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SUMMARY

An inspection of the firm was conducted with the Massachusetts Board of Pharmacy Investigators as directed by the May 22, 2007 Inspection Request from HFD-317 Div of New Drugs and Labeling Compliance under PAC 56D015 and FACTS assignment#843994 (See Attachment#1).

This is the initial inspection of the firm and is a fact finding inspection where 28 Pharmacy Compounding questions were asked of management and an inspectional tour of the facility was made to determine the firm's operations and its adherence to USP 797 and the Food Drug and Cosmetic Act and Compliance Policy Guide Section 460.200 Pharmacy Compounding.

The inspection revealed that the firm has made over (b) (4) Lots of products and (b) (4) batches of products of Admixtures for hospitals and packaged them into IV bags, syringes and vials since they opened in 2006. The articles the firm mainly orders for its operations are: sterile actives, diluents bags, and syringes for their compounding and manufacture of admixtures operations. Some packaging is also done in cassettes and vials to accommodate the instruments used in some hospitals. They have ordered (b) (4) different nonsterile powders which they reconstitute into large volume sterile stock solutions that are finished product tested and then used in Admixtures made for hospitals.

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No List of Observations was issued at the conclusion of the inspection; however, a discussion was held at which time I discussed the firms Formula Worksheets (batch records) and their content, SOPs, a reject bin containing labels, product validation and verification for the (b) (4) product processes, annual product stability studies, and annual product reviews.

ADMINISTRATIVE DATA

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

Dates of inspection: 12/7/2007, 12/10/2007
Days in the facility: 2
Participants: Richard H. Penta, Investigator

Credentials were shown and a Notice of Inspection (FDA482) presented to Mr. Gregory A. Conigliaro, General Manager and co-owner, on December 7, 2007 in the presence of two Board of Pharmacy Investigators, Sam Penta and Leo McKenna. Credentials were also shown to Ms. Sophia Pasedis, VP of Regulatory Affairs, Compliance and Auditing, at the same time. Both individuals accompanied us during our inspection of the facility. There was no List of Observations (FDA483) issued at the conclusion of the inspection.

HISTORY

The firm, a limited liability corporation, opened in July, 2007 and drug registered with USFDA, stamped July 13, 2006, as repacker and other of sterile and nonsterile mixtures and Admixtures. The firm reregistered June 15, 2007. The firm was told to get a State of Mass Drug Manufacturers registration which it did dated June 6, 2007 (See Exhibit#13 Photo#1). The firm is also registered in Massachusetts as a retail pharmacy (See Exhibit#13 Photo#2), and has DEA Licenses as a manufacturer and retail pharmacy for controlled substances (See Exhibit#13 - Photos#3 & 4). Mr. Barry J. Cadden R. Ph., Director and Manager of the LLC, and Mr. Gregory Conigliaro, General Manager, and Manager of the LLC are listed on the drug registration under "owners, partners or officers". The firm has applied in all 50 states, and accepted in (b) (4) to date for licenses to operate as a

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pharmacist or distributor of drugs in the states. Approximately (b) (4) of their business is outside of Massachusetts solely to hospitals. The firm's hours of operation are from (b) (4) (b) (4). The firm currently has (b) (4) employees. The firm employees in production and shipping are in the following positions: Pharmacists, Regulatory Technicians, Material Handlers, Labelers, and I.V. Technicians. Firm management arrives around 9:00 am.

Any correspondence can be addressed to Mr. Gregory Conigliaro, General Manager, at this address.

INTERSTATE COMMERCE.

The firm ships (b) (4) of their products outside of Massachusetts. All of their products are shipped to hospitals that order them. The Lots manufactured are specifically for the order requested by the hospital. The batches manufactured (b) (4)

(b) (4) None of these products are made on order of a prescription. The firm is drug registered as a manufacturer with the state of Massachusetts.

JURISDICTION

The firm receives both sterile and nonsterile powders and active ingredients (b) (4) (b) (4) for use in the manufacture of the Admixtures requested by their customers (See Exhibit#1). The firm produces Lots of product (b) (4) products to date) based on each order request (See Exhibit#2). They have NDC numbers identifying and representing each product and container size requested. The firm also manufactures batches (b) (4) products to date) of product based on multiple order requests from different hospitals for the same product and container closure system (See Exhibit#3). (b) (4) ships product like Oxytocin 20 units Lot#12062007@8 via (b) (4) to places like (b) (4)

(b) (4) See Exhibit#13 Photos 5-7). The firm has a written agreement with all the Boards of Pharmacy or Manufacturing License from those states that require licenses for distributions within.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

The following individuals were met during the inspection and provided us with information and possibly documents for review during this inspection:

Gregory Conigliaro, General Manager and Manager of the LLC, was presented with the Notice of inspection. He stated that he was one of the two co-owners of the business. Ms. Pasedis stated that she reports to him. He accompanied us during the entire inspection of the facility, provided documents and answered questions presented.

