

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax: (781) 587-7556 Industry Information: www.fda.gov/oc/industry	10/10/2012 - 11/09/2012*
	FEI NUMBER
	3005881167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Gregory A. Conigliaro, Vice President and General Manager

FIRM NAME	STREET ADDRESS
Ameridose, LLC	201 and 205 Flanders Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Westborough, MA 01581-1032	Sterile Drug Manufacturer

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

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically,

Your firm manufactures admixtures from stock solution of active pharmaceutical ingredients or commercially available finished products. However, the firm does not test the potency of the final drug product after numerous lots are further diluted from these bulk stock solution. Moreover, your firm has received approximately 33 complaints claiming lack of effect, patient response events and ineffectiveness for products. For example: Ephedrine lot 02142012@372, Fentanyl lot 09042012@820, Oxytocin lot 12272011@1099 in 2011 and 2012. These lots were not tested for potency before release for commercial distribution.

This is a repeat item to the FDA 483 issued on 08/06/2008.

OBSERVATION 2

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

Specifically,

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	Ramon E. Martinez, Investigator <i>Ramon E. Martinez</i> Justine M. Corson, Investigator Allison A. Rodriguez, Microbiologist Lauren M. Lawrence, Investigator Pamela L. Lee, Investigator Pamela L. Ogonowski, Investigator Douglas S. Joslin, Investigator Almaris N. Alonso, Microbiologist <i>Almaris N. Alonso</i> Ashley M. Whitehurst, Investigator Amy C. Jordan, Investigator Slater K. Bartlett, Investigator Philip Kreiter, Investigator <i>Philip Kreiter</i> Rory Geyer, Investigator Nichole B. Murphy, Investigator Mary Joemet McGarry, Investigator <i>Mary Joemet McGarry</i> Thomas W. Nerney, Investigator Richard L. Friedman, CDEB Microbiologist	11/09/2012

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FIRM NAME Ameridose, LLC	STREET ADDRESS 201 and 205 Flanders Rd	
CITY, STATE, ZIP CODE, COUNTRY Westborough, MA 01581-1032	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer	

Your firm manufactures admixtures from stock solution of active pharmaceutical ingredients or commercially available finished products. These bulk stock solutions are tested commonly for sterility, and only the ones manufactured from active pharmaceutical ingredients are tested for the presence of bacterial endotoxin. The firm performs numerous manual aseptic manipulations in the filling of the sterile injectable drug products intended for patient use. Your firm does not test final units of finished product lots for sterility and the presence of bacterial endotoxin in finished sterile drug product lots after aseptic manual filling operations before release (e.g. Ropivacaine 0.2%, Lot 09262012@104.)

This is a repeat item to the FDA 483 issued on 08/06/2008.

OBSERVATION 3

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,

A. Your firm failed to investigate microbiological contamination observed at least fifty three (53) times noted during (b) (4) sterility testing of sterile stock solutions intended to be used in the manufacture of sterile injectable drug products, including lots of Fentanyl, Ropivacaine, Morphine, etc. In approximately eighteen (18) instances your firm retested the affected stock solutions and microbiological contamination was also observed in at least one of the retest samples.

1. There is no documented evidence that suggests that a health hazard evaluation was initiated or conducted in order to assess the potential quality impact of microbiological isolates noted during the (b) (4) sterility testing.
2. There is no data to support your firm's claim that all the sterility failures were attributed

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to contamination during the performance of the (b) (4) sterility method.

- There is no documented evidence that your firm implemented permanent corrective actions to prevent these sterility events from recurring.

Furthermore, approximately (b) (4) lots of sterile injectable drug products were manufactured and released from the affected stock solutions lots.

- B. Your firm failed to adequately investigate three (3) sterility failures (OOS 12135 dated 04/26/2012 and OOS 12145 dated 05/03/2012). For example, the following was observed regarding two 2012 sterility failures (Sodium Bicarbonate stock solution lots S05022012@388 and S05022012@390 on 5/3/2012; and Hydromorphone 0.3 mg/mL stock solution lot S04242012 on 04/26/2012).

- The investigation into the two sterility failures did not determine possible root causes of the contamination. Notably, it also lacked any meaningful corrective or preventive actions to prevent future non-sterility events.
- The investigations failed to extend to all associated lots that may have been manufactured under the same inadequate practices or conditions that led to the microbial contamination of these lots.
- Sterility test positive results were routinely considered questionable by the laboratory, and re-testing was done without justification. More specifically, when a positive result is obtained using the (b) (4) sterility testing method, your firm considers the initial positive to be an "inconclusive" or "suspect" result and performs re-testing. This is done although no laboratory cause of contamination has been identified. It is noteworthy that when further (b) (4) testing was done, the testing often revealed additional non-sterile units. This includes but not limited to all lots that are named in this observation.

