

Establishment Inspection Report

Ameridose LLC
Framingham, MA 01702-6211

FEI: **3005881167**
EI Start: 07/21/2008
EI End: 08/06/2008

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SUMMARY

The firm was placed on the FY-08 New England District Work Plans as a High Risk facility and assigned under FACTS# 935703 (**Attachment#1**) and done in accordance with CP 7356002 Drug Process Inspection Program. The inspection covered the Quality, Production, Packaging and Labeling and Facilities and Equipment Systems at the firm. This was a follow-up to a fact finding inspection concluded 12/10/07 and is the initial drug cGMP inspection of this facility.

The firm has been drug registered since July 13, 2006 as a repacker and Other of Sterile and nonsterile mixtures and IV Admixtures. Its current drug registration is dated March 12, 2008. The firm’s customers are all Hospital Pharmacy operations. While on my inspection at this facility the firm received an approved license to practice pharmacy in the state of Delaware. They now have the appropriate licenses for operations in all 50 states of the Union.

An inspection of the facility found drug cGMP issues which resulted in a List of Observations being issued to Mr. Gregory Conigliaro, General Manager on 8/6/2008. The firm manufactures stock solution of an additive made from an Active Pharmaceutical Ingredient received and performs a potency, sterility, and endotoxin testing on the additive, and then manufactures an Admixture for

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review and release by the Clean Room Pharmacist and Freight Room Pharmacist prior to shipment. There is no potency or identity test done on the finished drug product, and the finished product is shipped immediately and prior to the (b)(4) day sterility test results are received by the firm. The firm's SOP 5.010 Product Procurement, Receipt and Inspection Version 1.0 dated 7/17/06 does not address how the received active pharmaceutical ingredients are sampled, tested and identified by a test method shown in the USP or verified and validated to be equivalent to a known method in the USP. A review of the firm's identity testing upon receipt of product reveals that, although not addressed in their SOPs, most but not all raw actives are identity tested prior to approval for use in production. The firm has received (b)(4) active ingredients of which I requested to see 17 identity test results. The firm was able to quickly locate 11 of the 17 identity tests requested. The master production and batch history records, known as Formulary Worksheets at the firm, are deficient in that they do not have where required statements of actual yield, percentage of theoretical yield at the completion of the process, and inspection of the packaging and labeling areas before and after production. A review of several SOPs revealed that there are two firm SOPs with noted issues as follows: one that does not address the firm's Out of Specification Procedures for Media fills not meeting specifications; and a second one addressing "lot samples for in-house Lab testing" when there is currently no in-house lab testing or the capabilities of testing the product in-house.

A review of the firm's Formulary Worksheets on Lot and Batch identification numbers and SOP 9.050 Beyond-Use Dating (BUD) of Products dated 5/22/08 reveals that the firm lot and batch numbers are assigned when the Formulary Worksheet is issued; however, some are issued in the afternoon and the products are not made until the next day or sometimes after the weekend. The lot number and BUD do not change when this occurs. The BUDs (expiry date) on the Formulary Worksheets and products I reviewed range from 30 days to 150 days.

ADMINISTRATIVE DATA

Inspected firm: Ameridose LLC
Location: 50 Fountain St
Framingham, MA 01702-6211
Phone: 508-656-2653
FAX: 508-820-0644
Mailing address: 50 Fountain St
Framingham, MA 01702-6211

Dates of inspection: 7/21/2008, 7/22/2008, 7/23/2008, 7/28/2008, 7/29/2008, 7/30/2008,
8/4/2008, 8/5/2008, 8/6/2008

Days in the facility: 9

Participants: Richard H. Penta, Investigator
LCDR Debra Emerson, Investigator

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Credentials were shown and a Notice of Inspection presented to Mr. Gregory A. Conigliaro, General Manager, on 7/21/08 by Investigators Penta and LCDR Emerson in the presence of Ms. Sophia Pasedis, VP Regulatory Affairs, Compliance and Auditing, who was also shown our credentials. LCDR Emerson was present for only the first day of the inspection. A List of Observations was presented to Mr. Gregory Conigliaro, General Manager and co-owner, on August 6, 2008 at the conclusion of the inspection. On July 28, 2008 Ms Pasedis signed a FDA 463a Affidavit regarding six documentary samples collected for drug cGMPs and finished product labeling. On August 5, 2008 Ms. Pasedis signed a FDA463a Affidavit regarding two physical samples collected for sterility, potency and identification analysis. She identified the photographs of labeling, and identified and provided me with all the documents and records collected by me regarding both the documentary and physical samples.

The entire report is written by Investigator Penta.

HISTORY

The firm is a Limited Liability Corporation (LLC) that opened in 2006 as a repacker and other of sterile and non sterile mixtures and Admixtures first registered with the USFDA (July 13, 2006), and also registered with the State Board of Pharmacy (exp.12/31/09). The firm's current USFDA drug registration is dated 3/12/2008. The firm was provided a Labeler Code Number (24200) in a letter dated 9/8/06 (See Exhibit#1). The firm is also drug registered as a manufacturer with the State of Massachusetts. The last inspection of the facility was in December 2007 regarding the firm's Compounding Pharmacy Operations. It was determined at that time that the firm was solely a repacker and manufacturer of drugs for their customers, Hospital Pharmacies. The current two Managers of Record (co-owners) are: Mr. Barry Cadden and Gregory Conigliaro, Vice President and General Manager. I was provided an Organization Chart by Mr. Conigliaro during the inspection (See Exhibit#2).

The firm's operations are from (b) (4) covered by (b) (4) shifts (b) (4). The firm currently has approximately (b) (4) employees. Approximately (b) (4) of the products are shipped out of state to Hospital Pharmacies. Firm management arrives at 9:00 am. Any correspondence can be addressed to Mr. Gregory Conigliaro, General Manager, who is the most responsible individual at this address.

INTERSTATE COMMERCE

The firm ships (b) (4) of their product outside of Massachusetts. They stated that all their customers that order the products are affiliated with hospitals. The firm manufactures small orders in Lot sized batches and combines multiple orders of one specific product into Batches of finished product. None of their manufactured or repackaged products are linked to a specific patient prescription. The firm has an internet site www.ameridose.com where they advertise Nationwide Sterile Admixing services, and Oral Syringe Repackaging Services for schedule II to VI products (See Attachment#2).

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There were six documentary samples collected for cGMP and label review which show what finished products were repackaged and/or admixtures manufactured from stock solutions for the follow actives: Fentanyl (as citrate), Hydromorphone HCL, Morphine Sulfate, Bupivacaine HCl, Ropivacaine HCl, and Oxytocin. There were also two physical samples Fentanyl in 0.9% NACL, 100 ml in 100 ml Injectable Bags, and Oxytocin 30 Units added to 500 ml 0.9% NACL Injection in a 500 ml Injectable Bag. These products have been shipped over the United States including to Illinois and Texas.

JURISDICTION

The firm currently markets over 600 products including 7 Antibiotics classes, 15 Class II, 1 Class III, 2 Class IV and many Class VI products as noted in a 7/10/2008 Listing provided by the firm (**See Exhibit#3**). The firm also provided a list of **(b)** finished product batches that they have manufactured and distributed in the past (**See Exhibit#4**). The firm has identified all the products manufactured and repackaged by them with an NDC number. Ms. Pasedis, when asked, stated that a person by the name of Mark told her back in 2006 that she did not have to drug list all her products. I told her that she should call CDER drug registration and Listing Branch to discuss with someone about her firm's need to drug list all their products because they are registered as a manufacturer and repacker of drug products and Admixtures.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

The following individuals were met during the inspection and provided me with information and/or documents for review during my inspection of the facility:

Gregory A. Conigliaro, General Manager, is overall in charge of the entire operations. He provided me with answers to many questions and directed others to get information and documents to me. Ms. Pasedis and Ms. Cerullo report directly to him. Mr. Conigliaro stated during the inspection that there were two DEA persons present to conduct an inventory and inspection. He left the room and upon his return later in the day stated that the DEA agents did an inventory of the scheduled products and reviewed security.