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Sophia Pasedis, VP of Regulatory Affairs, Compliance and Auditing, oversees the operations and ensures that all aspects are following the firm's SOPs and regulatory requirements. She accompanied us during the entire inspection, provided us with documents and answered many of the questions presented.

Vira Ajgaomkar, Narcotics Pharmacist, oversees all the Narcotics that are stored and dispensed at the firm. We meet her outside the Narcotics vault to which she provided us access for inspection of the items stored within.

Ryan O'Neill, Director of Pharmacy, oversees all the pharmacists that work in production and the packaging and shipping area.

Seth Traub, Director of Operations, according to Ms. Pasedis, oversees the entire processing, packaging and shipping operations at the facility. It was Mr. Traub who provided the inventory sheets that had the two labels of Oxytocin that an entry on the batch record stated that they were missing.

Melanie Cerullo, Director of Quality, reports to Ms Pasedis and oversees the training of the workers and also audits the entire operations of the facility.

FIRM'S TRAINING PROGRAM

The firm has a training program which requires drug GMP training both initially and as refresher courses. There was ongoing training being given by Melanie Cerullo, Director of Quality, while we were at the facility. Ms. Pasedis stated that the firm personnel are hired for the following positions for which they are in house trained: Pharmacists, Regulatory Technicians, Material handlers, Labelers, and I.V. Technicians

MANUFACTURING/OPERATIONS

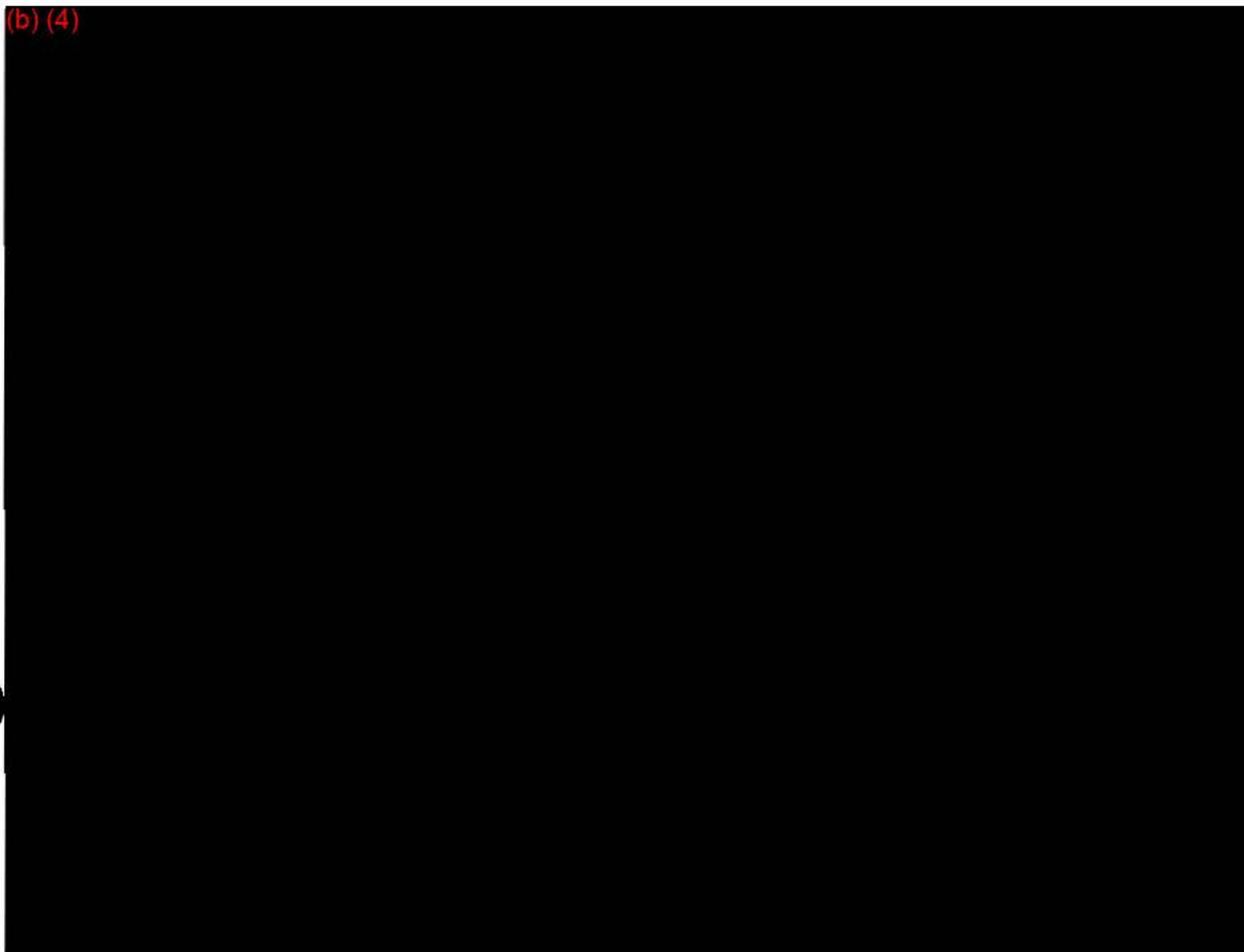
The firm is located in a former paper mill and furniture store that has been converted into a facility that can handle both Class II (Narcotic) and Class VI (Prescription) drugs. The firm warehouses Active Ingredients and finished drug products, bags from (b) (4) and also Admixtures made of known ingredients and held for sale to hospitals for patient use. The firm has an area qualified for the sterile handling, including hoods that meet ISO 5 (Class 100) standards. There is an open warehouse area for the storage of both quarantined and passed incoming goods (See Exhibit#13 Photo 18). The equipment and incoming goods are brought through a breakdown (freight) area (ISO 9) and brought into a middle room (ISO 8). Personnel enter from the other side through a gowning room (ISO 9) where they wash up and gown up prior to entry into the middle room and main, clean room, suite (ISO