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4. Your firm did not adequately differentiate or subculture microbes found in sterility test positives. Both lots that failed sterility were assumed to be cocci based on observation under microscope. However, despite multiple findings of contaminated units, no attempts were made to subculture the bacteria and further differentiate the microbe to determine its identity (e.g., gram stain, use of the ^{(b) (4)} available in your microbiology lab).
5. Insufficient relevant EM/personnel monitoring data was available from the production operations to correlate possible contamination sources in the environment with microbes found in sterility tests. Without knowledge of identity of microbes found during environmental monitoring, your firm lacked critical information to investigate possible root causes of the sterility failures.

C. The Quality Unit failed to adequately investigate, and implement permanent corrective actions after 45 environmental microbiological excursions (bacterial and mold) were isolated from critical areas such as personnel fingers inside class 100 hoods and controlled manufacturing areas (surfaces and air) during the manufacture of sterile injectable drug products in 2012. There is no documented evidence that suggests that a health hazard evaluation was initiated nor conducted in order to assess the potential quality impact of isolates present during the manufacture of sterile drug products. Furthermore, your firm does not perform identification of the observed microbiological isolates.

D. Your firm failed to adequately investigate complaints for the following reason(s):

1. Your firm's Quality unit failed to appropriately classify "patient response" complaints as adverse events. Additionally, your complaint investigations failed to address patient outcome or patient intervention.

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Sterile Drug Manufacturer

This includes the following complaints:

Complaint	Date Received	Drug Product	Lot	Description
AC11589	12/22/11	Oxytocin	12122011 @451	Communications between the firm and the complainant referenced "fetal distress and hyper stimulated uterus".
AC12430	9/6/12	Oxytocin	08252012 @73	Accompanying documentation states "customer called to report increased cases (5) of post partum hemorrhaging".
AC12118	2/15/12	Oxytocin	12162011 @131	Accompanying documentation states "patient had shortness of breath, the throat was closing, and coughing".
AC12070	1/24/12	Heparin	01062012 @336	Accompanying documentation submitted by the complainant states that the outcome of the adverse event to be "life-threatening".
AC12428	9/7/12	Fentanyl	09042012 @820	Accompanying documentation states "Patient was over sedated, unresponsive".

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AC12131	12/27/12	Fentanyl	01272012 @61	Communications between the firm and the complainant refer to 2 patients going into "respiratory distress" after receiving the medication.
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2. Your firm's Quality unit failed to evaluate complaint sample(s) associated with the following complaints:

This includes the following Midazolam complaints which are associated with a "patient response" and low potency claims:

Complaint	Date Received	Midazolam Lot
AC12244	5/9/12	05012012@41
AC12186	3/26/12	02112012@245
AC12195	4/2/12	03282012@674
AC12120	2/23/12	12222011@157

This includes the following Oxytocin complaints which are associated with a "patient response":

Complaint	Date Received	Oxytocin Lot
AC12030	01/11/12	12272011@1099
AC11589	12/22/11	12122011@451
AC12179	03/19/12	02162012@295, 02232012@260, 02242012@308
AC12409	08/27/12	08072012@301

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3. Your firm's Quality unit failed to investigate a trend of complaints associated with Midazolam for low potency / lack of effect.

The Table below summarizes this information:

Date Received	Complaint	Midazolam Lot	Additional Information
02/23/2012	AC12120	1222011@157	Made reference to an unspecified adverse event and the involvement of more than one patient being affected.
03/02/2012	AC12133*	02222012@654 02172012@248 02122012@1	Made reference to more than one patient being affected and that a few physicians were concerned about potency.
03/08/2012	AC12144*	03032012@39 02122012@1 01312012@42	Made reference to reports from more than one anesthesiologist about product response.
03/26/2012	AC12186	02112012@245	Made reference to more than one patient being affected.
04/02/2012	AC12195	03282012@674	Made reference to lack of effect despite using the max allowable dose.
05/09/2012	AC12244	05012012@41	Made reference to more than one patient being affected and reports from more than one nurse.
09/06/2012	AC12427	08272012@43	Accompany documentation states

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		08092012@786	"they have had three (3) pediatric patients require extremely large doses for relief".
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* Complaints AC 12133 and AC12144 reference the same lot (02122012@1) and were received from independent customers. The final, Quality approved reports state "No trends associated with this lot".