Sophia Pasedis, VP Regulatory Affairs, Compliance and Auditing, oversees those in charge of the narcotics inventory, Quality Control and the Pharmacists who review and release the finished products. She is the one who developed all the NDC numbers for all their products. Ms. Pasedis stated during the DEA inspection that as the Pharmacist of record all other pharmacists at the firm report to her.

Melanie Cerullo, Director of Quality, was gone many times to obtain documents requested. She is quite knowledgeable in the overall operations of quality and the processing of the products.

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Vira Ajgaonkar, RPh is in charge of overseeing the receipt, dispensing, and reconciling of all the narcotics used in log books maintained for DEA review. She pointed out and provided the narcotic products and labeling as requested.

FIRM'S TRAINING PROGRAM

The firm has a Training Program in which they follow SOP 2.010 Training Program dated 1/28/08 (See Exhibit#5). The SOP under 6.0 Frequency of New Hire Training and 10.4 GMP/USP/QS Training and in-Services refer to training as a new hire and also an (b) (4) update on drug cGMPs. A review was done on the individual training records of eight employees that worked at the facility. The review noted that the firm does its initial introduction to cGMPs. The majority of the people are new to the facility and the (b) (4) refresher course needs to be planned to capture the necessary refresher training for these relatively new employees after their (b) (4) with the firm is nearing completion. Mr. Brian O'Neill, Director of Pharmacy, did most of the cGMP training prior to Ms Cerullo arriving at the firm.

MANUFACTURING/DESIGN OPERATIONS

The firm operations revolve around orders being received from their Customers, approximately (b) (4) Hospital Pharmacies located in 49 of the 50 states, and the resulting Lot (single order) or batch (multiple orders) Formula Worksheets being issued by the front office repacking and/or manufacturing. The firm has signed contracts with each of their customers that specify the various products that they may be interested in purchasing. The firm follows USP 797 Pharmaceutical Compounding of Sterile Preparations and the drug cGMPs. The products manufactured are patient ready doses that are not filled on the order of a prescription but rather on the order of a Hospital Pharmacy. The orders that are received early in the morning are usually manufactured that day with orders received in the afternoon sometimes being shifted to the next day.

The firm currently has manufacturing done in (b) (4) Clean Rooms and (b) (4) (b) (4). The flow of personnel and equipment and product components come through the Class 1,000,000 (ISO 9) people room and freight room respectively and flows into the middle room, which is Class 100,000 (ISO8). Product and components are staged in locked cages at this location until needed for use in the Clean Room, Class 10,000 (ISO 7). Product manufacturing is done under separate hoods, Class 100 (ISO 5). There are (b) (4) hoods in Clean Room (b) (4) hoods in Clean Room (b) (4). The firm has an Environmental Monitoring Program following their SOP 3.030 Environmental Monitoring of Clean Room Areas, which includes personnel monitoring on a (b) (4) basis (See Exhibit#6). The monitoring is done as follows: Personnel and Surfaces (b) (4); Viable Air sampling (b) (4) and Non viable Air (b) (4). Results that exceed the Alert or Action Levels in the Sop are treated as OOS results and investigated. I reviewed the last two months of environmental testing and found the firm followed their SOP. Ms Cerullo, Director of Quality stated that the firm Gram stains any organisms found at the Action or Alert Level. The finished product is released (b) (4) to the Freight Room to await further review and packaging for storage and/or shipment.

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Quality

A request for the firm's Master SOP List resulted in the request for 15 different SOPs which were reviewed at various time during the inspection (**See Exhibit#7**). The review and findings will be discussed in this report with two specifically discussed under **Observation #6** regarding SOP 9.100 Sterile Technique Qualification (Media Fills) and SOP 6.021 Quality Assurance Sampling Process and Library along with SOP 8.010 Filtration and Sterilization Process. The firm does have an SOP for Method Deviations and also one for Corrective Action/Preventive Action (CAPA) Management, which they follow (**See Exhibits#8 & 9**). A review of Fentanyl/Ropivacaine in 0.9% NACL 1 mcg/0.2 100ml INJ bag included Deviation#D08118 dated 7/18/08 where two bags were contaminated with the wrong drug and after the investigation they were destroyed. The responsibilities of Quality and Compliance are noted in SOP 9.010 VER. 2 (**See Exhibit#10**), which is currently under review but signed by Sophia Pasedis, VP of Regulatory, Compliance and Auditing. Under Procedure no. 10.12 Trending the firm does a (b) (4) Report on product categories covering Environmental Monitoring, Deviations, OOS, Customer Complaints and Adverse Events. I told Ms Pasedis that her firm should include any recalls or returned goods information with this (b) (4) review.

Initially I reviewed Formula Worksheets for Oxytocin and Fentanyl type products, and then expanded to the review of Stock Solutions and finished product Formula Worksheets manufactured or repackaged from those stock solutions. The other product Formula worksheets reviewed include Hydromorphone HCL, Morphine Sulfate, Bupivacaine HCL, and Ropivacaine HCL. These can be seen in the Documentary samples 366485/490 that I collected. I also reviewed one Ephedrine stock solution. The firm provided me with their production from Ephedrine, Fentanyl, and Oxytocin Stock Solution for the past two weeks (**See Exhibit#11**). The issues noted missing in the Master Production and Batch History Records, known at the firm as Formula Worksheets are discussed under **Observations 4 & 5** under Objectionable Conditions.

A review of several Formulary Worksheets for both individual lots for a single customer and batches for multiple customers revealed that the firm does not always produce the product on the day that is typed into "Date made". On occasion that date is crossed out because the product is made after the expected "Date made" entry. Examples of these can be seen in the Documentary samples 366485/489 as follows:

- 1) Fentanyl Citrate 50 mcg/ml 100 ml INJ bag Lot#07162008@81 date made 7/17/08;
- 2) Hydromorphone in 0.9% NACL 0.2% mg/ml 50 ml in 60 ml INJ Syringe Lot#07032008@76 date made 7/08/08;
- 3) Morphine Sulfate in 0.9% NACL 1mg/ml 100 ml IPUMP Bags Lot#06302008@17 date made 7/2/08; and
- 4) Hydromorphone/Bupivacaine in 0.9% NACL 5 mcg/ 0.075% 250 ml IPUMP bag Lot#07082008@92 date made 7/09/08.

During my review of the consumer complaints and the sterility results on product produced and reviewed by me during the inspection I asked if any product had been recalled by the firm. Ms. Pasedis stated that they needed to recall (b) (4) Heparin diluent bags used in their production because of the recall that (b) (4) had on product using (b) (4). She also stated that the firm had received no Adverse Drug Experience complaints regarding their products. The firm

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has an Alert and Action level regarding their sterility results. None of the sterility results for the Formulary Worksheet I reviewed showed results that met either of these two levels.

Production

On 7/21/08 an initial inspection of the facility was conducted to see the warehousing operation, and any ongoing production. A review of the warehousing operation during the inspection revealed how products are received, entered into the network, and forwarded to a quarantine or release area dependent on the item and documentation, including a certificate of Analysis (C of A) received from the supplier. The warehouse receiver follows SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection dated 7/17/06 and added procedures of logging product into the network that is not noted in this SOP (**See Exhibit#35**). I was provided by Melanie Cerullo, Director of Quality Assurance, a Version 2 Draft of this SOP 5.010 which includes a more detailed description of how one receives, handles and data enters information into the network (**See Exhibit#36**). The firm uses the (b) (4) to track the ingredient through the production system. We discussed the differences between an (b) (4) numbering system and using the (b) (4) number and the need to be able to track all commodities coming into the facility and being used in the production process. I was referred to this drafted document SOP 5.010 regarding receipt and testing of incoming products. This is discussed under **Observation 2**. Additional requirements are needed for DEA Class II controlled substances which are addressed under 10.5 not 10.4 as stated in 10.4.9 of SOP 5.010. I was provided two computer printouts (**See Exhibit#37**) which show what data is currently entered into the network by the warehouse personnel. I observed a hard copy list maintained by the warehouse personnel which lists all products where one is waiting for the C of A to arrive for the product received and placed in Quarantine. The firm is currently going through its (b) (4) review of all SOPs and is updating those where needed as noted in SOP 5.010 and also their SOP 2.040 Order Processing dated 7/16/06 (**See Exhibit#38**) which was drafted and initially reviewed on 7/18/08 under the title Order Processing and generation of Formulary Worksheet (**See Exhibit#39**). This provides a step by step electronic entry account of how lot and batch orders are created into Formulary Worksheets for production.