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7). There are (b) (4) individual hoods (ISO 5) and (b) (4) banks of (b) (4) hoods (ISO 5) in the clean room area (See Exhibit#4) (See Exhibit#13 Photos 8 – 13).



Environmental Monitoring Action/Alert Levels for these ISO5 (Class 100) to ISO 9 (Class 1M) areas were provided. There were different Lots of product, including Fentanyl, being manufactured in the various hoods located within the clean room area (See Exhibit#13 Photo 14). The pressure differential between the four areas is monitored 24/7 with (b) (4) (See Exhibit#13 Photo 15) and checked by the firm (b) (4). The firm has an outside contractor, (b) (4) maintain and certify their clean rooms and hoods (See Exhibit#5).

An inspection of the firm's vault where Scheduled drugs are stored and inventoried was done. An Inventory is done every (b) (4) days. The operations are overseen by Vira Ajgaomkar, Narcotics Pharmacist. Both the bulk and finished products that are Class II to V are maintained inside this vault, including expired products (See Exhibit#13 Photos 16 & 17).

An inspection of the packaging and shipping area found Fentanyl being packaged and Oxytocin being picked and made ready for shipment. These activities were being overseen

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by Pharmacists to ensure that the proper orders were being filled (**See Exhibit#13 Photos 5,6,19 and 20**). The firm considers themselves as an extension of a hospital pharmacy in that they are filling orders from hospitals that do not have the capacity to make these Admixtures in house. There were (b) (4) bags (12/cs) Oxytocin 20 in Dextrose 5% and Lactated Ringers Batch# 12062007@8 EXP 1/17/2007 on the shipping floor awaiting picking for shipment to different hospitals. This was made for shipment to multiple hospitals. The firm ships its products mainly through (b) (4). Every box shipped has a packaging slip within but no package inserts. An inspection of the area found a reject bin unmarked next to where the products are verified prior to sealing into cases. These labels were awaiting collection and destruction. There was no log to record the destruction of the unused labels. I discussed with Ms Pasedis the need to have a label log documenting the disposition of these labels. She stated that they would look into getting rid of the bin and having a shredder in this shipping area so that labels could be shredded where necessary after being reconciled.

An inspectional review of one Batch of Oxytocin added to Dextrose 5% and Lactated Ringers Solution 20 units/ 1000ml Injection bag Lot#12062007@8 with a 42 day Beyond Use Date (BUD) of January 17, 2007 (**See Exhibit#6**). We discussed the Master Production Record for this batch and how all their Admixtures are a form of production using known ingredients and instructions for preparation and Admixing. All the Devices (Equipment) used for this product are listed, and the missing labels (471,472 & 473) were located on the Inventory record, and backroom Inventory sheet. The lot was made with a bulk stock solution of Oxytocin in Sterile water for Injection (SWFI) 10 units/ml 1000ml stock solution made 11/15/2007 Lot#11092007@51 with an Beyond Use Date (BUD) of April 13, 2008 (150 days after compounding) (**See Exhibit#7**). The Devices (Equipment) List in the lot and/or batch record does not list the Carboy used in producing this stock solution used to make multiple batches of other products requested by the Hospitals. To date (b) (4) lots of Oxytocin Admixtures were manufactured and (b) (4) of stock solution from an initial lot of (b) (4) was still available for use (**See Exhibit#7**). The firm uses up to 120 days as a BUD from time of manufacture. Oxytocin 20 Lot 11302007@7 has a BUD of 1/11/2008 (42 days).

