DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	10/22/2013 - 11/05/2013* FEI NUMBER 3003434971

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Charles W. Leiter, Pharm.D., Chief Executive Officer

FIRM NAME	STREET ADDRESS
Leiter's Cambrian Park Drugs, Inc., dba Leiter's Pharmacy	1700 Park Ave
CITY, STATE, ZIP CODE, COUNTRY	**TYPE ESTABLISHMENT INSPECTED**
San Jose, CA 95126-2033	Producer of Sterile Drugs

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

a) The "Sterile Compounding Personnel Qualification" document #2.030, version 1.0, dated 3-01-09 establishes that "All sterile compounding personnel must successfully complete (b) (4) sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he or she can prepare parenterals." The aforementioned aseptic process validation media fill procedure establishes, "The purpose of this procedure is to establish requirements for sterile compounding process validations (media fills)" and documentation requirements for media fills to include but not limited to for example, "number of units filled"; "number of units rejected at inspection and reason for rejection"; "number of units incubated and incubation time/temperature"; "number positive units at the conclusion of the incubation" and the media fill "results (pass/fail)."

The following table provides a summary to document the absence of media fill incubation records for the following individuals who perform aseptic process operations and the *March 14th 15th & 16th, 2013 media filled vials which were keep under refrigeration temperatures for 13, 12 & 11 days, respectively, prior to shipment of the media filled vials to the contract tests laboratory for appropriate incubation:

Employee	*Dates*	*Media Fill*	*Results*
Technician - (b) (6)	3/15/13 5/17/12	High Risk	No media fill incubation records

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	(b) (6)			
Technician -	[redacted]	3/1/12 9/6/12	High Risk	No media fill incubation records
Technician -	[redacted]	3/21/13	High Risk	"Test Invalid"
Technician -	[redacted]	9/6/12	High Risk	No media fill incubation records
Pharmacist -	[redacted]	6/3/13	High Risk	No media fill incubation records
-	[redacted]	-	-	-
Technician -	[redacted]	3/14/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/15/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/15/13 3/16/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/15/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/15/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/16/13	High Risk	Incubation began on 3/28/13*
Technician -	[redacted]	3/16/13	High Risk	Incubation began on 3/28/13*
Pharmacist -	[redacted]	3/14/13	High Risk	Incubation began on 3/28/13*

b) "Quality Assurance Program" document #9.010, version 1.0, dated 3-01-09 purpose "is to outline a quality assurance (QA) program at Leiter's Pharmacy" define QA as "A state of control sufficient to result in a safe and effective product achieved by utilization of mechanisms for monitoring, evaluating, correcting and improving activities and operational systems." And, it includes "Quality Process Controls" for "Media Fills - In regards to sterile compounding, media fills shall be performed." The "Sterile Compounding Personnel Qualification" document #2.030, version 1.0, dated 3-01-09, establishes that "Leiter's Pharmacy shall require basic qualifications for each employee active in the process of sterile compounding." Furthermore, "All sterile compounding personnel must successfully complete three sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he or she can prepare parenterals." Despite the establishment of the aforementioned standard operating procedures, the table in Observation summarizes a number of deficiencies with respect to media fill records that are needed to support that personnel can adequately and successfully perform aseptic processing operations.

c) The "Aseptic Processing Validation (Media Fills/Glove Sampling)" document #9.110, version

1.0, dated 4-12-13, does not contain any language that authorizes and approves that media filled vials are permitted to be refrigerated prior to shipment to the contract laboratory for incubation.

d) There is no record to document that the [redacted] (b) (4) has been subject to some form of equipment qualification and there is no record to document that the [redacted] (b) (4) processes are appropriately validated

e) There are no sterilization records for the glass vial and liquid dropper that are used for some sterile ophthalmic solutions and/or for the plastic squirt bottles that are used for the sterile 70% isopropyl alcohol

f) There are no [redacted] (b) (4) parameters (e.g., time, temperature, pressure) established for the [redacted] (b) (4), that are used for the sterilization processes for various components (e.g., glass vials) and materials (e.g., plastic cleaning bottles), used for either the sterile drug products and used during the aseptic operations.