The firm personnel were staging product in the Clean room (b) Freight Room area where the stainless steel table is used as the dividing line between incoming goods and staged for production goods (**See Exhibit#12 Photo #1**). Pallets of Finished Product were noted staged on the floor awaiting pick up towards the back receiving area. These were next to sanitary materials that were stored on shelving in the peripheral storage area near the Narcotics vault and Clean Room (b) (4) (**See Exhibit#12 Photo#2 & 3**). These cleaning and non pharmaceutical materials were removed on order of management and placed in the upstairs warehouse area by the next day. During inspection of the production area both reconstitution and "Pooling" of the received product and manufacture of admixtures were observed. The calibration of the syringes and verification by a Pharmacist was observed prior to production of the product involved. I also observed the repackaging of Cefazolin 2g Lots into syringes. There were no personnel handling of product issues observed during the multiple days I was observing the manufacturing and repackaging of product.

During my inspection of the production area Ms. Pasedis explained that Clean Room (b) was where the Oxytocin, Magnesium and all the Narcotic products are manufactured. She stated that Clean

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Room (b) is where all the stock solutions and the High risk syringes (fatalities if misused), including High dosages, are manufactured. The firm repackages the Oral syringes in the long room in between the Freight area and Clean Room (b).

Ms Sophia Pasedis discussed with me the firm's approach to conducting a Process Validation on all the processes and a Product Verification of all the products. The firm follows the following two SOPs: SOP 5.060 Process Validation dated 7/10/08 VER 2; and SOP 9.050 Beyond-Use-Dating (BUD) of Products dated 5/27/08 VER 2 (See Exhibits#13 & 14 respectively). Although the SOPs under 10.1 Process Validation and 10.10 Product Verification refer to "Chemical and physical Characteristics" and "appearance" respectively, there is a need for an Identity Test as per the USP. This is discussed in **Observation#2**. Ms. Pasedis stated that the firm has (b)(4) active processes that they have done a process validation. Some examples are the Carboy, bag, syringe, Cassette, and IPump containers that all have one or more processes, like adding or withdrawing product from an IV bag, to be validated. According to management product verification has been done on all products produced at the facility. The firm does an (b)(4) process validation on one product for Potency. A review of several examples was made during the inspection and only one Process Validation Report regarding the Uniformity of the Product Hydromorphone 10 mg/ml 50 mL in 50 mL Evacuated Bag Lot# 07232007@14 was missing the raw data entry. A request for the raw data provided Certificate of Analysis Test result that was within specifications (See Exhibit#15). A complete set of the testing data for Morphine 1mg/ml in 55 ml 0.9% NACL 60 ml (b)(4) Syringe was also reviewed and obtained (See Exhibit#16). The firm does do a periodic (b)(4) test on all the incoming active materials received and compare their test results to the Certificate of Analysis provided by the manufacturer. A review of these initial and (b)(4) review tests revealed that many but not all actives are identity tested upon receipt. Again, this is discussed under **Observation#2**.

The firm's stability testing program follows SOP9.050 Beyond-Use-Dating (BUD) of Products dated 5/27/08 VER 2 and is done on the (b)(4) active processes. A review of the firm's Beyond-Use Dating of products SOP revealed that the firm does have a stability program in place for it various processes and products. A review of several stability reports was made which showed that Potency, Endotoxin and Sterility testing was done (See Exhibit#40). Other physical characteristics, like pH, are considered and for example are done as an in-process test for all stock solutions. The product verification of all products includes physical, chemical and microbiological tests (See Exhibit#15). The stability testing is done at an outside laboratory (b)(4). The time points for their stability testing for new finished products are: (b)(4) for all container closure types.

The firm through its stability program provides information to the Stability Committee noted in SOP 9.050 Beyond-Use Dating(BUD) of Products dated 5/22/08 (See Exhibit#14), which they use to develop a BUD or expiration date for their many products. A review of the 6 documentary Samples and the Formulary Worksheets reviewed and collected during the inspection revealed the following for BUDs (expiration dates): 1) Fentanyl Concentrate (120 days), stock (90 days) and finished product (45 days); 2) Hydromorphone stock (90 days) and finished product (60 days); 3) Morphine Sulfate stock (90 days) and finished product (60 days); 4) Bupivacaine stock (90 days) and finished product (45 days); 5) Ropivacaine stock (90 days), finished product with Fentanyl (45 days), and finished product with Sufentanil (30 days); 6) Oxytocin stock (120 to 150 days plain or with SWFI), with Lactose Ringers (42 days), with NACL or D5W (90 days); and 6) Ephedrine (75 days). This coincides with the stability program. Ms Pasedis stated that all products on stability are run for

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towards (b) (4) days. This is so that the data can be collected and used by the Stability Committee with other data to decide on the BUD (expiry date).

The firm also has a repacking operation where they pool known product into large IV bags and then with a calibration machine repackage the products into syringes. They also take stock solution that has been sterility, endotoxin, and potency tested and repackage the product into syringes and/or cassettes for use at the Hospitals.

The firm does maintain a reserve sample on both refrigerated and room temperature finished products. Ms. Pasedis stated that the firm has a policy of moving to an area for disposal any products that are (b) (4) beyond expiry. The same disposal company, (b) (4) handles these out of date reserves.

Facilities and Equipment

A discussion was held with management regarding the Sterile Water for Injection (SWFI), equipment, and materials used by the firm to produce their products. The Formula Worksheet lists everything used under chemicals and devices. The majority of the equipment used is disposable, for example, a (b) (4). The stock solutions use a Carboy and some finished products are packaged in syringes and cassettes. The firm has multiple (b) (4) pumps (See Exhibit#17) by (b) (4) that are all located in Clean Room (b) (4). The units are continually calibrating a set amount. The firm also has an SOP 4.060 Operation and Maintenance of (b) (4) Sterilizer dated 5/28/08 (See Exhibit#18) for their (b) (4) Sterilizer which they use to sterilize components used in the process. The firm does a (b) (4) (b) (4) and records the findings on Attachment#2 Sterilization Record (See Exhibit#19). The firm brings in all the SWFI that it uses in production from an outside vendor. The firm has an outside Vendor do the testing and maintains the Air Exchange system which services the Clean rooms. (b) (4) gauges are in place outside the clean room areas to monitor the pressure differential.

Packaging and Labeling

The firm has all their labels stored on a computer where a limited number of authorized persons can access and print out the quantity requested by production for manufacturing of a lot. A specific number of extras are printed so that they can be kept with the Formula Worksheet and Quarantine/Release logs used by the office and the freight area. The firm does follow its SOP 5.040 Product Labeling dated 3/19/08 (See Exhibit#20); however, there is no mention of the need for a line clearance both before and after production, including the documentation necessary. The firm does maintain a labeling reconciliation regarding all labels issued. The firm does have an SOP 1.040 Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment (See Exhibit#21), and Ms. Pasedis stated that they did have a separate log book recording line clearances at each hood; however, this was stopped on 2/4/2008. I discussed with management the lack of documenting line clearances of packaging and labeling materials under **Observation #4** under Objectionable Conditions. They stated that they would update the Formula Worksheets and necessary SOPs to reflect line clearances being done and documented.

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An inspection of the Freight area where product is held for order picking and also stored in sealed cases was done throughout the inspection. The inspection revealed that some product was left in storage for longer than the day manufactured. On 7/23/08 I observed 4 cases of Oxytocin LR 20 units/ 1000 ml INJ bags made 7/8/2008 still stored in the Freight Room storage racks. A check of the Office Quarantine/Release Log showed (b) (4) units to (b) (4) dated 7/9 crossed out while the Quarantine/Release Log from the Freight Room does not show (b) (4) but does have a (b) (4) entry dated 7/14 for 24 units. All other entries match (See Exhibit#22). There was still no reconciliation of the Office and Freight Log sheets on 7/23/08 for this Oxytocin lot. I discussed with Ms. Pasedis the need for the Office Quality personnel to reconcile in a timely manner the shipment of all units with any inventory in the Freight Room area. There is an Area Cleaning Log in the repacking area that noted for the July 15 through 21/2008 period that this batch was produced on 7/8/2008. Ms. Pasedis stated that they had stopped using Cleaning logs but would reinstitute line clearance in the Formula Worksheets. On 7/23 the firm authorized the remaining four cases of product for destruction through (b) (4) firm follows SOP 5.050 Packaging and Shipping Process where 10.0 Procedure discusses how to prepare and handle shipments (See Exhibit#23).