COMPOUNDING PHARMACY QUESTIONS

- 1) **According to the Board of Pharmacy, does the pharmacy operate in conformance with applicable state law regulating the practice of pharmacy?**

The firm is registered as a retail pharmacy and is also registered with the State of Massachusetts as a Manufacturer of Drugs (**See Exhibit#13 Photos 2 and 1** respectively). The firm is not currently set up to act as a retail pharmacy; however, they see that as an option in the future and are maintaining their retail Pharmacy License.

- 2) **Is the pharmacy licensed in other states? Is the pharmacy distributing compounded products out of state? If so, to what states and how many**

prescriptions per year does it mail or distribute outside of the state?

The firm has submitted for certification in all 50 states and currently has the licenses needed to operate in (b) (4) of the 50 states. These licenses vary from pharmacy, distributors, and control substances licenses. They ship the products produced on orders to only hospitals. None of these shipments are under the order of a prescription.

3) What is the pharmacy's annual revenue? What is its annual revenue from compounded products?

Management stated that the firm currently does less than (b) (4). This is all on compounded products sold solely to hospitals. These are mostly Admixtures in bags of 100, 250, 500, and 1000 ml with less than (b) (4) processed in vials and syringes.

4) Are written prescriptions/physician orders for identified individual patients received before dispensing compounded injectable products each time they are dispensed? If not, what is the volume (e.g., number of doses) distributed per year without prescriptions/physician orders?

The firm does not deal with written prescriptions. The handling of prescriptions and patient information is done at each individual hospital. The firm distributes (b) (4) units per year. This includes the (b) (4) product lots and (b) (4) product batches manufactured to date. The average number of units sold in 2007 (Jan. to Nov) daily is (b) (4).

5) Does the pharmacy compound drug products in anticipation of receiving prescriptions? If so, what drugs does the pharmacy compound in anticipation of receiving prescriptions, and in what volume (e.g., number of doses) per year?

The firm manufactures lots of product which are the size of the order received from (b) (4). (b) (4) When it is noted that there are multiple orders for the same product (all of which are identified with a distinct NDC number) from different hospitals, the firm makes a Batch of the product and then distributes the tested and released batch according to the individual orders received from each hospital. It is the hospital that determines how many units it needs for their patients. It is the hospital pharmacies that handle the prescriptions at their locations.

6) What is the volume of the pharmacy's compounding? How many different compounded products does it produce? How many doses of each product does it compound on a daily and annual basis? How many total prescriptions for all compounded products does the pharmacy annually dispense?

The firm in January to November 2007 distributed (b) (4) different product strength product lots and (b) (4) different strength product batches (See

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Exhibits#2 & 3). There are approximately (b) (4) different products processed. A review of this list reveals that the products with the most strengths and combinations are Hydromorphone, Magnesium Sulfate and Oxytocin followed by Fentanyl, Fentanyl/Bupivacaine, and Morphine. The average daily rate is (b) (4) units, which is (b) (4) units for 11 months of the year 2007. The firm does not at this time see individuals or any prescriptions.

7) How many prescriptions for compounded products does the pharmacy annually dispense? What dosage forms, strengths, and quantities of the products does the pharmacy compound?

The firm dispenses no products under a prescription because it is operating on an annual drug registration license with the state of Massachusetts issued June 7, 2007 as a manufacturer, and as a repacker and other of Admixtures both sterile and nonsterile under its USFDA drug registration stamped 15 JUN 2007. Ms Pasedis stated that the firm was told by personnel in CDER to register as a repacker and other of admixtures.

8) Does the pharmacy compound copies or essentially copies of commercially available FDA-approved drug products (i.e., products that have the same active ingredient, dosage form, and strength)? If so, which commercially available drugs are being copied, and in what amounts (e.g., number of prescriptions per year)? Please obtain formulation information that will enable us to compare the compounded product formulations to FDA-approved formulations.

A review of the Lot and Batch product lists (**Exhibits# 2 and 3**) was made at the office and compared to two commercial lists of I.V. Solution products available through the Internet from two pharmaceutical manufacturers. Only one product from two sources was found to be commercially available from my brief review. The product is #552 Potassium Chloride 20mEq in 1000ml 0.45% Sodium Chloride Hospira bag NDC# 24200-035-16, which appears to be the same as Baxter Deerfield, IL Product#2B1357X 20 mEq/L Potassium Chloride in 0.45% Sodium Chloride Injection, USP in a 1000mL VIAFLEX Plastic Container and NDC#0338070434 (**See Exhibit#16**). It was also found in the B. Braun Medical Bethlehem, PA product listing REF no. L8650 and NDC 0264-7865-00 (**See Exhibit#18**). The compounded formulation for Ameridose product 552 is Potassium Chloride 20mEq in 1000ml 0.45% Sodium Chloride Hospira Bag (**See Exhibit#3**).

9) In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a product that is only slightly different than a commercially available FDA-approved product (such as by removing a preservative or coloring agent for an individual patient with an allergy). In these circumstances, does the pharmacy have documentation from the health care practitioner that demonstrates the medical need for the particular variation of the compounded product for each individual patient?

