is run for each set-up, at least one negative control sample is run on each testing day. Essentially, this is analogous to running a media fill each day. During the calendar year 2000, approximately [redacted] negative control samples were run of which only one sample showed growth.

Sterility Test Data
The failure rate for sterility testing of production lots is extremely low. In calendar 2000 year, [redacted] sterility tests were performed with Zero (0) failures. (Note: A development group submitted one sample of non-sterile material to the sterility lab in 2000. There was growth when this sample was tested. The sample was not prepared in a controlled environment and therefore was not sterile.)

The ongoing testing and monitoring data support the conclusions of the multiple successful validation and requalification studies performed over the years.

Observation No. 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.

Response to Observation No. 51

As stated in the response to Observation 50m, a description of a "full" isolator was incorporated into the protocol for the 1997 Empty vs. Full isolator study. The quantity and type of samples vary on a daily basis; therefore, predetermined static pattern loads for testing are not feasible. Procedure 001-001361, revision 005, [redacted] System Operation [Attachment 51-1], has been revised to establish guidance in regard to load placement and configuration. An assessment of load configurations will be incorporated into the cycle development study to determine maximum load for the new isolators. A description of any resulting constraints will be incorporated into operational procedures and training upon completion and approval of the Performance Qualification. Validation of the new isolator units has begun. The first units to use the new protocols will be completed by [redacted]

Observation No. 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]

Response to Observation No. 52

Trained maintenance technicians perform leak tests on the HEPA filters to check integrity. Preventative Maintenance Procedure YA241#, version 001, Leak Test Inspection for [redacted] Half-Suits HEPA Filter [Attachment 52-1], has been approved to describe the HEPA filter integrity tests that are performed for the [redacted] The procedure, which is attached and was provided to the inspector, became effective [redacted]

Observation No. 53.

There is no diagrams or system description for the Pressure Test Equipment that is used to leak test the Isolator Half Suits. In addition:

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

Response to Observation No. 53

The operational qualification includes a diagram and system description for the ammonia leak testing of half suits and waste containers. A protocol for the Installation Qualification for Sterility Leak Testing Apparatus [Attachment 53-1] and Operational Qualification for Sterility Leak Test Apparatus [Attachment 53-2] for the Sterility Leak Testing Apparatus has been written and approved and will be executed by [redacted]

Observation No. 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 [redacted]) 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 *Citrobacter freundii, Staphylococcus epidermidis, Burkholderia cepacia, and Bordetella brochiseptica* 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.

Response to Observation No. 54 (a)

The validation document, Final Summary Report for the Validation of the [redacted] Microbial Identification Automated Sample Preparation [redacted] [Attachment 54a-1], [redacted] Microbial Identification Automated Sample Preparation [redacted] – Critical Parameter Optimization Experimental Design Protocol [Attachment 54a-2], [redacted] Microbial Identification Automated Sample Preparation [redacted] Performance Qualification Protocol [Attachment 54a-3],directs the analyst to use the laboratory method GP5209, revision 1.2, Microorganism Identification by the [redacted] Microbial Identification System [Attachment 54a-4], to identify organisms being tested. Method [redacted] directs the analyst to use other validated identification systems other than the [redacted] in certain defined circumstances.

Specifically, this procedure describes the following:

a) For enteric bacteria (e.g. *Citrobacter freundii*), another validated identification system (e.g. [redacted] System) other than the [redacted] System would be needed to confirm the identification prior to reporting results;
b) For pathogens (e.g. *Bordetella brochiseptica*), additional confirmation testing would be necessary prior to reporting results;
c) Various media (i.e. *Trypticase Soy Broth Agar (TSBA), Trypticase Soy Agar with 5.0% Sheep Blood, Sabouraud Agar*) are listed as choices to cultivate microorganisms for analysis on the [redacted] System. The statement in the Final Report in reference to utilizing a different medium for the cultivation of *Staphylococcus epidermidis and Burkholderia cepacia* was based on historical data from manually extracted samples.