MANUFACTURING CODES

The firm uses a month, day year coding system followed by a “@” (b) (4) (b) (4). For example: 07092008@51 shows the product is produced on July 9, 2008 and (b) (4). The firm also identifies all its finished drug products with an NDC number which includes the labeler code 24200 that is unique to the firm (See Exhibit#1). The firm (b) (4) software system, which is developed for Pharmacy Compounding Operations, requires them to use an Rx numbering system that then allows them to track the product lot number, NDC number, product description, and who purchased the product.

The Orders that the firm receives result in Formulary Worksheets for the lots and batches being issued with a Lot number and BUD (expiry date). Some lots and batches issued in the afternoon are not produced until the following day or after the weekend. This results in the “date made” being different from the portion of the lot or batch number that shows the month and day made, e.g. 0714.

COMPLAINTS

A review of the firm’s SOP 9.110 Consumer Complaints dated 3/19/08 VER 2 (See Exhibit#24) and request and review of complaints received the past two months revealed that the majority were due to shipping damage. There were no ADE complaints and only three Product Experience complaints received under AC08155 dated 5/13/08, AC08156 dated 5/12/08, and AC08184 dated 7/1/08 (See Exhibit#25). Two complaints AC08155 and AC08184 on two different lots of Oxytocin did not get the expected patient response. The third complaint AC08156 was regarding labels peeling off syringes and sticking to each other. The issue was fixed by Pharmacy Technicians at the Hospital; however, the firm retired (b) (4) label and introduced a (b) (4). No

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further follow-up could be done as the pharmacy technicians could not get further response from the doctors. Written responses are normally sent as per 10.9 of the SOP.

RECALL PROCEDURES

A review of the firm SOP 9.070 Recall Procedure dated 4/11/08 VER 2 (See Exhibit#26) was reviewed. The firm has had no recall of its own; however Ms. Pasedis did relate to me how they needed to recall (b) (4) Heparin diluent bags used in their production because of the recall that (b) (4) had on product using (b) (4). The firm will conduct an investigation, document the event, and determine if a product needs to be recalled. They would then generate a Recall Notification Letter (See Attachment 1 of the SOP 9.070) for issuance, and then may additionally contact them by telephone prior to sending the hard copy Recall Notification Letter.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**Observations listed on form FDA 483**

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, the firm manufactures stock solution of an additive made from an Active Pharmaceutical Ingredient received and performs a potency, sterility, and endotoxin testing on the additive, and then manufactures an Admixture for review and release by the Clean Room Pharmacist and Freight Room Pharmacist prior to shipment. There is no potency or identity test done on the finished drug product, and the product is shipped immediately and prior to the (b) (4) day sterility test results are received by the firm. Three examples are as follows: a) Fentanyl/Bupivacaine in 0.9% NACL Lot#07152008@134 manufactured on 7/16/08 and shipped immediately; b) Sufentanil/Ropivacaine 0.4 mcg/0.2% ml Cassette Lot#07082008@136 manufactured on 7/09/08 and shipped immediately; and c) Oxytocin added to LR 20 units/ 1000 ml INJ BAG Lot#07142008@3 manufactured on 7/14/08 and shipped on 7/16/08. The firm SOP 9.060 Sterility Product Process VER 1 dated 7/17/06 under 9.0 PROCEDURE reveals the statement at 9.1.5 "Due to limited Beyond Use dating on our products, products free of contamination...shall be released on day (b) (4) by the quarantine Pharmacist".

Reference: 21 CFR 211.165(a)

Supporting Evidence and Relevance:

The firm receives their Active Pharmaceutical Ingredients (Bulk Chemicals) both in the powdered state as non-sterile powders and also as finished sterile actives products from firms like (b) (4) (b) (4) (See Attachment#3). A review of SOP 9.010 Responsibilities of Quality Assurance dated 7/18/08 VER 2.0 as a draft states under 10.3.6: "Pharmacists are responsible for final approval, release, or rejection of all preparations." (See

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Exhibit#10) A review of SOP 6.021 QA Sample Process and Library VER 1.0 dated 6/11/07 (See **Exhibit#27A**) under 9.0 Procedure describes the sample size (“withdraw (b) (4) of the lot quantity, a minimum of (b) (4) preparations, a (b) (4) sample”), documentation and reporting results, testing and storage of the samples obtained. The revised Version 2 of SOP 6.021 (See **Exhibit#27B**) under 10.4.2 states “(b) (4) collected in a (b) (4) vial”. The firm currently sends product to one of (b) (4) outside laboratories for testing, mainly (b) (4) (See **Attachment#4**). The firm has a program in place to test all stock solutions made in-house for Potency, Sterility, and Endotoxin. They wait the (b) (4) days for the sterility results prior to using these Stock Solutions in production of Admixtures or repackaging into syringes or cassettes. These stability and finished product stock solution tests that they conduct are noted in SOP 9.050 Beyond-Use Dating (BUD) of Products dated 5/27/08 under 10.7.5 (See **Exhibit#14**).

The firm does collect the (b) (4) or (b) (4) of any Admixtures produced and send them out for Sterility testing only. There is no identity or potency test performed on the finished Admixture product. A review of SOP 9.060 Sterile Product Process dated 7/17/06 under Procedure and 9.1.5 states “ Due to limited Beyond Use dating on our products, products free from contamination and inspections are complete and meet all requirements, shall be released on day (b) (4) by the Quarantine Pharmacist. Results shall be obtained until (b) (4) (See **Exhibit#28**). Ms Pasedis stated that they once did adhere to the SOP requirement of awaiting the (b) (4) day results prior to use, but do not now. Currently the firm starts shipping the product immediately. The firm gets both a (b) (4) sterility result on all samples sent out for sterility testing. Ms. Pasedis stated that their contract laboratory would notify them immediately if a positive result was seen earlier than the (b) (4) day report.

The Chart below shows that the finished products were shipped immediately after production. The Pharmacist and/or Quality Assurance do not wait the (b) (4) days for preliminary sterility results as per SOP# 9.060 Sterile Product Process nor the (b) (4) days for the final sterility results from the contract laboratory, (b) (4). The products listed below, save one, were collected as documentary samples 366485 through 366490 as all six were manufactured from non-sterile active powders. The other product, Oxytocin added to LR 20 Units/ 1000ml INJ bag was made from a known source of a sterile product received by the firm.