4. Your firm failed to investigate the following complaints as they were defined as "non-complaints" by your firm's Quality unit:

Drug	Date Received	Lot	Description
Norepinephrine	09/28/2012	09242012 @553	Concerns related to potency; related to an adverse event.
Succinylcholine	09/17/2012	06212012 @309	Concerns related to potency; associated with an adverse event.
Meperidine	08/31/2012	08272012 @598	Complaint stated "bubbles of drug along the rim, outside of the drug reservoir"; sterility concerns
Fentanyl Bupivacaine	09/07/2012	07132012 @472	Under-filled product concerns.
Nalbuphine	08/30/2012	08282012 @978	Syringe fill volume concerns.

Furthermore, all of these complaint files were reviewed and deemed acceptable by your Quality Unit.

- E. Your firm failed to investigate aberrant peaks in HPLC chromatograms associated with finished sterile product. This includes the following:

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1. On 03/23/2012, a Diliazem, lot 02152012@318 complaint sample (AC12165) was evaluated by HPLC analysis to determine potency. The chromatograms associated with the sample exhibited several unknown peaks when compared to the control (reference standard). Additionally, the complaint was associated with a "patient response" in which the recipient of the drug "developed a phlebitis-type reaction with tracking up the veins". The unknown peaks have not been investigated nor have they been evaluated with respect to the "patient response".
2. On 08/08/2012 a Ropivacaine, lot 07022012@344 complaint sample (Complaint AC12382) was evaluated by HPLC analysis to determine potency. The chromatograms associated with the sample exhibited an unknown peak when compared to the control (reference standard). Additionally, the complaint was associated with a "patient response" in which the product "was not giving relief to 4 patients". The unknown peak has not been investigated nor has it been evaluated with respect to the "patient response".
3. The HPLC chromatograms used to evaluate potency for Morphine stock lots S09252012@381, S09252012@382, and S09252012@448 exhibited an unknown peak when compared to the control (reference standard). The lots were released on 09/27/2012 for further manufacture. The unknown peak has not been investigated nor has it been evaluated with respect to patient risk.

OBSERVATION 4

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

Specifically,

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- A. The sterile technique qualification (media fills) do not represent your routine operating conditions and does not evaluate worst-case activities that can provide a challenge to manual aseptic operations. Specifically,
1. Your media fills do not challenge the maximum number of times drug product lots can be filled from sterile stock solutions or the maximum number of units filled without increasing the risk of contamination of the manufactured sterile drug product. For example stock solutions can be stored and used to fill over a course of (b) (4) days. Stock solution of Ropivacaine 0.2% lot S09132012@312 was used to fill approximately (b) (4) final products lots in 09/2012.
 2. Your aseptic process validation does not challenge representative container closure systems currently used at your facility that represents a worst case challenge. For example, your firm performs media fill studies with (b) (4) bags when the following sizes: 25mL, 50mL, 150mL, 250mL, 500mL, 1000mL, 3000mL and 4000mL bags are used during routine production.
 3. Your media fills do not simulate aseptic manufacturing operations that incorporate worst-case activities and conditions that provide a challenge to aseptic operations. For example: maximum number of personnel and their activities, and an evaluation of critical routine and non-routine interventions (e.g. the continuous entering and exiting of the class 100 hoods used in the manufacture of sterile drug products.)
- B. Sterile Filtration has not been validated for its intended use. For example:
1. Bacterial retention challenge has not been performed for product contact (b) (4) filters used to sterile filter injectable drug products intended for patient use for example Fentanyl, Ropivacaine, etc.

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2. (b) (4) is recommended to be use for general laboratory use and not intended for direct patient care applications.
3. The firm does not have the data, procedures, and controls to assure that additional rounds of filtration do not adversely impact product. Your firm re-filtered, at least one time, all sterile stock solutions lots involved in the sterility failures before releasing final drug product lots for patient use.

OBSERVATION 5

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

Your firm utilizes a (b) (4) pump to manually administer drug product to individual units from stock solutions during the processing of sterile finished products. The number of pumps ("pump count") is not routinely reconciled with the total number of units manufactured to ensure labeled potency. This includes the following lot which was also associated with low potency complaints and a "patient response":

For example: Midazolam, lot 02122012@1 (released on 02/12/2012) which is also associated with lack of effect / low potency complaints AC12133 (approved by Quality on 03/12/2012) and AC12144 (approved by Quality on 03/16/2012).