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There were no products noted that solely removed allergenic aspects of a product. The firm does formulate different product strengths for products commercially available. Examples are product strengths for Ondansetron in 50ml 0.9% Sodium Chloride at 4, 8, 16, and 20 mg, which are products 494, 496, 490, and 492 respectively (See Exhibit#3). The commercial Baxter product is 32 mg per 50ml (See Exhibit#17).

There were no products observed on the firm list (See Exhibit#2 or3) that made minor or slight changes in the drugs available commercially.

10) Does the pharmacy compound any products that have been withdrawn or removed from the market for safety reasons? If so, please obtain documentation showing the types and amounts of compounded drugs.

The firm has removed none of its processed drugs from the market. They do have a recall procedure in place to follow, if needed. None of the drugs compounded are the same as those on the list of withdrawn drugs listed in the Compliance Policy Guide Section 460.200.

11) Is the pharmacy offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale? If so, please obtain documentation showing the types and amounts of compounded drugs.

NO. The facility manufactures products solely on an order request from the hospital.

12) Please describe/document the processes used to make the compounded products including the scale of production and any in-process controls. Does the firm adhere to its standard operating procedures concerning labeling, environmental testing, and product quality? What quantity of compounded products is on hand for sampling?

The firm receives both sterile and nonsterile active pharmaceutical ingredients and finished product actives which it uses in making its Admixtures. The firm receives nonsterile actives noted by an * in Exhibit#1. These actives are reconstituted into stock solutions like Oxytocin in Sterile Water for Injection 10 units/ml 1000 ml bags of stock solution consisting of (b)(4) of Lot#11092007@51 (See Exhibit#7). One uses a sterile cup, weigh cup and carboy in the production process of this stock solution. Potency, endotoxin and sterility tests are done on the stock solutions and results approved prior to use in the finished product Admixtures. I discussed with Ms. Pasedis that the Master and Batch/Lot records were missing under "Devices" (Equipment) the Carboy used to mix and process the stock solution of Oxytocin.

The firm also manufactures lots and batches of admixtures for hospitals who order small quantities for use at their hospitals. An example of a Batch production for multiple hospital orders received is Oxytocin added to D5LR 20 units/1000 ml injection bags Lot# 12062007@8 for (b)(4) bags (See Exhibit#6 & 13 Photo#5 & 6). The firm

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brings the received approved active in liquid or powder form along with the needed equipment (b) (4)

(b) (4) through the middle ISO 8 Room into the Class 10,000 (ISO 7) Clean room where people are fully clothed in protective garb ("bunny suits"). The process is conducted under a Hood that is ISO 5 (Class 100) Certified. The hood is not listed in the batch history record as a piece of equipment used in the process. The product is sampled and tested for sterility. The product is shipped, in some cases on the same day it is admixed.

The firm provided me with their labeling SOP No. 5.040 version 2 dated 12/7/07 and effective 12/9/07 (See Exhibit#8). This was a merge of the labeling and repackaging SOPs into one SOP. The firm's employees are expected to follow this labeling SOP. The firm in this lot stated that two labels were "missing". These labels were found by the Director of Operations attached to the Inventory List and the on the Inventory record, and backroom Inventory sheet. The firm does try to account for all labels printed for use in production. The firm has environmental SOP's, and I reviewed data on the testing and classification of clean rooms and the hoods within. Ms. Pasedis stated that she audits the Narcotics room (b) (4). She is the one that oversees the Quality Assurance for the operations. We discussed the need for her workers to be trained and to follow the SOPs in place.

The firm has a small inventory of Batched products in the shipping/freight area, some of which are awaiting clearance for shipment; otherwise, only the reserve and stability samples are available for sampling and testing.

13) Does a quality assurance program exist? How does it monitor the facilities, equipment, and personnel to assure proper performance? What does the QA program do with a finding that does not meet specification?

The firm has a quality assurance program that Ms. Pasedis manages. She oversees the quality of the operations in both the pharmacy compounding/repacking and clean room Admixing and repackaging operations. The firm solely handles liquid preparations. They have (b) (4) however, she stated they would be (b) (4) (See Exhibit#13 Photo 21). The firm has written procedures in place to address what quality control procedures need to be followed and how to react to and handle both laboratory errors, through OOS Deviation procedures, and production/packaging and shipping errors, through Method deviation procedures. The firm also has both a complaint and Adverse Drug Reaction (Experience) procedures to follow regarding any issues brought to their attention by others. They have received complaints; however, none were adverse drug experiences.

14) Does the pharmacy have in place a system for handling patient complaints and adverse events? If yes, please describe the system. What complaints and adverse events are in this system? What complaints and adverse events

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associated with compounded injectable products are in the system?