Sample No.	Product	Lot No.	Mfgr. Date	Start Ship Date	End Ship Date	(b) (4) Day Sterility Result	Lab Lot No.
366486	Hydromorphone HCL	070322008@10	7/8/08 Repacker	7/7/08	7/10/08	7/28/08	(b) (4)
366488	Hydromorphone HCL/Bupivacaine	07082008@92	7/9/08	7/09/08	Only 1	7/25/08	(b) (4)
366489	Sufentanil/ Ropivacaine	07082008@136	7/9/08 Mfgr.	7/10/08	Only 1	7/28/08	(b) (4)
Exhibit31	Oxytocin	07142008@3	7/14/08	7/16/08	7/16/08	7/30/08	(b) (4)
366485	Fentanyl	07162008@81	7/17/08	7/17/08	Only 1	8/4/08	(b) (4)
366487	Morphine Sulfate	06272008@153	6/30/08 Repacker	6/27/08	7/15/08	7/21/08	(b) (4)

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Sample No.	Product	Lot No.	Mfgr. Date	Start Ship Date	End Ship Date	Day Sterility Result	Lab Lot No.
366485	Fentanyl/ Bupivacaine	07152008@134	7/16/08	7/17/08	Only 1	8/4/08	(b) (4)
366490	Oxytocin	07162008@13	7/16/08	7/18/08	7/21/08	8/4/08	(b) (4)
Exhibit32	Oxytocin	07112008@102	7/11/08	7/11/08	Only 1	7/29/08	(b) (4)

The Sterility Test Results for the above lots in Table 1 were received by the Contract Laboratory after the (b) (4) day. All shipments were shipped prior to the (b) (4) sterility testing results were complete and provided to the firm (See Exhibit#29). The Oxytocin 10 units/ml vial injectable (b) (4) manufactured by (b) (4) was used to make the Stock Solution of Oxytocin Lot#07112008@35 (See Exhibit#30), and the (b) (4) Oxytocin package insert labeling stored in the narcotics vault was collected. Oxytocin Lot#07142008@3 noted in the above table was produced using this Oxytocin Stock solution Lot#07112008@3 (See Exhibit#31). The Oxytocin Lot#07112008@102 was shipped immediately on 7/11/08 although the sterility test results were not in until 7/29/08 (See Exhibit#32). The Ephedrine Sulfate Lot# (b) (4) comes from (b) (4) (b) (4) as a sterile product in ampoules and was used to make an Ephedrine Stock Solution Lot#07082008@114 on 7/10/2008 and sterility tested under (b) (4) batch No. (b) (4) and found to be negative. The product was used in the manufacture of finished product from 7/10 through 14/08 (See Exhibit#33). There were also two physical sample collected 366491 10 mcg/ml Fentanyl in 0.9% NACL 100 ml, and 366492 Oxytocin 30 units added to 500 ml 0.9% NACL, which were also released for shipment prior to a (b) (4) stability result being received.

Discussion with Management:

A discussion with Ms Pasedis and Mr. Conigliaro was held during the inspection. We discussed how they did test the Stock Solutions for Potency, Sterility and Endotoxin. Those stock solutions that are solely repackaged into syringes or cassettes are basically the same product. I discussed with them that at minimum an identity and potency or strength test is needed along with a sterility test for any sterile products. They stated that they currently do a sterility test on all Admixtures and products manufactured. This is done at (b) (4) where they pool the product samples into groups and do a (b) (4) test on the pooled products and provide the firm with the results at (b) (4). Ms. Pasedis stated that they stopped holding the finished product for (b) (4) days in order to get a preliminary sterility result because of the short shelf life of the products along with their Customers who wanted the maximum amount of time to use the product they ordered. At the conclusion of the inspection Management stated that they would respond within 10 to 14 days and that they expected to have a plan to address the need for finished product testing. The firm provided me with a new draft of SOP 6.021 QA Sample Process and Library where they eliminated the reference to in-house testing of samples collected. All samples are sent out to a contract laboratory. The firm only does Environmental testing in-house at their small laboratory next to the Offices in the main building (See Exhibit#34). The correction of this SOP is mentioned in **Observation #6**.

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The firm provided me with a Draft of a Final Preparation Specification for Hydromorphone 0.2mg/ml in 50 ml 0.9% Sodium Chloride 60 m^{(b) (4)} Syringe NDC 24200-297-80. This document provides an Appearance Specification, label specification, Visual identification, Physical tests, and Final Preparation Strength (See Exhibit#34). This was provided by Ms Pasedis who stated that they are in the process of creating Final Preparation Specification documents for their products. Mr. Conigliaro stated at the end of the inspection that he expects to be one of the first in the industry to find a way to test his finished product preparations.

OBSERVATION 2

Written procedures are lacking which describe in sufficient detail the identification, sampling, testing, approval, and rejection of components.

Specifically, SOP 5.010 Product Procurement, Receipt and Inspection Version 1.0 dated 7/17/06 does not address how the received active pharmaceutical ingredients are sampled, tested and identified by a test method shown in the USP or verified and validated to be equivalent to a known method in the USP. The firm receives a Certificate of Analysis on the Active Pharmaceuticals received and has validated the test results on the Certificate of Analysis of the initial lots from the suppliers, along with periodic tests on future lots received; however, some but not all API lots received have a specific identity test done on them. For example, the active pharmaceuticals for Hydromorphone HCL Lot#65723/C and 65300/E, and Ropivacaine 64719 were received by the firm and not specifically identity tested by test methods shown in the USP.

Reference: 21 CFR 211.80(a)

Supporting Evidence and Relevance:

An inspection of the warehouse, Clean Room ^{(b) (4)}, Clean Room ^{(b) (4)} and the CII Vault for Narcotics was conducted during this inspection. A review of SOP 5.010 Product Procurement, Receipt and Inspection VER 1 dated 7/17/06 (See Exhibit#35) and SOP 9.010 The Responsibilities of Quality Assurance VER 2 dated 7/18/08 (See Exhibit#10) and discussion with Ms Pasedis and Ms Cerullo about these two documents and how they related to receipt and acceptance of materials and active products for production was done at different points during the inspection. The firm has a limited description under 9.4 Item Receipt and Inspection of SOP 5.010 dated 7/17/06 and does not mention any incoming testing or visual and physical examination of the incoming product. Under 10.5 Materials of SOP 9.010 dated 7/18/08 the firm refers to SOPs 5.010 and 6.010 (Controlled Substances) and also to what Quality Assurance and Quality Controls responsibilities are regarding these received materials. There is no mention of any incoming identification test for all actives received with a Certificate of Analysis (C of A). I explained to management that there are specific identity tests noted in the USP for the ^{(b) (4)} non-sterile powders that they receive from an outside vendor with a Certificate of Analysis. I commented that without a C of A the firm is expected to do a full active ingredient specifications test on incoming products. The firm provided me with an updated Ameridose Vendors List (See Exhibit#41) which has ^{(b) (4)} firms listed. I also received from the firm a List of Powder Lots received on the ^{(b) (4)} powders that were the focus of my inspection (See Exhibit#42). A request for and a review of the Certificates of Analysis from outside Contract

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Testing Laboratories on the initially received powder lots (See **Exhibit#43**) and the follow-up lots done annually (See **Exhibit#44**) shows that the firm have done identity tests on many incoming materials even though not directed in their SOP to do tests on all incoming ingredients. For example, the active pharmaceuticals for Hydromorphone HCL Lot#65723/C and 65300/E, and Ropivacaine 64719 were received by the firm and not specifically identity tested by test methods shown in the USP. The firm was in the process of its (b) (4) review of all SOPs and I was provided copies of those initially reviewed and approved for circulation and final approval by their Quality Assurance Committee.

Discussion with Management:

Various discussions were held with three members of management during my inspection regarding my findings, including this issue of incoming product identity testing. I explained to them that an identity test is needed on each incoming active and product that will be used in production of their repackaged items and manufactured Admixtures. I discussed how this needs to be a specific identity test listed in the USP or a scientifically justified equivalent. Ms Pasedis stated that they did tests on all the initially received lots of product and may have done all others because of the fact that they receive the same lot of product over several shipments. I commented that they should have as a procedure the testing of every new lot of product for identity that they receive. Ms Pasedis stated that they were considering the (b) (4) for identity testing of received chemical materials.

A request was made for 17 different lots of active powders out of (b) received by the firm on their (b) non-sterile powders. The firm provided the incoming test results on 11 that were initial or annual (4) tests, and could not find test results on 3. One of the 17 was new and not yet in inventory for use, and I asked them to stop looking for the other two from October and November 2007. There were (b) other lots of active powders listed (See **Exhibit#42**) that I did not request to review. The firm provided me with a draft of SOP 2.040 Order Processing and Generation of Formulary Worksheet dated 7/18/08 in which under 10.7 Filling the Order and 10.8 Send Orders to Clean Room/Repack for preparation they discuss how to create Batch or Lot Orders and provide formulary Worksheets to the Production Area (See **Exhibit#39**). The firm also provided me with a draft of SOP 5.010 Procurement and Receipt of Product, Components and Consumables undated that under 10.4 Receipt of Materials it discusses how materials are accepted, C of As are obtained and reviewed, and materials are logged into the network (See **Exhibit#36**). The firm has also drafted a new Raw Material Specification Document. I was provided a draft for Ropivacaine Powder Specification # 38779-2431-05 which provides a Visual identification, and appearance specification for the product received (See **Exhibit#45**). There is no physical identity test as per the USP or equivalent listed in this document.