g) *Geobacillus stearothermophilus* (1.8×10^5) biological indicators (BI) is used to demonstrate the acceptability of a [redacted] (b) (4) process. The BIs are subsequently incubated via a heat block with a recommended temperature of 55-60°C for 24 hours. However, there is no temperature monitoring device (thermometer/temperature probe) to assure that the incubation temperature is achieved and there is no record to document the results of the BI challenge.

h) The "Use and Maintenance of the [redacted] (b) (4)" document #4.210, version 1.0, dated 3-01-09 "establish requirements for the use and maintenance of the [redacted] (b) (4)." All aseptically filled drug products that are not terminally sterilized are subject to sterilization via the use of [redacted] (b) (4). The [redacted] (b) (4) are integrity tested post use via a [redacted] (b) (4) procedure. The Manager of Quality Control and Clinical Trials confirmed that the [redacted] (b) (4) procedure is not part of the aforementioned 3/01/09 document and it has not been officially formalized as a standard operating procedure.

i) There is no record to document that the [redacted] (b) (4) lyophilizer has been subject to equipment qualification verification and there is no record to document that the freeze drying process for the Dapriprazole HCL 300mg has been appropriately validated.

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FIRM NAME Leiter's Cambrian Park Drugs, Inc., dba Leiter's Pharmacy	STREET ADDRESS 1700 Park Ave
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OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically, The Bevacizumab 2.5mg/0.1ml (1cc syringe) Injection lot number 08282013@15 was Sterility Tested by the contract laboratory. The August 29, 2013 laboratory report documents the result as "Positive Aerobic at 5 days" with a confirmation of the microbial identification as *Cupriavidus metallidurans* (renamed from *Ralstonia metallidurans* a soil borne gram negative bacillus). The Director of Quality Assurance explained that the pharmacy technician has been retrained. However, no root cause analysis has been performed to determine the source(s) and/or personnel activities that may have generated the microbial contamination to preclude the reoccurrence of the microbiological contamination.

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

Specifically,

a) "Quality Assurance Program" document #9.010, version 1.0, dated 3-01-09 purpose "is to outline a quality assurance (QA) program at Leiter's Pharmacy" define QA as "A state of control sufficient to result in a safe and effective product achieved by utilization of mechanisms for monitoring, evaluating, correcting and improving activities and operational systems." And, it includes "Quality Process Controls" for "Media Fills - In regards to sterile compounding, media fills shall be performed." The "Sterile Compounding Personnel Qualification" document #2.030, version 1.0, dated 3-01-09, establishes that "Leiter's Pharmacy shall require basic qualifications for each employee active in the process of sterile compounding." Furthermore, "All sterile compounding personnel must successfully complete [redacted] (b) (4) sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he or she can prepare parenterals." Despite the establishment of the aforementioned standard operating procedures, the table in Observation summarizes a number of deficiencies with respect to media fill records that are needed to support that personnel can adequately and successfully perform aseptic processing operations.

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b) There are no airflow pattern evaluations (aka smoke studies) performed of the ISO-5 clean room, ISO-5 cabinets, and/or the surrounding ISO-7 support areas e.g., personnel gowning and clean room entryway, preparation and material ante-room. Note: the ceiling HEPA filters provide vertical airflow that impact with (b) (4) of the airflow cabinets' horizontal airflow, which have not been assessed.

c) The Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that there is no established procedure regarding the clean room attire for personnel that perform aseptic filling operations. In addition, there is no established procedure to describe the acceptable manner with which personnel are required to don sterile clean room attire e.g., quality controls to preclude cross contamination onto the sterile attire.

d) The "Environmental Monitoring of the Clean Room Facility" document #3.030, version 2.0 dated 7/08/13 establishes "The purpose of this procedure is to establish requirements for non-viable and viable environmental monitoring (EM) of the clean room facility", which include personnel monitoring. However, there is no personnel monitoring performed for technicians who work within the ISO-5 clean room, ISO-5 cabinet and personnel who perform the aseptic operations.