Therefore, by following the procedure referenced, the requirements of the validation protocol were met.

NOTE: The following observations (54b., 54c., and 54d.) have a combined response

Observation No. 54b.

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.

Observation No. 54c.
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.

Observation No. 54d.
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, environmentally compromised contaminants, and that the same level of correct identification can be obtained by the [redacted].

Response to Observation No. 54b-d

The [redacted] system identifies microorganisms by performing a fatty acid analysis and comparing the results to the library contained in the [redacted]. The [redacted] library is the established reference standard and each test of an environmental monitoring isolate is a comparison to that library.

The validation protocol for the [redacted] Automated Workstation (AWS) was designed to start with known reference standard microorganisms, use the [redacted] Automated Workstation for sample preparation and then establish that the organisms had not been affected during the sample preparation process by identifying them as the same known organisms we started with. The protocol required multiple runs for [redacted] different known microorganisms to assure reliability of the process. All acceptance criteria of the protocol were met. The value of starting with a known "reference standard' organism was necessary to assure that clear acceptance criteria could be set – we had to know the definition of "truth".

We acknowledge the interest in taking environmental monitoring isolates of unknown identity, preparing samples with them manually and with the [redacted] Automated Workstation, and then comparing the results of identification tests. We will develop a performance qualification protocol to include EM isolates from manufacturing facilities to determine that comparable data is generated on the [redacted] Automated Workstation as compared to manually prepared samples. This will be completed by [redacted]

Observation No. 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 review the software source code which operates the [redacted] Automated Microbial Identification Sample Prep Workstation to see if it met their user requirements before installation and operation.

Response to Observation No. 55 and 55a.

There is no requirement in Corporate Procedure 009138, revision 002, GMP Computer Systems and Purchased Automated Systems in Quality Control Laboratories (FDA-Regulated) [Attachment 55a-1] to review software source code to ensure a system meets user requirements before installation and operation.

The need for review by the user of source code developed by a vendor has been debated for years. According to the 1987 article "Source Code Availability and Vendor-User Relationships" by K.G. Chapman, J.R. Harris, A. R. Bluhm and J.J. Errico, Pharm. Technol. 11 (12), 24-35 [Attachment 55a-2] "code review is not the way to establish "proof of correctness" or that a software program satisfies its specifications." The best way to ensure that a system meets user requirements is to obtain assurance that the vendor has followed software development standards and to conduct functional testing. "Well-designed functional tests should exercise the system extensively enough to establish that it works under all intended, as well as most unintended, conditions".

In the case of the [redacted] Microbial ID AWS system, Lilly's process for ensuring that the computer system met user requirements was consistent with procedure 009138 and consisted of the following:

Developer Qualifications

The [redacted] workstations were developed by a team of three technically qualified professionals from [redacted] an Applications Scientist, a Design Engineer, and a Software Engineer.

User Requirements and System Specifications

These individuals worked with Lilly to jointly establish requirements and specifications (known as the protocol) for the workstation. Both [redacted] and Lilly approved the protocol as part of the development process. See [redacted] Automation, Inc. Protocol Review and Approval Forms [Attachments 55a-3 and 55a-4 respectively].

Functional and Structural Testing

The system (hardware and software) was thoroughly tested based on the specifications in the protocol, both by the vendor prior to shipment (see [redacted] Automation, Inc. Application Scientist Integration/Testing Checklist

[Attachment 55a-5]) and at Lilly as part of the qualification and validation processes.

System Acceptance

To ensure that [redacted] met the specifications defined in the protocol, on-site acceptance of the system via the [redacted] Automation Inc.Customer Approval Form [Attachment 55a-6] was completed at [redacted] by Lilly prior to shipment, installation, and operation of the system. This included a review of the testing performed by [redacted]

Documentation

A Master file was created by [redacted] at the completion of the workstation. The Master File contains key project documents such as the source code, the executable files, the CAD files, the AWS Protocols, and the AWS Operator's Manual. These records are retained both on-site at [redacted] and in an off-site storage location to ensure access and future support. See [redacted], Software Backup and Archiving Procedure [Attachment 55a-7].