OBSERVATION 3

The master production and control records are deficient in that they do not include a statement of theoretical yield and minimum, maximum, and yield percentages.

Specifically, a review of two Master Production records (Master Formula Worksheets) revealed no statement of theoretical yield nor a percentage range of theoretical yield that the produced batch should fall within. This can be seen in the following two Master production (Formula Worksheet) examples: a) Fentanyl (as citrate) in SWFI

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50 mcg/ml 4000 ml Stock Solution, and b) Oxytocin in SWFI 10 units/ ml 4000ml Stock Solution.

Reference: 21 CFR 211.186(b) (7)

Supporting Evidence and Relevance:

The firm has their entire Master Formulary Worksheets in a program on the computer and they restrict access to that program. They also keep a hard copy approved Master Formulary Worksheet in the Director of Quality's office area. After reviewing some batch records a request was made for some Master Formulary Records for review. I reviewed two stock solutions Fentanyl in SWFI 50 mcg/ml 4000 ml stock solution (**Exhibit#46**) and Oxytocin in SWFI 10 units/ml 4000ml stock solution (**See Exhibit#47**). The review revealed that, although the firm records the product weight at steps #**(b) (4)** for the Oxytocin and Fentanyl respectively, and also the total number of bags filled at Steps **(b) (4)** for Oxytocin and Fentanyl respectively, they do not list and expected actual yield nor a percentage range of the theoretical yield at these two steps of the operation.

I also requested and received two finished product Master Formulary Records to document the various steps and information in these master records. My review confirmed that the firm did not have a statement of the expected theoretical yield in the Master Formulas for Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringe 1 syringe (**See Exhibit#48**) and Oxytocin added to LR 20 units/1000 ml INJ bag 1 bag (**See Exhibit#49**). This is also seen in Documentary Sample 366485 where lot size for Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringes was **(b) (4)** syringes to one customer. The firm states the batch size is **(b) (4)** syringes to be made but does not record the actual number of units manufactured at the end of **(b) (4)**, and does not have a percentage of theoretical yield that is expected (**See Documentary Sample 366485 dated 7/28/08**).

Discussion with Management:

I discussed with Ms Pasedis and Mr. Conigliaro the need to document the number of units produced and also to determine an actual yield and to compare it to the percentage of theoretical yield that is expected from the process. Ms Pasedis stated that it is a DEA requirement to track the yield of all Class II- IV products. The firm has established a range of **(b) (4)** loss on Fentanyl, due to the double handling of the concentration (**See C/R 366485**). The firm has determined a Hydromorphone loss of **(b) (4)**. The firm keeps this in a separate tabulation and does it for all their products. The information is not currently used to provide a theoretical range in the master or batch formulary records.

OBSERVATION 4

Batch production and control records do not include results of the inspection of the packaging and labeling area before and after use for each batch of drug product produced.

Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the

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firm does not document the line clearance inspection of the packaging and labeling area before and after use. For example, a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008, and b) Oxytocin added to LR 20 units/1000 ml INJ BAG Lot#07162008@13 made 7/16/08 do not include instructions or have documented a line clearance before and after the packaging and labeling of the products involved.

Reference: 21 CFR 211.188(b) (6)

Supporting Evidence and Relevance:

A review was made of several Formulary Worksheets of both stock solutions and finished product syringes and Admixtures in Injectable bags. The Formulary Worksheets show steps where labels are staged and reconciled in Steps (b) (4) of the Formulary Worksheet for Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 (See Exhibit#50); however, there is no record of a line clearance before or after the production and labeling process starts. This can also be seen in the various Documentary Samples (366485/490) collected on 7/28/08 where the finished products produced from the stock solutions do not show any documentation of line clearance. One example is Oxytocin Added to LR 20 Units/ 1000 ml INJ Bag Lot#07162008@13 made 7/16/08 which is part of documentary sample No. 366490. I discussed the issue of line clearances with Ms Pasedis. The firm in the past maintained Cleaning logbooks which included the recording of line clearances at each Hood in the clean room. This was changed near the start of this year. The firm has SOP 1.040 The Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment VER. 2 dated 2/4/08 (See Exhibit#21) which covers the cleaning and maintenance of Hoods and pumps, various storage equipment, and general equipment. This is separate from any labeling and packaging line clearance that is needed before and after each lot or batch is produced. The firm also has SOP 5.040 Product Labeling VER. 4 dated 3/19/08 (See Exhibit#20), which addresses the label generation, accuracy, and reconciliation of the product. The label reconciliation is completed after the product is packaged and brought to the Freight Room floor for final disposition. This does not cover line clearances inside the hoods in the Clean rooms. An inspection of Clean Room (b) (4) on two occasions resulted in seeing the Technicians and Pharmacist producing the products and clearing the areas prior to the next lot of batch were produced; however, there was no documentation showing the line clearance of the areas.

Discussion with Management:

On July 30th I discussed with Ms Pasedis how the firm has handled the labeling of the products and the line clearance and maintenance and cleaning of the equipment, including the hoods in the clean room. She stated that the firm prior to 2/4/08, when they revised SOP 1.040 The Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment VER. 2 dated 2/4/08 (See Exhibit#21), the firm followed the LUMAC SOP which required a line entry every time that the hood was cleaned prior to a new product being introduced to each of the hoods located in the (b) (4) clean rooms. We discussed different ways of reintroducing the documentation of these cleanings and line clearances, including putting a line item at the start and completion of each production run so that the Admixing Technician can sign off on these actions.

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OBSERVATION 5

The batch production and control records are deficient in that they do not include a statement of the actual yield and percentage of theoretical yield.

Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the firm does not have a statement of the actual yield and the percentage of theoretical yield at the completion of the process. For example, there is no actual yield or percentage of theoretical yield noted in the following two Formula Worksheets: a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008 (Step# (b) (4)) and b) Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for (b) (4) bags made 7/16/2008 (Step# (b) (4)).

Reference: 21 CFR 211.188(b) (7)

Supporting Evidence and Relevance:

Several Formulary Worksheets were reviewed at the start and during the inspection which revealed that the firm did have a lot or batch size posted at the start and on each page of the Formula Worksheet; however, there is no actual yield or percentage of theoretical yield noted in the following two Formula Worksheets: a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008 (Step# (b) (4)) (See Exhibit#50), and b) Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for (b) (4) bags made 7/16/2008 (Step# (b) (4)), which is included in Documentary Sample#366490. In regard to the Stock Solutions, the firm calculates under (b) (4) , but does not determine the actual size of the batch produced. There also is no theoretical range listed to compare with the actual amount of stock solution produced. The example provided is Exhibit#50 of Oxytocin in SWFI Lot#06172008@130 where the batch size is (b) (4) and they write in the (b) (4) is made. Although, in this case, the active is less than (b) (4) and would be rounded down, the weight of the finished stock solution is C (b) (4)) - (b) (4) which rounds to (b) (4) . This is (b) (4) % of the theoretical yield from a batch of (b) (4) . The (b) (4) bags filled are documented under Step# (b) (4) .

A review of a finished product like the Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for (b) (4) bags made 7/16/2008 (Documentary Sample#366490) or Hydromorphone in 0.9% NACL 0.2mg/ml 30 ml in 30 ml glass syringe Lot#07032008@10 for (b) (4) syringes manufactured 7/8/08 (Documentary Sample#366486) shows a batch yield (b) (4) typed in on each page but no actual amount made written in by the Admixing Technician under Step# (b) (4) . There is also no mention of a percentage of the theoretical yield that is produced. The (b) (4) bags of Oxytocin were produced from one lot of stock solution while the (b) (4) syringes of Hydromorphone were produced from (b) (4) of stock solution. There is no indication on either batch record regarding the disposition of any stock solution material left over after the units of product were produced. It appears that the (b) (4) of Oxytocin and (b) (4) of Hydromorphone as listed on the Formulary Worksheet were used in the production of these respective (b) (4) and (b) (4) units of finished product.