e) The preceding observation regarding personnel monitoring documents that Leiter Compound Pharmacy is not adhering to the requirements established in their standard operating procedure

f) Currently, the EM program consists of obtaining EM samples ((b) (4) and air viable samples at the end of the aseptic operations (b) (4). The EM program does not include obtaining EM samples during the preceding (b) (4) days of aseptic operations

g) The "General Aseptic Technique" document #1.060, version 1.0, dated 3-01-09 establish the aseptic technique performed in the laminar airflow cabinet, that is, "Work shall always be performed approximately in the center of the work surface. When working in a horizontal LAFW, all work must be performed at a distance of no less than (b) (4) from the front edge of the work surface." Despite the establishment of the standard procedure for aseptic technique, the EM sampling consists of obtaining samples from the left and right hand side of the airflow cabinets and not from the work areas that personnel come in direct contact with.

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h) The "Use, Verification and Maintenance of the [redacted] (b) (4)" document #4.030, version 1.0 dated 3-01-09 "establish requirements for the use, verification and maintenance of the [redacted] (b) (4) However, the standard operating procedure is silent with respect to the use of BIs for the [redacted] (b) (4) process.

OBSERVATION 4

Each batch of drug product purporting to be sterile is not laboratory tested to determine conformance to such requirements.

Specifically, the Sterility Tests and microbiological testing of sterile parenterals', finished products and media fill vials, which include for example, the Avastin® finished dosage form (100mg & 400mg bottles) that is repackaged into sterile Bevacizumab 2.5 mg/0.1ml Injection 1cc syringes. That is;

As previously reported, the Avastin® finished product vials are repackaged into 1cc T.B., sterile syringes. The repackaged drug is sterility tested by the company's contract testing laboratory i.e., [redacted] (b) (4) Regarding the sterility tests, the Certificate of Analysis documents that the analysis, "Does not meet all the requirements for sampling and/or method suitability specified in USP<71>". The aforementioned Sterility Test results are not exclusive to the repackaged syringes of Avastin®. The following is a summary of the various compounded sterile drugs with the same Sterility Test results:

Compounded Sterile Drug	*Lot number*
Acetyl Cysteine 10% Ophthalmic Solution	10032013@3
Autologous serum eye drops 100%	10102013@54
Bevacizumab 2.5 mg/0.1ml Injection	10092013@7,8,9, 11,17,18,19
Calcium Gluconate 10% (PF) Injection	09062013@1
Calcium Chloride 10% (PF) Injection	09052013@69
Cefuroxime 1mg/0.1mg Intravitral	10102013@18
Chlorhexidine 0.02% Ophthalmic Solution	1003213@4
Cromolyn 4% (PF) Ophthalmic Solution	10042013@23
Cyclop/Phenyleph 02%/1% Ophthalmic	09092013@43
Cyclopentolate/Phenylephrine 1%/2.5% Ophthalmic Solution	09162013@23

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Cyclosporine 0.05% Alpha Cyclodex Ophthalmic Solution	10032013@2
Cyclosporine 1% Ophthalmic Solution	09042013@51
Cyclosporine 2% Ophthalmic Solution	10072013@40
Dexamethasone Phospate 40mg/ml Injection	09192013@38
Dextrose 25% Injection	09172013@2
Dipivefrin HCL (Preserved) 0.1% Ophthalmic	10012013@1
Ethanol 100% Injection	09302013@52
Fluconazole 2mg/ml Ophthalmic Solution	10032013@42
Glycerin 50% Ophthalmic Suspension	09202013@7
Gum Cellulose 0.625% Ophthalmic Solution	10092013@3
Hydroxyzine 25 mg/ml Injection	09042913@3
Hyaluronidase 150 units/ml Injection	09242013@28
Hydroxocobalamin 25 mg/ml Injectable	09112013@41
Hydroxocobalamin 5 mg/ml Injectable	10012013@19
Hydroxyprogesterone Caproate 250 mg/ml Inj.	10082013@2
Ibopamine HCL Base Solution Ophthalmic	09202013@8
Lidocaine/Phenylephrine 4/1% Nasal Spray	10072013@73
Lidocaine 2% Injection	10082013@30
Lidocaine 4% Preserved Ophthalmic Solution	09232013@5
Lidocaine/Phenylephrine 2%/0.5% Nasal Spray	09262013@64
Lissamine Green 1% Preserved Ophthalmic Soln.	10112013@20
Medroxyprogesterone 1% CMPD Suspension	09182013@2
Metacholine 4 mg/ml Injection	10082013@24
Mitomycin 0.2 mg/ml Ophthalmic Solution	09242013@2
Moxifloxacin 0.1 mg/0.1ml Ophthalmic in BSS	10092013@5
Phenol 5% in Almonld Oil Injection	10012013@2
Phentolamie/Prostagland/Lidocaine 0.5mg/20mcg/20mg/ml Injection	10042013@4
Polyhexamethylene Biguanide	10112013@2
Potassium Phosphate 4.4 meq k/ml 3 mm Phos/ml Injection	10072013@1
Povidone-Iodone 5% Ophthalmic Solution	10022013@1

