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SUMMARY

The inspection of this human drug manufacturer was assigned as part of the KAN-DO workplans and identified as a FY12 Performance Goal (WAID No.1325377). The inspection of this high-risk pharmaceutical manufacturer was conducted according to Compliance Program (CP) 7356.002, Drug Manufacturing Inspections. The current inspection covered the aseptic processing facility (referred to as Brentwood – FEI 1950222) and the packaging, inspection and labeling facility (referred to as Westport – 1937280) concurrently. Both inspections will be covered under one establishment inspection report (EIR) including all exhibits obtained during the inspection of both sites referenced under the Brentwood facility - FEI 1950222 where the inspection was initiated. Most of the firm's documents are stored at the Westport site.

The previous inspection of the Brentwood facility, conducted 5/9-12/11, was a directed inspection to cover manufacturing operations for the firm's ATTNA (Mark I/Combo Pen Antidote Treatment Autoinjector Nerve Agent) Drug Product with emphasis on the needle used for delivery of this

product. There was no FDA 483, Inspectional Observations, issued. There were verbal concerns discussed at the conclusion of the inspection and the inspection was classified NAI.

Inspection of 8/9-18/10 covered the sterile manufacturing facility and the packaging, inspection and labeling facility (both Brentwood and Westport facilities). Observations found and included on a FDA 483, Inspectional Observations, were the following: a rust-like substance observed on the bottom of the stainless steel plate located across the top of the window in the class 100 area; improperly gowned employee working in the class 100 area; and written production and process control procedures are not followed in the execution of production and process control functions. The inspection was classified VAI. Corrective action were covered during the current inspection and found acceptable.

King Pharmaceuticals, Inc. was purchased by Pfizer in March of 2011. With this change the firm has a new name, Meridian Medical Technologies A Pfizer Company. The current inspection evaluated Quality, Production and Laboratory Control systems of CP 7356.002. Packaging and Labeling, Materials, Facilities and Equipment systems received limited coverage. The firm continues to manufacture sterile injectables including EpiPen and injectable nerve gas antidotes for the Department of Homeland Security and the Department of Defense.

At the conclusion of the inspection a four-item FDA 483 was issued. Observations include seven examples where the firm did not follow procedures in the execution of production and process control functions and documented at the time of performance including actual times not recorded but theoretical times recorded for a validated (b) (4) minute hold time. A (b) (4) start time and theoretical end time of (b) (4) was documented by an employee who exited the aseptic area at (b) (4) and did not return that day. There were several examples of poor aseptic practices, four of (b) (4) employees were observed to not follow the gowning procedure, and cleaning of a Class 100 Room (b) (4) did not include cleaning of the [redacted] (b) (4) The firm does not have microbial alert and action levels established to initiate investigations of environmental monitoring results based on historical environmental monitoring sampling data. The firm's media fill procedure is inadequate to qualify personnel in that (b) (4) operators were qualified during a media fill without any documentation they performed any filling event. No documentation of which incubator is used to store environmental monitoring plates; there are (b) (4) incubators for (b) (4) degrees C and (b) (4) for (b) (4) degrees C. In addition times when environmental monitoring microbial plates are placed into the incubator are not documented. The firm does not document times of a validated soak time for washing of needles. Several verbal concerns were also discussed at the conclusion. Management stated they plan to respond to the FDA 483 within 15 working days.

Inspectional coverage focused on EpiPen® and AtroPen® products. On 02/6/12 the inspection of the Westport facilities was initiated. No deficiencies were noted relating to the packaging and labeling operations at the Westport facility.

Documentary sample no. DOC 730681 was collected to document the movement in interstate commerce of Atropine, USP, Lot no. (b) (4) used as the main component in the AtroPen Auto-Injector, Lot no. 1PT716 and distributed into interstate commerce. An FDA 463a, Affidavit, was prepared for interstate documentation for Clint R. Lawson, Senior Director Quality. Mr. Lawson refused to read or sign per corporate policy.

The firm was reminded of its responsibilities under the FD&C Act and sanctions available to the FDA for non-compliance were outlined for them.