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Discussion with Management:

A discussion was held during the inspection with Ms Pasedis and Mr. Conigliaro regarding the Formulary Worksheets and the actual vs. theoretical yield of product for each stock solution and finished product produced. Ms. Pasedis stated that they know the amount of product in each stock bag at the end of the usage of each and all bags. I explained to her that they need to know the amount of product in the stock solution lot and individual bags prior to finished product production. One can use Step^{(b)(4)} and Step^{(b)(4)} to determine the amount manufactured. One can then use Step#^{(b)(4)} in the finished product production to determine how many units are produced and how much, if any is not used, or used for a different finished product. I showed her that currently there is no entry by the Admixing Technician on how many units are produced by the Admix Technician using the calibrated ^{(b)(4)} Pump.

OBSERVATION 6**Written production and process control procedures are not followed in the execution of production and process control functions.**

Specifically, during the review of several SOPs it was noted that the firm was not following what was expected as noted in the following two documents:

a) SOP 9.100 Sterile Technique Qualification (Media Fills) VER 2 dated 6/16/08 under 10.12 response to Positive results refers to "retraining" only throughout the section, and does not refer to the firm's Out of Specification Procedure SOP 3.030 for positive test result follow-up; and b) SOP 6.021 Quality Assurance Sample Process and Library VER 1 dated 6/11/07 reveals under 9.4 Testing of Q A Sample a section on "lot samples for in house Lab testing" when there is currently no in house lab testing or capabilities of testing a product in house.

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

A request for the firm's Master SOP List resulted in the request for 15 different SOPs which were reviewed at various time during the inspection (**See Exhibit#7**). The review of the SOPs throughout the inspection revealed that the firm was going through a review process of all SOPs. Melanie Cerullo, Director of Quality was initiating and Sophia Pasedis, VP of Regulatory Affairs, Compliance and Auditing was doing the initial sign off prior to full QA Committee final review. A review of SOP 9.100 Sterile Technique Qualification (Media Fills) VER 2 dated 6/16/08 under 10.12 Response to Positive Results (**See Exhibit#51**) revealed a referral to "retraining" only throughout the section, and does not refer to the firm's Out of Specification Procedure SOP 3.030 for positive test result follow-up. This was pointed out to management who in turn drafted a version 3 of the SOP 9.100 in which they added reference to the OOS firm documents (**See Exhibit#52**), and provided me with the pertinent pages containing Section 10.12

A review of SOP 6.021 Quality Assurance Sample Process and Library VER 1 dated 6/11/07 reveals under 9.4 Testing of Q A Sample a section 9.4.3 on "lot samples for in house Lab testing" when there is currently no in house lab testing or capabilities of testing a product in house (**See**

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Exhibit#27A). The firm drafted a new SOP 6.021 Version 2 and provided me a copy that showed that the firm had rewritten the SOP and eliminated references to in-house laboratory testing, by eliminating the Section 9.3.1 and 9.4.1.

Discussion with Management:

During the inspection discussions were held with Sophia Pasedis and Melanie Cerullo regarding various SOPs. It was brought to my attention that Ms. Cerullo was in the process of doing a review on all SOPs as per their firm policy of reviewing all documents (b) (4). This has led to different SOPs that are in the draft stage, signed and dated 7/18/08 by Sophia Pasedis and undergoing final review and full QA Committee sign off. I was provided drafts showing corrections made on the above two mentioned documents.

Another document that was reviewed and discussed with all three management persons accompanying me during this inspection was SOP 8.010 Filtration Sterilization Process VER 2 dated 6/26/08 (See Exhibit#53), which is a revision to Version 1 dated 7/17/06 (See Exhibit#54). Under the Procedure Section 9.2.7 of Version 1 it states "An integrity (b) (4) shall be performed. When I asked firm management present with me during the inspection for documentation of previous (b) (4) tests conducted they were unable to provide me with any documentation that the (b) (4) it was performed prior to 6/26/08. Ms. Pasedis confirmed that when they revised SOP 8.010 in June 2008 they started doing (b) (4) tests and included the documentation in with the Formulary Worksheet. This can be seen in Morphine Sulfate in 0.9% NACL 1 mg/ml 4000ml Stock Solution Lot#06302008@122 manufactured 7/1/2008 (See Exhibit#55) where Attachment#1 Post-Use (b) (4) Integrity Testing of Filters for Filter Lot# (b) (4) used in production of Filter Sterilized Lot#06302008@122 passed.

REFUSALS

There were no refusals on cGMP document requests. I did request an actual or the template of the type of contracts used with their customers, which are solely Hospital facilities. Ms. Pasedis stated and Mr. Conigliaro concurred that there was no cGMP regulation that required them to provide me with either a template contract or signed contract that they have with any of their clients.

GENERAL DISCUSSION WITH MANAGEMENT

Prior to leaving on 8/5/08 I discussed with Sophia Pasedis and Gregory Conigliaro the observations that I had from my inspection to date. I also collected at this time two physical samples 366491 and 366492 with documents and submitted them for sterility, potency and identification testing. They were identified and shipped to NRL on 8/11/08.

On 8/6/08 prior to leaving the firm in the afternoon an exit discussion was held with the three management persons who accompanied me during the inspection. A List of Observations (FDA483) was issued to Mr. Gregory A. Conigliaro, General Manager, in the presence of Sophia Pasedis, VP Regulatory, Compliance and Auditing, and Melanie Cerullo, Director of Quality, after discussing two other issues with them. I discussed with the firm the following two points:

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- 1) The firm currently tracks all incoming ingredients and products used in production by the supplier/manufacturer's lot number, which they use throughout the recording of the identity of the item. The firm has some container closures and other materials that do not have lot numbers and need to be identified. Although they can continue with their current method we discussed their looking into a better method, especially when they get a new software tracking system for the documentation and production of their products; and
- 2) I discussed with them SOP 8.010 Filtration and Sterilization Process Version 2 dated 6/26/08 and the earlier Ver.1 Sterilization dated 7/17/06. The firm had no documented record that the filter integrity (b) (4) test was being done as per SOP prior to the revision of 6/28/08. They had provided me with an example of a (b) (4) test done on 6/30/08 to show that it is now being done.

I proceeded to read each of the six (6) Observations to those present. When asked, I provided clarification and examples of what was missing in the Master and Batch Formulary Records. I also acknowledged that the firm was conducting a (b) (4) review of all SOPs and that they were in the process of updating these SOPs even before I stated my inspection. I emphasized the importance of the first observation and explained to them that my observations may lead to Regulatory Action, which includes a Warning Letter, Seizure or Injunction after prior warning. I also explained to them that the documentary samples I collected during the inspection were so that we could review the various labeling and products produced by the firm at this location. Ms Pasedis asked to whom and how soon should they respond to the List of Observations. I gave them our current District Director's name and asked that I be copied on any correspondence. They stated that they would respond within 10 to 14 days.

The inspection was concluded.

SAMPLES COLLECTED

The following two physical samples were collected:

- 1) 366491 dated 8/6/08 FENTanyl (as citrate) in 0.9% NACL, 100 ml Injectable bags 24/10 mcg/ml units of Lot# 07302008@4 EXP September 13, 2008 collected and shipped to NRL for Sterility, Potency and identification; and
- 2) 366492 dated 8/6/08 OxyTOCIN 30 units added to 500 mL in 0.9% Sodium Chloride Injectable bags 24 units of Lot#08022008@54 EXP November 2, 2008 collected and shipped to NRL for Sterility, Potency and Identification.