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Prednisolone Acetate 1% Ophthalmic Suspension	09122013@22
Progesterone 50 mg/ml In Ethyloleate Injection	10072013@6
Renacidin Irrigation Solution	10082013@23
Retnoic Acid 0.01% Ophthalmic Ointment	09172013@66
Reboflavin 0.5% Ophthalmic Solution	10032013@14
Rose Bengal 1% Reserved Ophthalmic Solution	09272013@6
Sodium Phosphate 4 meq/ml 3 mm/ml	10102013@1
Sodium Thiosulfate 25% Injection	10022013@3
Tacrolimus 0.02% CMPD Ophthalmic	09262013@27
Testosterone 0.5% Ophthalmic Solution	09202013@31
Testosterone/Progesterone 0.05%/0.05% Ophthalmic Solution	10092013@4
Tetracaine 0.5% Ophthalmic Ointment	09242013@55
Tropicamide/Phenylephrine/Tetracaine 1%/2.5%/0.5% PSD Solution	09052013@40

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

a) We observed personnel working in the ISO-5 hoods, which was followed by obtaining equipment/utensils/material from the material transfer cabinet (non-classified/ non-sterile environment) and subsequently performing aseptic operations.
b) We observed, on numerous occasions, clean room personnel adjusting the eyewear with their gloved hands. The gloved hands were not subject to [redacted] (b) (4) prior to or after adjusting the eyewear.

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OBSERVATION 6

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the "Required Garb for Clean Room Facility Access" document #9.100, version 1.0 and the "General Aseptic Technique" document #1.060, version 1.0, both dated 3-01-09 establish the "gowning requirements for entering the clean room facility" and the "requirements for using aseptic technique in any area to minimize contamination", respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

a) The Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that there is no established procedure regarding the clean room attire for personnel that perform aseptic filling operations. In addition, there is no established procedure to describe the acceptable manner with which personnel are required to don sterile clean room attire e.g., quality controls to preclude cross contamination onto the sterile attire.

b) We observed personnel with head-covers and eyewear that did not cover all of the exposed skin surfaces and as of 10/28/13 no eyewear if worn by personnel performing aseptic operations in the ISO-5 room and airflow cabinets.

c) Eyewear/goggles are not cleaned, sanitized and/or sterilized prior to use; the eyewear is shared by clean room personnel and the eyewear is commonly stored in a drawer in the ISO-7 ante-room.

d) Prior to commencing the aseptic filling operations, the ISO-5 airflow cabinets are initially cleaned with [redacted] (b) (4). The clean room operator's uncovered forehead is exposed to the interior surfaces of the ISO-5 cabinets during the initial cleaning process.

e) Personnel are required to don their clean room attire [i.e., sterile one piece gown (bunny suit) as of April 28, 2013] in the ISO-7 ante-room, which is performed at the entryway that leads into the ISO-5 clean room and it is within the same area that is contaminated with personnel's street shoes; the sterile shoe covers come in direct contact with the entryway that is contaminated with the street shoes.