Based on the steps we took above which take into consideration the fact that the software and hardware must be evaluated together as a system, we concluded that the system met our user requirements.

Since the inspection, we have reviewed the validation documentation including system requirements, procedures, and maintenance records. Based on this review, we continue to believe that the system meets our user requirements.

Because this is an area of great controversy, we feel that it is critical that we establish a Corporate Policy on Software Vendor Assessment and Selection. Since the inspection, we have established a policy [Attachment 55a-8] that requires the user of software customized by a vendor to assess a sample of source code to ensure that it meets software development standards before system acceptance.

Observation No. 55b

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.

Response to Observation 55b

Security requirements are addressed in the Operational Qualification For [redacted] Automation, Inc. Automated Microbial Identification Sample Prep [redacted] in the Computer Validation Requirements section

[Attachment 55b-1]. This is consistent with the Corporate Computer System Validation Policy (CSVP) [Attachment 55b-2]. The Corporate Procedure 009138, revision 003, GMP Computer Systems and Purchased Automated Systems in Quality Control Laboratories [Attachment 55b-3] has been revised to be consistent with the CSV overarching policy statement.

Procedure 009138 revision 003 also states "2.g.5) Virus protection will be installed on all computers, if available." The [redacted] Microbial ID AWS currently runs under [redacted] for Workgroups. There is no commercially available virus protection software for this system. It is important to point out that the workstation is not attached to the network and therefore the risk of the system becoming infected by a virus is minimized.

NOTE: The following observations (55c and 55d) have a combined response.

Observation No. 55c

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.

Observation No. 55d

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".

Response to Observation No. 55c and 55d.

Electronic records generated by the system have been backed up and archived. Appropriate personnel have been retrained to ensure procedural requirements for backup and archiving will be consistently performed.

Observation No. 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.

Response to Observation No. 56

A trained analyst compares the microorganism being viewed with the reference illustration to identify the microorganism. Procedure B08137, revision 2, Guidelines for Identification of Fungi [Attachment 56-1], requires that the analyst "record all observations on appropriate OLDD and refer to a suitable reference such as Illustrated Genera of Imperfect Fungi, or similar, for identification". This

procedure has been revised to require the analyst record the reference book and page number [Attachment 56-2] and was effective March 6, 2001.

Observation No. 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:

Response to Observation No. 57

Procedure QCL-767-M00008-001, Culture Preparation and Distribution to Analytical Laboratories [Attachment 57-1], effective on February 20, 2001 and procedure QCL-767-M00009-001, Culture Inventory Maintenance [Attachment 57-2] effective March 12, 2001 were approved to document the established practices regarding the use of the inventory logbook that contains an ATCC culture index, Seed Culture List, ATCC Lyophilized Cultures in Stock, Department [redacted] in Stock, and [redacted] Tank Inventory List. The procedures were provided to the investigators during the course of the inspection.

NOTE: The following observation (57a., 57b., and 57c.) will have a combined response

Observation 57.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.

Observation 57.b.
It was explained that the liquid [redacted] tank's storage temperature is approximately [redacted]. However, the temperature is not monitored and there is no record to document the actual temperature.

Observation 57.c.
There is no record to determine the level of liquid [redacted] in the tank in order to assure that there is sufficient volume in order to maintain the requisite sub-freezing temperature.