ADMINISTRATIVE DATA

Inspected firm:	Meridian Medical Technologies a Pfizer Company
Location:	2555 Hermelin Dr Brentwood, MO 63144-2504
Phone:	314-236-4200
FAX:	314-236-4201
Mailing address:	2555 Hermelin Dr Brentwood, MO 63144-2504
Dates of inspection:	1/30/2012, 1/31/2012, 2/1/2012, 2/2/2012, 2/3/2012, 2/8/2012, 2/13/2012
Days in the facility:	7
Participants:	Shirley J. Berryman, Investigator Sandra A. Hughes, Investigator Justin A. Boyd, Investigator Matthew H. Hunt, Investigator

On 1/30/2012 we (Investigators Berryman, Hughes, Boyd, & Hunt) presented our credentials and FDA 482, Notice of Inspection, was issued at the Brentwood facility to Clint R. Lawson, Senior Director Quality. Investigators Boyd and Hughes were present 1/30-2/3/2012. I, Investigator Berryman, was present at this site 1/30-2/3/2012 & 2/13/2012. Investigator Hunt was present 1/30-2/3/2012, 2/9/2012 & 2/13/2012.

On 2/6/2012 we (Investigator Berryman & Hunt) presented our credentials and FDA 482 was issued to Stephen C. Natsch, Vice President and General Manager at the Westport facility. I, CSO Berryman, was present 2/6-9/2012 and CSO Hunt was present 2/6-9/2012 & 2/13/2012.

On 2/13/2012 FDA 483, Inspectional Observations was issued to Stephen C. Natsch, Vice President and General Manager at the Brentwood facility.

A FDA 463a, Affidavit, was prepared but Clint R. Lawson, Senior Director Quality refused to review or sign the Affidavit per corporate policy.

FDA 483 items 1.A, 1.B, 1.C, 2.A, 2.B, 2.C, 3 and Verbal items 1 & 2 were written by Investigator Boyd. FDA 483 items 1.D, 1.E, 1.F, 2.F, 4 and Verbal item 3 were written by Investigator Hughes. FDA 483 item 1.G. was written by Investigator Hunt. Item 2.D, 2.E and Verbal item 4 were written by me, Investigator Berryman. Sections of this report are identified with the author's initials. Sections not identified were written by me, Investigator Berryman. Exhibits are identified by the investigators initials and sequential exhibit number.

HISTORY
(written by MHH)

The firm's history has mostly remained the same as listed in the 2010 established inspection. The only change was King Pharmaceuticals, Inc. was purchased by Pfizer, Inc. in March 2011 and was renamed Meridian Medical Technologies a Pfizer Company. The firm has an establishment size code of (b) (4) and has approximately (b) (4) employees. The firm is registered as a human drug manufacturer, at both the Brentwood and Westport sites. The sterile product manufacturing (SPM) facility located at the Brentwood site continues to operate (b) (4) (b) (4) with business hours 8:00am to 5:00pm. The Westport site, packaging operations for the EpiPen NGA product line operates (b) (4) . Packaging functions for all other products operate on a (b) (4) cycle.

The FMD-145 and all official correspondence should be addressed to Stephen C. Natsch, Vice President and General Manager, at 1945 Craig Rd., St. Louis, MO 63146.

INTERSTATE COMMERCE
(written by MHH)

The percentage of products shipped in interstate commerce, approximately (b) (4) %, has not changed since the 2010 establishment inspection. Domestic products continue to be shipped to the Department of Defense and to local emergency authorities associated with the Department of Homeland Security. EpiPen and Atropen (atropine sulfate) continue to be shipped internationally, as well as ATOX (obidoxime chloride/atropine sulfate) which is an exclusively international product. EpiPen NGA and EpiPen Jr. NGA (next-generation auto-injector) is currently only distributed in the U.S and Canada, while the firm is still waiting for approval to distribute the products to other countries.

The Mark I nerve agent antidote is a product manufactured by the firm, but was not covered during the current inspection. (b) (5)
(b) (5)

JURISDICTION
(written by MHH)

The firm manufactures drug products used for treatment of anaphylaxis and antidotes to nerve gas. A list of the firm's top 5 current products, based on volume, can be viewed in **Exhibit MHH-1**. The list of firm's top 5 current products contains domestically and international distributed products. Approximately (b) (4) % of the business is EpiPens.