The firm has in place a SOP#9.110 dated 12/7/07 Consumer Complaint (See Exhibit#9), and SOP#9.080 dated 7/17/06 Adverse Drug Reporting (See Exhibit#10), which were provided. The firm procedure is to fill out Attachment II Customer Complaint Record and get the report(s) to the Director of Quality immediately, so that he can determine if an investigation is needed. QA also determines if CDER needs to be notified due to the nature of the adverse event reported. A timely investigation is expected to be made when necessary. Ms Pasedis provided me with the number of complaints and their paperwork for the past 6 weeks. Seven complaints were received in this period and they were all about people not having enough units in their requested shipments, and one wrong product (identified by the unique NDC number) being received. There were no adverse events noted in this period. The firm also has a recall procedure to follow when needed.

15) How does the firm receive, generate, use, and examine labels and labeling to assure that they are accurate, complete, and suitable for use?

The firm follows its SOP#5.040 Version 2 dated 12/7/07 Product Labeling. All labels are printed from a master for each NDC numbered product located on a computer program that has limited access. Melanie Cerullo, Director of Quality, oversees label production and distribution. Brian O'Neill, Director of Pharmacy, and Leah Jarkko coordinate the labeling for the production area. Three ring binders showing all the labels are made available to workers while they are working to ensure that the proper and current version of labels are being used. The printed labels are placed into a plastic sleeve identified with the Lot or batch number and sent to the Clean room area. Labels are reconciled on the production floor and packaging and shipping area. All labels are accounted for and those not needed are destroyed. I discussed with Ms Pasedis the need to document the destruction of any unused preprinted labels, including those found in the reject bin located in the packaging and shipping area. The firm will develop a log sheet to document the destruction of those labels not used after they are counted and reconciled.

16) What labels and labeling are provided by the pharmacy to accompany the compounded products when it is dispensed to each patient? Please obtain copies of any and all labels, labeling, and other materials associated with dispensed compounded products.

Ms. Pasedis stated that there are no package inserts that are placed in the shipping cartons with the units of product packaged and sealed for shipment to their customers (hospitals). She stated that administrative directions can be located in pharmaceutical publications like Facts and Comparisons, to which the hospital pharmacists should have access. Administration of these admixtures is normally a common practice in these hospitals. Only the Unit label and the label on the

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shipping carton of schedule VI drugs only, along with the packing slip that accompanies the product during shipment.

17) What are the specific batch sizes that are prepared for each product and how often is each batch prepared?

The firm has a separate NDC number for every one of the (b) (4) Lots and (b) (4) batches that they have produced to date. The size of the lot is equal to the order from one customer. These are all IV Admixtures in bags, syringes, cassettes and vials. The batches produced are a combination of orders for one product from multiple hospital customers. The firm normally produces individual lots of product; however, batches for multiple hospitals are produced as determined by personnel at the firm receiving the daily orders. After production they are counted, packaged and shipped in the quantities ordered by the individual hospitals. Again these are all Admixtures where an active is added to a bag, syringe, cassette or vial that was pre-filled with a solution, i.e. 5% Dextrose, SWFI, 0.9% Sodium Chloride. The sizes of the lots and batches vary according to the orders placed.

18) Does the pharmacy compound drug products from bulk drug substances/active pharmaceutical ingredients (APIs) that are not components of FDA-approved products? If so, what are the bulk drug substances/APIs and what is the volume of drugs (e.g., number of doses or prescriptions per year) compounded from the bulk drug substances/APIs?

No. All products received are from known sources (See Exhibit#14) and are known actives with Certificates of Analysis attached to the shipments when received. The C of As are reviewed and the products are identified for release and use.

19) What are the names and addresses of the suppliers of the bulk drug substances/APIs used to compound products?

The firm has received over (b) (4) active ingredients, including (b) (4) non sterile actives from (b) (4) different vendors (See Exhibit#1). The (b) (4) vendors were provided by Mr. Greg Conigliaro, General Manager, (See Exhibit#14) and are as follows:

(b) (4)

20) Are these bulk drug substances/APIs manufactured in FDA registered establishments? How does the firm assure the accuracy and quality of the bulk drug substances/APIs and are they guaranteed or otherwise determined to meet official compendia requirements? Is this verified, and if so, how?

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The firm obtains a Certificate of Analysis for every product that they receive from the firm supplying the product. These products are identified prior to accepting the shipment of the product into the approved portion of the warehouse area. The firm uses a product verification sheet when identifying the received product. The personnel only organoleptically inspect the incoming product. When asked, and explained to me by management, there is no firm procedure in place to verify periodically by chemical testing the results stated on the Certificates of Analysis received on the incoming active pharmaceutical ingredient (API) products.

21) Is the compounding area in the facility designed to prevent contamination or cross-contamination of products and to avoid unnecessary traffic and airflow disturbances? Are drug products and supplies stored under appropriate temperature, light, moisture, sanitation, and ventilation conditions? Is routine environmental monitoring and documentation performed to prove that the compounding environment is properly maintained?