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f) Personnel commonly wear green color scrubs that are worn to and from their residence. During the gowning process there is no assurance that the sterile gowns (bunny suit) does not come in direct contact with the personnel's green color scrubs.

g) We observed the reusable (disposable) white color lab coats that are worn over the green color scrubs hanging in the men/women restroom with some lab coats observed on the restroom floor (fallen off their hook/hanger). Personnel wear the lab coats in the ISO-8 general compounding area and the ISO-7 anteroom that is used to gown into the sterile gowning attire prior to entry into the ISO-5 clean room. The Manager of Quality Control and Clinical Trials confirmed that they have limited available space for employee lab coats, which has led to the use of the men/women restroom as a storage area.

OBSERVATION 7

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

a) There are no nonviable particle (NVP) measurements taken for three of the [redacted] (b) (4) ISO-5 airflow cabinets. Rather, the Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that air velocity measurements are taken, which are subsequently used to support that the airflow cabinets are ISO-5 environments.

b) NVP measurements are taken once every [redacted] (b) (4) that is, during static conditions; there exists no NVP measurements to demonstrate that the ISO-5 environment is maintained under dynamic and/or routine aseptic operations.

c) Technicians performing aseptic operations [e.g., Avastin (bevacizumab) Injection] have to access the ISO-5 negative air pressure room via the colorless plastic curtains, which are used to partition the ISO-5 negative air pressure room from the ISO-5 clean room. However, the plastic curtains are not sampled and/or part of the EM sampling program.

d) The "Environmental Monitoring of the Clean Room Facility" document #3.030, version 2.0 dated 7/08/13 establishes "The purpose of this procedure is to establish requirements for non-

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viable and viable environmental monitoring (EM) of the clean room facility", which include personnel monitoring. However, there is no personnel monitoring performed for technicians who work within the ISO-5 clean room, ISO-5 cabinet and personnel who perform the aseptic operations.

e) The preceding observation regarding personnel monitoring documents that Leiter Compound Pharmacy is not adhering to the requirements established in their standard operating procedure

f) Currently, the EM program consists of obtaining EM samples ([redacted (b) (4)] and air viable samples at the end of the aseptic operations on [redacted (b) (4)]n. The EM program does not include obtaining EM samples during the preceding [redacted (b) (4)] days of aseptic operations

g) The "General Aseptic Technique" document #1.060, version 1.0, dated 3-01-09 establish the aseptic technique performed in the laminar airflow cabinet, that is, "Work shall always be performed approximately in the center of the work surface. When working in a horizontal LAFW, all work must be performed at a distance of no less than [redacted (b) (4)] from the front edge of the work surface." Despite the establishment of the standard procedure for aseptic technique, the EM sampling consists of obtaining samples from the left and right hand side of the airflow cabinets and not from the work areas that personnel come in direct contact with.

OBSERVATION 8

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically, the Manager of Quality Control and Clinical Trials confirmed that there is no record to document that the air pressure measurements are periodically reviewed to assure that the appropriate air pressures are maintained during the routine aseptic operations.
Note: the air pressure limits for the ISO-5 clean room and ISO-7 ante-room are summarized on the yellow color posted notes.

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OBSERVATION 9

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

a) There is no HVAC equipment qualification and/or document regarding the validation of the air handling system (HVAC) and ISO-5 airflow cabinets that are used in support of the aseptic operations performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.
b) Magnehelic gauges are used to monitor the air pressure differentials between the room classification areas (i.e., ISO-5, ISO-7 and ISO-8). The Manager of Quality Control and Clinical Trials confirmed that the magnehelic gauges are not, and have not been, calibrated to a reference standard.
c) The Manager of Quality Control and Clinical Trials confirmed that there is no standard operating procedure that establishes the monitoring of air pressure differentials between the ISO classified areas on a routine base.