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax: (781) 587-7556 Industry Information: www.fda.gov/oc/industry		10/10/2012 - 11/09/2012*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED		FBI NUMBER
TO: Gregory A. Conigliaro, Vice President and General Manager		3005881167
FIRM NAME	STREET ADDRESS	
Ameridose, LLC	201 and 205 Flanders Rd	
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED	
Westborough, MA 01581-1032	Sterile Drug Manufacturer	

OBSERVATION 6

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

Specifically,

A. The environmental monitoring and conditions of the aseptic core are deficient for the following reasons:

1. Gowning used to manufacture sterile drug products is inadequate:
 - a. Personnel gowns, eye-protection and gloves are not sterile. In addition gowns are only laundered and re-used for up to (b) (4) before they are sent for cleaning.
 - b. Personnel exposed foreheads were observed as part of their gowning procedures. These operators can work inside the open-faced class 100 hoods in the manufacture of sterile injectable drug products.
2. Environmental monitoring of the class 100 (b) (4) hoods is not performed in association with daily operations. Sterile drug products are aseptically manipulated in these hoods as part of daily operations. However, environmental monitoring for non-viable particulates is performed every (b) (4) and monitoring for viable particulates is performed (b) (4) in the class 100 hoods.
3. The firm failed to perform environmental monitoring during the manual aseptic connections from the stock solutions or during the manual filling of sterile injectable drug products.
4. Personnel monitoring is limited to the assessment of the manufacturing technician's

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fingers and this sampling is done only (b) (4). Other critical areas such as forehead, forearms, chest and shoulders are not monitored.

OBSERVATION 7

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.

Specifically,

Method validation and performance qualification for the (b) (4) to test the sterility of sterile injectable drug products manufactured is inadequate for the following reasons:

1. Your firm did not adequately execute a side by side comparison of this method with compendia sterility method as required in your validation. There is no justification for comparing the (b) (4) results with a (b) (4) when the current USP method requires a 14 day incubation.
2. The population for the challenge microorganisms used in validation was never evaluated.
3. The method was validated by (b) (4) of the challenge microorganisms. Furthermore, there is no data to support that the lowest level of detection was challenged during validation.
4. There is no adequate data to support the reproducibility of the (b) (4) method. Specifically, on numerous occasions the firm performed multiple (b) (4) of the same sample

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rendering all negative results in the first (b) (4) and showing viability in the following (b) (4)
All samples are (b) (4) s part of routine production.

OBSERVATION 8

The operations relating to the manufacture, processing, and packing of penicillin are not performed in facilities separate from those used for other drug products for human use.

Specifically,

There is no data to support that the firm's processing procedures will not increase the risk of cross-contamination between products. For example: the firm manufactures beta-lactam drug products in a non dedicated facility where sterile injectable drug products are manufactured. Your firm's employees can manufacture beta-lactam and non beta-lactam products in any hoods interchangeably. Furthermore, the firm does not test/assess for the presence of beta-lactams in other sterile manufactured drug products at building (b) (4)

OBSERVATION 9

Buildings used in the manufacturing, processing, packing, and holding of a drug product are not maintained in a good state of repair.

Specifically,

- A. The firm failed to perform a microbiological assessment after penetrating leaks were found in building (b) (4) dripping above the clean room in 06/2012. During the inspection 10/2012 we observed totes placed in the location of the penetrating leaks containing water. There is no documented evidence that the leaks were permanently corrected.
- B. Walls were observed to be cracked, corroded, and covered with what appeared to be adhesive material in Room A of Building (b) (4), where sterile drug products are aseptically prepared.

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CITY, STATE, ZIP CODE, COUNTRY

TYPE ESTABLISHMENT INSPECTED

Sterile Drug Manufacturer

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

During the inspection we observed the following conditions:

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- D. (b) (4) Hoods (b) (4) and (b) (4) utilized in the preparation of sterile drug products, were observed to contain what appeared to be brownish discoloration within the HEPA filters of the hoods.
- E. (b) (4) class 100 (b) (4) hoods in Building (b) (4) used to manufacture sterile products were observed to contain the following:

Hood*	Observation
(b) (4)	Exterior: visible rust on exterior.
	Interior: damaged light cover; foreign material (red substance on HEPA filter).
	Interior: broken glass; foreign material (red and white substance on HEPA filter).
	Interior: broken glass; foreign material (white substance on HEPA filter).
	Interior: exposed, uncovered strip lights
	Interior: damaged light cover; foreign material (red substance on HEPA filter and white substance on interior wall).
	Interior: foreign material (red substance on HEPA filter).