The firm has a clean room area that is ISO certified. The peoples gowning room and freight room are ISO 9, the middle room ISO 8, and the clean room ISO 7 (Class 10,000). The hoods used are ISO 5 (Class 100) certified. The air is monitored and (b) (4) are on an outside wall in the open corridor where one can check the pressure differential. The personnel inside the clean room area are all gowned from head to foot. The products observed were all stored at their expected range of room temperature.

The firm performs (b) (4) pressure, temperature and humidity checks on the environment inside the clean room area including sampling for microbial testing. There is also a (b) (4) check of the personnel entering the area. A review of the last three weeks of environmental data was made during this inspection and found adequate.

22) Does the pharmacy use industrial scale manufacturing equipments? If so, please identify these equipments.

The firm does not use any large scale manufacturing equipment in the production of their products. All production steps are done under hoods (b) (4) (b) (4)

23) Are equipments maintained, calibrated, serviced, cleaned, and monitored to assure that they are operating properly and within acceptable tolerance limits (e.g., water system, HVAC, autoclaves, filling equipment, scales/balances, etc)? Are cleaned equipments and utensils protected from contamination

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prior to use?

The firm has an active maintenance and calibration program for the instruments and hoods that they use in the production of these admixtures. Their Air handling system has (b) (4) air exchanges/minute and the firm has procedures to follow for maintaining the calibration and maintenance of the equipment, instruments and air exchange units in the rooms and hoods.

24) Are sterile products made in an environment that prevents contamination? Is this environment properly maintained? If the company compounds sterile products from non-sterile starting materials, what methods of sterilization are employed by the facility?

Yes. The environment is properly maintained. A review of some of the airflow and filter calibration and testing was reviewed and found to be adequate (see Exhibit#5). The firm uses (b) (4) (b) (4) that are used in creating these admixtures. The Lot record (See Exhibit#6) and the batch record (See Exhibit#7) describe the equipment used in the making of these admixtures.

25) Do the mixing instructions on formula worksheets include the order of mixing, diluting, or manipulating the raw materials used to make the compounded products? What type of in-process or finished product testing is performed and at what frequency?

The formula worksheets have a step by step procedure to be followed and signed off, along with the calibration of the pump used in the hood during mixing (See Exhibits #6 and 7). The firm performs potency/purity, endotoxin and sterility testing for each lot or batch of stock solution or finished product produced. The firm has (b) (4) outside laboratories that conduct chemical testing for them. They are (b) (4) (b) (4) (See Exhibit#12). The firm does its own in house testing of all environmental and microbiological testing. They also conduct the filter integrity sterility tests in house.

26) Are production personnel adequately trained to manipulate sterile products to reduce the potential for contamination? Are the movement of people, materials, and equipment minimized so as not to compromise the aseptic conditions in the class 100 area? Does the firm perform media fill runs?

The firm has a training program. While at the firm Ms. Melanie Cerullo, who also oversees the issuance of labels, provided a cGMP refresher course to some of the employees at the facility. Ms. Pasedis stated that the firm is continually providing training to its employees throughout the year. The flow of materials and personnel in and out of the clean room and its adjacent rooms were observed. The actual admixing is done under a laminar flow hood, Class 100, and aseptic conditions in the

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room and with the process is maintained. There are no media runs done as the ingredients used are in sterile containers and being transferred directly into sterile containers during the process.

27) How are the packaging materials chosen to prevent any type of physical or chemical interaction with the drug product? Do packaging materials preserve the sterility and strength of the finished preparation until it is administered?

The container closure systems used are received both empty (bags, vials and syringes) and bags with diluents within in a sterile state and not compromised during the admixing process. The firm does (b) (4) stability tests on their entire finished product stocks of actives. The firm uses from 14 to 120 days of expiry or end use dates for the admixtures made and the stock solutions made. The container closure systems have shown that the sterility of the product can be maintained.

28) How is the compounded products' beyond-use-date determined? Is it based on direct testing or extrapolation from reliable literature sources? Is there written justification to support the beyond-use-date?

The firm has SOP#9.050 Beyond-use Dating (BUD) of Sterile Products dated 7/17/06 (See Exhibit#11) that provides a procedure and timeline to perform stability testing from day one to the Beyond Use Date whether 30 or 160 days, and from the data determine a BUD to use on the product admixed. The firm places each lot of finished product from an active ingredient into the stability program. I discussed with Ms. Pasedis that the firm has to submit annually one lot of each active product for stability testing. It is from this stability testing that they confirm the BUD date to be placed on the container label. The firm maintains the stability data to support their BUD.

MANUFACTURING CODES

The firm uses a Lot/Batch numbering system that shows the month/day/year and (b) (4) (b) (4) i.e. 12062007@8.