The products which are sold to the general public most often are the EpiPen, EpiPen NGA, and EpiPen Jr. NGA. The EpiPen NGA and EpiPen Jr. NGA are only sold in the United States and Canada. Nerve gas antidote products are sold to the US military and foreign military organizations.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

On 1/30/2012, prior to initiation of the inspection I called Stephen C. Natsch, Vice President & General Manager and left a message on his voice mail informing him of the initiation of the Brentwood inspection starting at approximately 9:00a.m. that morning. This was to allow time for key officials located at the Westport facility to travel to the Brentwood (manufacture) site. Upon arrival at the firm on 1/30/2012, credentials were presented (by Investigators Berryman, Boyd, Hughes & Hunt) and FDA 482 issued to Clint R. Lawson, Senior Director, Quality. Mr. Lawson has dual reporting to Mr. Natsch and to Allan Larsen, VP, Established Products QO, Pfizer New York Office.

On 2/6/2012 credentials were presented by Investigators Berryman & Hunt at the Westport facility and FDA 482 issued to Stephen C. Natsch, Vice President & General Manager. Mr. Natsch is the most responsible individual for both facilities and should received FMD-145 correspondence at the Westport address. Mr. Natsch was present 2/6/2012 through the end of the inspection. He reports to Dennis O'Brien, EVP, King President, Meridian Franchise. Mr. O'Brien reports to William C. Kennally III, Regional President, North America-EP in Peapack, New Jersey. I (SJB) was provided with organizational chart for this site reporting to the ultimate Pfizer authority. Copies of the organizational charts for Meridian Medical Technologies Franchise St. Louis Operations are attached as **Exhibit SJB-1**. Copies of the Pfizer Organization Charts reporting to Allan Larsen, is attached as **Exhibit SJB-2** and reporting to William C. Kennally, III are as **Exhibit SJB-3**. Official correspondence should be addressed to Ian C. Read, Pfizer Chairman & CEO who is located at 235 East 42nd Street, New York, NY 10017-5703.

The following individuals were key contacts who were present during the inspection, accompanied us on inspection of the facilities, provided various levels of information contained in this report and/or attended daily wrap-up meetings. The job description for some of the key individuals listed above can be located in **Exhibit MHH-2**.

- Stephen C. Natsch, Vice President & General Manager (Westport)
- Clint R. Lawson, Senior Director Quality
- Carolina Santangelo, Director Quality Assurance & Microbiological Services
- Daniel A. Jendrycki, Senior Director Operations
- Neal J. Nelson, CQA, MM, Manager, QA & Microbiological Services
- Kevin W. Sitts, Senior Manager for Sterile Products Manufacture
- Henry Slodkowski, Director, Validation
- Mike Rapisardo, Director of Engineering
- (b) (6), (b) (7)(C) Supervisor Microbiology Services
- Charles Coerver, Senior Manager, Quality Engineering & Statistical Quality Control (Westport)

Other individuals, who were interviewed, accompanied us on inspection of the facility and/or provided information during the current inspection included but are not limited to the following:

- (b) (6), (b) (7)(C) CQA, Quality Compliance Auditor (Westport)
- (b) (6), (b) (7)(C) Supervisor of Clean and Prep
- (b) (6), (b) (7)(C) Microbiologist II
- Jim Kallaos, Packaging Inspection Manager Westport
- (b) (6), (b) (7)(C) Warehouse Supervisor (both Brentwood and Westport)
- Mark Morse, Sr. Director, Logistics (Westport)
- (b) (6), (b) (7)(C) Supervisor QC Westport
- (b) (6), (b) (7)(C) Production Supervisor
- (b) (6), (b) (7)(C) Sr. Supervisor, Quality Assurance
- (b) (6), (b) (7)(C) Production Supervisor
- Joe Sulentic, Manager, Metrology provided information on the HEPA re-qualification.
- (b) (6), (b) (7)(C), Project Engineer II
- Glenn Walsh, Senior Manager, Engineering
- (b) (6), (b) (7)(C) Supervisor Raw Materials

FIRM'S TRAINING PROGRAM

(written by SAH)

Training is tracked using a database called (b) (4) I reviewed the training for (b) (6) – (b) (6) date of hire (b) (6) (b) (6) – (b) (6) date of hire (b) (6) and (b) (6) – (b) (6) date of hire (b) (6) for GMP and job related training. No discrepancies were noted.