OBSERVATION 10

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

Specifically,

a) The "Cleaning and Maintenance of the Clean Room Facility" document #3.020, version 2.0, dated 7-08-13 "establish requirements and documentation for cleaning and maintenance of the clean room facility", which requires the use of a variety of cleaning solutions e.g., [redacted] (b) (4) However, there is no record to document the preparation and/or calculations that are performed when preparing the [redacted] (b) (4) and the Compounding Director and Pharmacy Technician confirmed that there is no record to document the [redacted] (b) (4)

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	Jennifer H. Rhyu, Investigator Thomas J. Arista, Investigator	11/05/2013

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	10/22/2013 - 11/05/2013* FEI NUMBER 3003434972

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Charles W. Leiter, Pharm.D., Chief Executive Officer

FIRM NAME	STREET ADDRESS
Leiter's Cambrian Park Drugs, Inc., dba Leiter's Pharmacy	1700 Park Ave
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
San Jose, CA 95126-2033	Producer of Sterile Drugs

[redacted] (b) (4)

b) The "Cytotoxic or Hazardous Drug Spills" document #7.030, version 1.0, written date 04-12-06 is to "establish guidelines for the handling of cytotoxic or hazardous drug spills in a safe and efficient manner." However, the standard procedure has not been reviewed and approved by the Quality Unit.

c) The "Handling of Cytotoxic or Hazardous Drug Compounds" document #7.010, version 1.0, dated 3-01-09 "establish guidelines for safe handling of cytotoxic or hazardous drugs." The standard operating procedure does not contain any language with respect to the use of decontamination solutions (e.g., [redacted] (b) (4) [redacted] for cytotoxic drugs.

d) The Manager of Quality Control and Clinical Trails confirmed that they do not have any records to document efficacy studies for the [redacted] (b) (4) [redacted]

e) Mitomycin USP Powder is weighed on an analytical balance that is within a small enclosure (something akin to a hood) with air exhaust vented to the outdoor environment. The mitomycin powder is hand carried (via a small weigh boat) to the ISO-7 ante-room (preparation and personnel gowning area) and subsequently transferred to the ISO-5 hood in the ISO-5 negative room. There is no record to document that the aforementioned areas are decontaminated with an appropriate cytotoxic decontamination solution.

f) The October 5, 2013 Protocol regarding "[redacted] (b) (4)" provides a plan "to reduce the level of potential bioburden in the cleanroom areas that cannot be effectively addressed through conventional manual cleaning methods after a maintenance shutdown. The [redacted] (b) (4) will provide Leiters with an opportunity to decontaminate their Sterile room. The project occurred on October 5, 2013." [redacted] (b) (4) [redacted] was used during the [redacted] (b) (4) decontamination process. There is however no record to document that the number of chemical indicators (CI) that were used and/or identification of the CI locations (more difficult areas/locations to decontaminate) and/or a record to document the efficacy [e.g., use of Biological Indicators (BI)] of the [redacted] (b) (4).

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OBSERVATION 11

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

a) The "Avastin Processing Procedure" document #12.0, version 3.0, dated 4-26-13 establishes that Avastin vials "are stable at [redacted] (b) (4) Avastin vials shall be protected from light. Do not freeze or shake. Store vial in the original carton until time of use." Despite the establishment of the aforementioned temperature and controls there is no standard operating procedure that establish quality control conditions for the shipment of the test materials from San Jose, CA., to the contact test laboratory located in [redacted] (b) (4).

b) There is no record to document that the test materials (i.e., Sterility Tests samples, EM samples, Media fills vials) are shipped under temperature controlled conditions (e.g. [redacted] (b) (4) [redacted]

c) There is a document entitled "Leiter's Pharmacy Refrigerated shipping validation" dated 4/6/09. There is however, no corresponding protocol or report to describe for example the purpose, scope, shipment procedure, Quality Control conditions and/or the establishment of the acceptance criteria with respect to the shipping conditions. In addition, there has been no evaluation performed to determine that the shipment conditions do not negative affect the test materials and/or negatively impact the Quality Control tests.

OBSERVATION 12

The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, in-process materials, and drug products and to prevent contamination.

Specifically,

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a) The ISO-7 personnel ante-room is used as a material transfer and storage area as well as a gowning room for personnel to don the sterile gowning attire. However, the approximate (b) (4) space is insufficient in that there is no manner with which personnel can don their sterile attire without coming into contact with non-sterile attire and/or contaminated areas.

b) There are (b) (4) airflow cabinets (b) (4) airflow hoods) that are used to provide an ISO-5 environment for the aseptic operations. The ISO-5 room (approximate (b) (4) .) also contains a Lyophilizer and (b) (4). During routine operations there can be up to (b) (4) technicians performing aseptic operations. The ISO-5 area has insufficient space to perform the aseptic operations.