I also collected the following 6 Documentary Samples:

- 1) 366485 dated 8/6/08 Fentanyl Concentrate in Water 10mg/ml 1592.1 ml Concentrate Stock Solution Lot#06162008@31 EXP October 14, 2008 collected for cGMPs and labeling of finished product;
- 2) 366486 dated 8/6/08 Hydromorphone HCL in 0.9% NACL 0.2 mg/ml 4000 ml Stock Solution Lot#06162008@81 EXP September 15, 2008 collected for cGMPs and Labeling of finished product;
- 3) 366487 dated 8/6/08 Morphine Sulfate in 0.9% NACL 1 mg/ml 4000ml Stock Solution Lot#06112008@92 EXP September 10, 2008 collected for cGMPs and labeling of finished product;

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- 4) 366488 dated 8/6/08 Bupivacaine 0.75% 4000 ml Stock Solution Lot#06172008@125 EXP September 16, 2008 collected for cGMPs and labeling of finished product;
- 5) 366489 dated 8/6/08 Ropivacaine 0.5% 4000 ml Stock Solution Lot#06172008@127 EXP September 16, 2008 collected for cGMPs and labeling of finished product; and
- 6) 366490 dated 8/6/08 Oxytocin in SWFI 10 units/ml 4000ml Stock Solution Lot#06252008@121 EXP November 23, 2008 collected for cGMPs and labeling of finished product.

VOLUNTARY CORRECTIONS

The previous inspection concluded 12/10/2007 was not a cGMP inspection and no List of Observations was issued. The firm has corrected discussion points regarding labeling accountability on destroyed labels, listing all equipment used in production on the Formulary Worksheets, and conducting annual product reviews on their product categories.

ATTACHMENTS

- FDA482 Notice of Inspection dated 7/21/08
- FDA483 List of Observations dated 8/06/2008
- Attachment#1: FACTS Assignment#935703 target date 5/30/2008
- Attachment#2: List of (b) (4) Contract Servicing laboratories from 12/07 EIR
- Attachment#3: List of (b) (4) Actives received for Production from 12/07 EIR
- Attachment#4: List of (b) (4) outside Laboratories from prior 12/07 EIR

EXHIBITS COLLECTED

- Exhibit#1: Ameridose Labeler Code letter dated 8/8/2006 (1 pg)
- Exhibit#2: Organization Chart (1 pg)
- Exhibit#3: Ameridose Products List (26 pgs)
- Exhibit#4: Product Batches List (3pgs)
- Exhibit#5: SOP 2.010 Training Program dated 1/28/08 (12 pgs)
- Exhibit#6: SOP 3.030 Environmental Monitoring of Clean Room Areas dated 7/17/2008 (32 pgs)
- Exhibit#7: Master SOP Index (3 pgs)
- Exhibit#8: SOP 1.030 Method Deviations dated 1/28/2008 (9 pgs)
- Exhibit#9: SOP 9.030 Corrective Action/Preventive Action (CAPA) Management dated 2/1/2008 (3 pgs)
- Exhibit#10: SOP 9.010 Responsibilities of Quality and Compliance dated 7/18.2008 Draft (9 pgs)
- Exhibit#11: 3 Product Stock Solution Batches July 7-21, 2008 (3 pgs)
- Exhibit#12: Photos #1-3 Facility (2 pgs)
- Exhibit#13: SOP 5.060 Process Validation dated 7/10/2008 (4 pgs)

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- Exhibit#14: SOP 9.050 Beyond-Use-Dating (BUD) of Products dated 5/22/2008 (5 pgs)
- Exhibit#15: Product Verification report and Certificates of Analysis on Hydromorphone (C of A) (6 pgs)
- Exhibit#16: Product Verification and C of A (4 pgs)
- Exhibit#17: List of (b) (4) Pumps (1 pg)
- Exhibit#18: SOP 4.060 Operation and Maintenance of (b) (4) Sterilizer dated 5/28/08 (7 pgs)
- Exhibit#19: Attachment 2 Sterilization record Cycle 79B dated 7/29/08 (3 pgs)
- Exhibit#20: SOP 5.040 Product Labeling dated 3/19/08 (6 pgs)
- Exhibit#21: SOP 1.040 Log Of Use, Maintenance, and Cleaning (LUMAC) of Equipment dated 2/4/2008 (9 pgs)
- Exhibit#22: Formula Worksheet Oxytocin added to LR 20 Units/ 1000 ml INJ bag Lot#07082008@1 made 7/8/08 and destruction comment (7 pgs)
- Exhibit#23: SOP 5.050 Packaging and Shipping Process dated 6/16/2008 (5 pgs)
- Exhibit#24: SOP 9.110 Consumer Complaints dated 3/19/2008 (8 pgs)
- Exhibit#25: Attachment#1 Complaint Log AC08152 to 08189 and Complaints 08155/56 and 8184 (9 pgs)
- Exhibit#26: SOP 9.070 Recall Procedure dated 4/11/2008 4 pgs)
- Exhibit#27A: SOP 6.021 Ver. 1 QA Sample Process and Library dated 6/11/2008 (4 pgs)
- Exhibit#27B: SOP 6.021 Ver. 2 QA Sample Process and Library undated draft (4 pgs)
- Exhibit#28: SOP 9.060 Sterile Product Process dated 7/17/2006 (6 pgs)
- Exhibit#29: Sterility Test Results on Products from 5 powdered active materials (14 pgs)
- Exhibit#30: Formula Worksheet Oxytocin 10 Units/ml 1000ml stock sol Lot#07112008@35 made 7/11/08, insert label (b) (4) C of A (13 pgs)
- Exhibit#31: Formula Worksheet Oxytocin added to LR 20 Units/ 1000 ml INJ Bag Lot#07142008@3 made 7/14/2008 (13 pgs)
- Exhibit#32: Formula Worksheet Oxytocin added to D5W 10 Units/ 500ml INJ bag Lot#07112008@102 made 7/11/2008 w/sterility results (10 pgs)
- Exhibit#33: Ephedrine 50 mg/ml 500 ml Stock Sol Lot#07082008@114 made 7/10/2008 w/sterility results (8 pgs)
- Exhibit#34: Final Preparation Specification Hydromorphone 0.2 mg/ml in 50ml 0.9% NACL 60 ml (b) (4) Syringe undated Draft (3 pgs)
- Exhibit#35: SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection Ver. 1 dated 7/17/2006 (2 pgs)
- Exhibit#36: SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection Ver. 2 undated draft (11 pgs)
- Exhibit#37: Receiving Materials electronic Log and c of a list (3 pgs)
- Exhibit#38; SOP 2.040 Order Process Ver. 1 dated 7/17/2008 (4 pgs)
- Exhibit#39: Order Processing and Generation of Formulary Worksheet Ver. 2 undated Draft (8 pgs)

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- Exhibit#40: Stability Test results as C of As (5 pgs)
Exhibit#41: List of Ameridose Vendors (2 pgs)
Exhibit#42: List of Powdered Lots received since day 1 (3 pgs)
Exhibit#43: Original Tests on incoming Actives, C of A reports (17 pgs)
Exhibit#44: Annual Tests on incoming Actives, C of A s (14 pgs)
Exhibit#45: Raw Material Specifications Ropivacaine Powder undated draft (2 pgs)
Exhibit#46: Master Formula Worksheet Fentanyl in SWFI 50 mcg/ml 4000 ml Stock Sol 1 Lit size (6 pgs)
Exhibit#47: Master Formula Worksheet Oxytocin in SWFI 10 units/ml 4000 ml Stock Sol 1 Liter Size (6 pgs)
Exhibit#48: Master Formulary Worksheet Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringe 1 syringe (3 pgs)
Exhibit#49: Master Formulary Worksheet Oxytocin added to 20 Units/ 1000 ml in INJ Bag 1 Bag (3 pgs)
Exhibit#50: Formulary Worksheet Oxytocin in SWFI 10 units/ml 4000 ml Stock Sol Lot#06172008@130 made 6/18/2008 (14 pgs)
Exhibit#51: SOP 9.100 Sterile Technique Qualification (Media Fills) Ver. 2 dated 6/16/2008 (18 pgs)
Exhibit#52: SOP 9.100 Sterile Technique Qualification (Media Fills) Ver. 3 undated Draft (2pgs)
Exhibit#53: SOP 8.010 Filtration Sterilization Process Ver. 2 dated 6/26/2008 (7 pgs)
Exhibit#54: SOP 8.010 Filtration Sterilization Process Ver. 1 dated 7/16/2006 (3 pgs)
Exhibit#55: Formulary Worksheet for Morphine Sulfate 0.9% NACL 1 mg/ml 4000 ml Stock Solution Lot#06302008@122 made 7/1/2008 (3 pgs)



Richard H. Penta, Investigator