Response to Observation No. 57a, 57b and 57c

The observations were in reference to a manual-fill [redacted] tank. During the inspection, the liquid nitrogen tank procedure 001-001608, revision 002, Liquid [redacted] Tank Operation, [Attachment 57a-1] was revised to include the requirements for monitoring fill levels and documenting each manual fill in a logbook. The monitoring is done weekly on the manual tank, but is not necessary on the auto-fill tanks, as the manufacturer has incorporated this function into the equipment. [redacted] new [redacted] tanks have been purchased and are in the process of being moved to the new lab facility. Installation qualification and operational qualification will be performed on the tanks by [redacted] [Attachments 57a-2

and 57a-3 respectively]; subsequent to the execution of the qualifications, a performance qualification will be performed. The temperature and level monitoring functionality will be qualified and linked to an electronic data historian. The manual-fill tank will not be relocated to the new lab. The tank fill information in the logbook will only be recorded in the event that a manual override of the automatic system is needed.

Observation 57.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.

Response to Observation No. 57 (d)

Procedure QCL-767-M00009-001, Culture Inventory Maintenance [Attachment 57-2], has been written and approved to require a second person reviewer for the inventory records. This procedure will be effective [redacted]

Observation No. 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.

Response to Observation No. 58

Procedure No. QCL-767-M00006-001, Handling of Purchased or Locally Prepared Culture Media that Requires Growth Promotion Testing [Attachment 58-1], was written and approved to describe the practice that is used to identify and label approved and non-approved media. Media in different states of approval for use will be segregated and effectively labeled. This procedure became effective on February 19, 2001. The procedure was provided to the investigators during the inspection.

Additional Observations

Observation No. 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 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.

Response to Observation No. 59.

Procedure 001-001972, revision 002, Maintenance of Critical Drawings [Attachment 22-2] will be effective by [redacted]. The [redacted] diagrams referenced in the observation fall within the scope of this new procedure. These drawings will be reviewed and approved by the appropriate engineering and quality unit personnel by [redacted]

Observation No. 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.

Response to Observation No. 60 and 60a.

A new Preventive Maintenance Procedure 001-001986, revision 001, Inspection of Ceiling Tiles in Building [redacted] [Attachment 60a-1], has been written to perform periodic [redacted] evaluations of all ceiling tiles in Building [redacted]. This procedure will be trained on and effective by [redacted] In addition, work order WO848552 [Attachment 60a-2] has been executed to assure all ceiling panels are appropriately in place. The Work Order was completed on [redacted]

Observation No. 61.

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

Response to Observation No. 61

An assessment of the manufacturing areas is being performed, and non approved documents are being either discarded or controlled through procedure 001-001837, revision 001, Creating and Maintaining Job Aids [Attachment 61-1]. This will be completed by [redacted]

Observation No. 61a
In the event of an alarm from the DPS the operators are to acknowledge the alarm, call or contact a designated individual.

Response to Observation No. 61a.

Procedure 001-001754, revision 006, Air Pressure Differential Monitoring [Attachment 17-1], has been revised to include names of designated individuals in the event of an alarm. This was provided to the investigators during the inspection.

Observation No. 61b.
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.

Response to Observation No. 61b.

The small orange color book binder was removed from the area on [redacted] and has been discarded.

Observation No. 61c.
There was a small videotape titled "[redacted] dated 6/00 in [redacted] in the lyophilizer's control room.

Response to Observation No. 61c.

The tape has been appropriately labeled and maintained through procedure 001-001131, revision 003, Site Training Plan [Attachment 61c-1].

Observation No. 61d.
"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"

Response to Observation No. 61d.

This sign has been removed. All of the information that was housed in the folders have been relocated to a locked file cabinet for EM personnel.

Observation No. 61e.
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.

Response to Observation No. 61e.

The documents detailed in section 61a through 61d have either been removed or approved as detailed in their individual responses. As of [redacted], all

documents utilized in the production areas will be controlled either by procedure 001-001837, revision 001, Creating and Maintaining Job Aids [Attachment 61-1], or procedure 001-001838, revision 001, Managing Procedures and Attachments Printed from an Electronic Source or Copied from Controlled Files [Attachment 61e-1]. Both these procedures require the documents they control to be approved by Quality Control.