OBSERVATION 13

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, we observed white color paint either peeled and/or rubbed off from the front and sides of the ISO-5 airflow cabinets and on the cabinet's supports.

OBSERVATION 14

Written calibration procedures for instruments, apparatus, gauges, and recording devices are deficient in that they do not include specific directions, schedules, limits for accuracy and precision, and provisions for remedial action if limits are not met.

Specifically, the Dapriprazole HCL process specifies subfreezing shelf temperatures (°C) with defined vacuums (mBar) for a specified amount of time. However, there is no record to document that the monitoring devices for the aforementioned lyophilization parameters have been calibrated to a reference standard.

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OBSERVATION 15

The master production and control records are deficient in that they do not include a statement concerning any calculated excess of component.

Specifically, Avastin® (bevacizudmab) is repackaged from Genentech's finished product vial into 1cc T.B., sterile syringes. The Compounding Director and a Pharmacy Technician confirmed that not all of the 1cc sterile syringes of Avastin® are identified (e.g., quarantine, approved) and accounted for in the batch records. The following table provides some examples to briefly illustrate the concerns. Please note that the summary table is not intended to be an all-inclusive list of the repackaged Avastin® batches;

Batch/ Lot number	*Aseptic fill date*	*Qty. made*	*Batch yield*	*Syringes QC tests*	*Qty. remain*	*Number of syringes unaccounted for*
07122013@9	07/12/13	[redacted] (b) (4)				22 - statusunknown
08192013@1	08/19/13					10 - status unknown
08272013@3	08/27/13					8 - status unknown
08272013@4	08/27/13					4 - status unknown
08272013@5	08/27/13					4 - status unknown
08272013@15	*08/27/13					1 - status unknown
09202013@14	09/20/13					24 - status unknown
09202013@20	09/20/13					9 - status unknown
09202013@27	09/20/13					5 - status unknown
10242013@2	10/24/13					14 - status unknown
10242013@32	10/24/13					1 - status unknown

*August 29, 2013 laboratory report documents the result as "Positive Aerobic at 5 days" with microbial contamination identified as *Cupriavidus metallidurans*.

*** DATES OF INSPECTION:**
10/22/2013(Tue), 10/23/2013(Wed), 10/24/2013(Thu), 10/28/2013(Mon), 10/29/2013(Tue), 10/30/2013(Wed), 10/31/2013(Thu), 11/01/2013(Fri), 11/05/2013(Tue)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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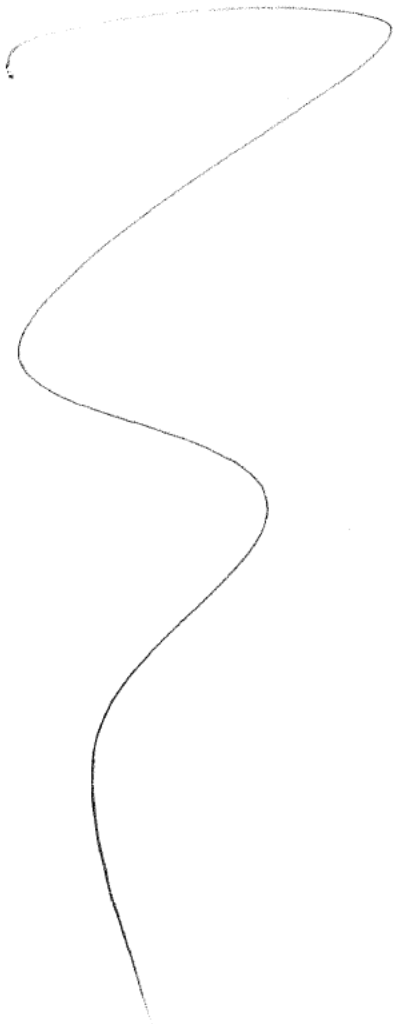

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."