COMPLAINTS

The firm has both a Customer Complaint (SOP#9.110 The Consumer Complaints dated 12/7/07- Exhibit#9) and Adverse Drug Reaction (SOP#9.080 Adverse Drug Reporting dated 7/3/06 – Exhibit#10) which they followed when reviewing comments received from customers. The firm received 7 complaints in the 6 weeks prior to my inspection which I reviewed. Most of the complaints were due to the wrong item or an insufficient quantity being delivered to the customer.

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RECALL PROCEDURES

Ms Pasedis stated that the firm has a recall procedure SOP 9.07 Sterile Recall dated 07/03/06. They have not had a recall to date.

REFUSALS

There were no refusals by management.

GENERAL DISCUSSION WITH MANAGEMENT

A general discussion about the firm's operations took place at the start of the inspection. The firm currently has three local licenses: Mass Board of Pharmacy, State of Massachusetts Drug Control, and USFDA drug registrations. They have also registered as required in (b) (4) of the 50 states with the other (b) (4) state registration requirements pending. The firm has no prescriptions or patient names as they work solely on orders from hospitals. They opened on July 13, 2006 and have had two DEA inspections since that date. This is the first inspection by USFDA and the first by the Massachusetts State Board of Pharmacy since it was opened for business. Investigators Sam Penta and Leo McKenna from the Mass. State Board of Pharmacy had an exit discussion on the first day, but left their investigation open.

An exit discussion was held between Investigator Richard Penta, U.S.F.D.A, and Ms. Sophia Pasedis V.P. of Regulatory Affairs and Compliance, and Gregory Conigliaro, General Manager on December 10, 2007. I discussed with them that they are manufacturing an active pharmaceutical solution for use in the compounding/manufacturing of admixtures when taking the sterile of nonsterile powder and manufacturing into a sterile stock solution. Ms. Pasedis stated that someone at CDER Admixtures is a subcategory of manufacturing and that she needed to drug register. I discussed with her the reject bin for labels in the packaging and shipping area and the need to account for the destruction of any labels after reconciliation of the labels for each batch. The master production and Batch history records need to list all equipment used in the production of their admixtures. This includes the hoods, pump and carboy used in production. I also discussed conformance and validation batches for the (b) (4) different product processes that they have and need to validate/verify. We also discussed the need to sample one lot of each product process per year to do the annual stability tests required as a manufacturer of drugs. We also discussed the need to do annual product reviews, verification and validation of the processes. The discussion included grouping the reviews by the active ingredient used in the product so that the product reviews were not on (b) (4) products but more on the approximately (b) (4) different single ingredient and combination products.

ATTACHMENTS

FDA482 Notice of Inspection dated 12/07/2007

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Attachments#1: FACTS Assgt# 843994 dated May 22, 2007 with Medwatch Complaint and confidential interview memo.

Attachment#2: e-mail correspondence on assignment

EXHIBITS COLLECTED

- Exhibit#1: List of Actives received for Production (2pgs)
- Exhibit#2: List of Batched Items produced (1 pg)
- Exhibit#3: List of Lot Items produced (9 pgs)
- Exhibit#4: Environmental Monitoring Clean room layout and specifications (2 pgs)
- Exhibit#5: Unidirectional flow (b) (4) reports 11/30/07 (7 pgs)
- Exhibit#6: Batch #12062007@8 Oxytocin added to D5LR 20 units/1000ml (7 pgs)
- Exhibit#7: Lot#11092007@51 Oxytocin in SWFI 10 units/ml 1000ml stock sol (10 pgs)
- Exhibit#8: SOP#5.040 dated DEC09 2007 Ver.2 Product Labeling (5pgs)
- Exhibit#9: SOP#9.110 dated DEC13 2007 Ver.1 Customer Complaints (8 pgs)
- Exhibit#10: SOP# 9.080 dated 7/17/06 Ver.1 Adverse Drug Reporting (5 pgs)
- Exhibit#11: SOP#9.050 dated 7/16/06 Ver.1 Beyond Use Dating (BUD) of Sterile products (3 pgs)
- Exhibit#12: List of (b) (4) Analytical Labs (1 pg)
- Exhibit#13: Photos of Facility Used (21 photos)
- Exhibit#14: Sealed Envelope with CD of pictures taken during inspection by State Board of Pharmacy.
- Exhibit#15: List of suppliers of Active Pharmaceutical Ingredients (2pgs)
- Exhibit#16: Baxter 20 mEq/L Potassium Chloride in 0.45% Sodium Chloride Injection, USP (1 pg)
- Exhibit#17: Baxter Ondansetron Injection USP in 50ml of Sodium Chloride diluent 32 mg/50 ml (1 pg)
- Exhibit#18: B. Braun Medical 20mEq K+/liter Potassium Chloride in 0.9% Sodium Chloride Injection (3 pgs)


Richard H. Penta, Investigator