*All hoods were indicated to be clean and available for sterile processing.

OBSERVATION 11

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable to facilitate cleaning, maintenance, and proper operations.

Specifically,

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- A. Doors accessing Isolation Room (b) of Building (b) (4) (Class 1,000), where sterile drug product is prepared, were observed to be opened simultaneously with doors accessing the Vestibule (Class 10,000).
- B. Gaps were observed beneath doors located between Room (b) of Building (b) (4) (Class 1,000), where sterile drug products are prepared, and the Gowning Room (Class 10,000).
- C. (b) (4) loading bay doors which separate the outdoors from the unclassified area in Building (b) (4) were observed contains gaps of approximately 1 inch. Sterile finished product is packaged and stored in the unclassified area.
- D. Several gaps of approximately 0.25-0.5 inches were noted in the "pass-through boxes" and under doors which connect the unclassified area and classified area in Building (b) (4). Sterile finished product is manufactured, packed and stored in these areas.
- E. The aseptic processing clean room design was inadequate. Specifically;
- Several aseptic processing rooms at the facility lack adequate space and segregation to prevent contamination and mix-ups. Numerous lots of different products are produced simultaneously in a single room. Aseptic processing and labeling operations occur in very close proximity in an open room (e.g., Aseptic Processing Rooms (b) and (b)). For example, up to (b) personnel generally operate in Aseptic Processing Room (b) the same time. This operation requires products to be produced in separate hoods at the same time, which generally requires (b) personnel per operation.
 - The facility is not adequately designed and controlled to prevent influx of contamination from lesser controlled areas. Staff enters through the Ante room (which connects to the gowning room) to initially access the clean room area from an uncontrolled, unclassified

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hallway. This hallway has many activities and offices, and multiple insects were observed in this area. Furthermore, there are no interlocking door or other design controls were in place to assure there was control over the entry to the facility from the controlled, unclassified hallway.

OBSERVATION 12

Buildings used in the manufacture, processing, packing or holding of drug products are not free of infestation by rodents, birds insects, and other vermin.

Specifically,

- A. Insects were observed to be located in the unclassified area (Building (b)(4)) where finished sterile product is packaged and stored. The insects were also located within approximately 3-10 ft of the controlled area where sterile products are manufactured.
- B. At least one (1) bird was observed flying in the unclassified area (Building (b)(4)) where sterile finished product is packaged and stored.

OBSERVATION 13

Equipment for adequate control over air pressure is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.

Specifically,

Differential pressure is not adequately balanced and controlled between clean rooms. Specifically:

- A. The firm does not monitor the pressure differential between all adjacent clean rooms, and any adjacent uncontrolled areas

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- B. The firm does not evaluate any alarms resulted from their air handling system. Specifically, multiple events where air went from a higher classification toward a lower classification.
- C. Not all alarms are configured to detect pressure reversal events.
- D. The firm did not investigate the potential product impact of these events. Furthermore the firm has not evaluated the potential for ingress of microbial contaminants to the manufacturing areas.
- E. The firm does not keep more than ^(b) days of pressure data. The Quality Unit does not routinely assess these alarms.
- F. There are no formal limits for delta P between adjacent rooms, or between rooms and the adjacent uncontrolled corridors.
- G. There are no visible or audible alarms when differential pressure problems occur.

OBSERVATION 14

Procedures describing the handling of written and oral complaints related to drug products are deficiently written or followed. Specifically,

Your firm maintains a separate file of "non-complaints" which were not processed according to your approved procedure. Additionally, your firm has not adequately defined "non-complaint" in your current approved procedure.

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OBSERVATION 15

Written complaint records do not include, where known, nature of complaint.

Specifically,

- A. The formal complaint record does not include the initial communication between your firm and complainant. This information was frequently observed to contain more descriptive information regarding adverse events when compared to your firm's Quality approved complaint record.
- B. Your firm's Quality approved complaint records contain vague, canned language to describe adverse events. This includes the wording "patient did not achieve the expected response" (or a subtle variation).

*** DATES OF INSPECTION:**

10/10/2012(Wed), 10/11/2012(Thu), 10/12/2012(Fri), 10/15/2012(Mon), 10/16/2012(Tue), 10/18/2012(Thu), 10/19/2012(Fri), 10/22/2012(Mon), 10/23/2012(Tue), 10/26/2012(Fri), 11/06/2012(Tue), 11/07/2012(Wed), 11/08/2012(Thu), 11/09/2012(Fri)

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