MANUFACTURING/DESIGN OPERATIONS

(written by SJB)

The inspection started with a general walk-through of the process flow starting with the warehouse operations, at the Brentwood facilities, covering the receipt of components and raw materials and then to the aseptic processing area (APA) located within walking distance in an adjacent building. The Westport facility is the primary warehouse except for chemicals which are stored at the Brentwood facility. The microbiology and chemistry laboratories are also located within walking distance of the Brentwood warehouse on Litzinger Road and were also covered during the inspection. The stability chambers are located in the laboratory facility. The environmental monitoring testing laboratory entrance is located on the upper level of the APA building. The packaging and labeling operations were assessed separately from the general walk-through during the second week of the inspection by me (Investigator Berryman) and Investigator Hunt.

The inspection included coverage of several Memorandums to File of concerns observed during the St. Louis Office's field exam/record review of a government contract acceptance and signature of the DD Form 250. Review did not reveal any new concerns and no reoccurrences of the instances were noted during the inspection.

Quality System

Review of the Quality System included the following procedures and related documents: product reviews, complaints, discrepancies, out of specifications (OOS), change control, rejects, system to release raw materials, batch production records, reprocess/rework, recalls, validation, field alerts, supply agreement and training. Ms. Santangelo stated they have had no sterility failures, no false positives, and no endotoxin failures.

The firm has had one NDA-Field Alert Report (FAR) since the previous inspection. On 4/8/2011, MMT reported an OOS (b) (4) result in one of the (b) (4) units tested for EpiPen Autoinjector lot 9GN788 at the (b) (4) month stability testing point of a (b) (4) month shelf-life. The test results for the (b) (4) units were (b) (4) with a specification of NMT (b) (4) %. (b) (4) is formed by the reaction between (b) (4) that is added to EpiPen products as an antioxidant preservative. All other test results meet specifications. The investigation

included testing related batches and (b) (4) additional stability samples units of this batch and all were within specifications.

MMT filed an NDA supplement June 2, 2011 requesting the (b) (4) limit change from (b) (4)% to (b) (4)%. (b) (4) specification range is based upon the firm's history and not a reference specification. The firm has reviewed literature and has found no reports of (b) (4) toxicity or toxic pharmacological effect. I asked Mr. Lawson the status of the supplement. He provided a copy (**Exhibit SJB-33**) of the Approval Letter dated 11/7/2011. I also reviewed (b) (4) data since the FAR and did not observe any results over (b) (4)%.

I requested a list of products contained in the rejected controlled area of the warehouse. There were (b) (4) items and documentation appeared acceptable. The firm is in the processes of merging their SOPs with Pfizer SOPs. One objection was discussed at the conclusion of the inspection regarding the Quality System - verbal item 4.

(Written by SAH)
I reviewed the following procedures and various reports:

Notice of Events

SOP/Document #	Title	Dated
SOP-QLA-MQA-00720-SL	Notice of Event (NOE) and Cross Functional Investigations (CFI) Reports	Retired
SOP-QLA-MQA-00719-SL	Notice of Event (NOE)	01/03/12
NOE 11-02-011-SL	NOE report	02/15/11
NOE 11-11-008-SL	NOE report	11/08/11
NOE 11-11-011-SL	NOE report	11/18/11
NOE 11-12-008-SL	NOE report	12/13/11
NOE 11-12-016-SL	NOE report	12/16/11
NOE 11-12-019-SL	NOE report	12/21/11

I (SAH) found issues with the following investigations:

- NOE 11-11-008-SL concerns steam generator failures for all (b) (4) walk-in stability chambers ((b) (4) within an approximate three week period in November 2011, see **Exhibit SAH-1**. The investigation states, *"***Impact from the humidity and temperature excursions on the product quality for products stored in Stability chambers (b) (4) was evaluated and is considered minimal***"*. There is no discussion as to what was being stored in the chambers or why the excursions were considered minimal. I discussed the importance of capturing this information in the report with firm management.

- It was observed that the both the retired and the current NOE procedure states, *"***An NOE number should be requested within* [redacted] (b) (4) *from the date that the deviation*

*was found****", see **Exhibit SAH-2** and **SAH-3**. This did not happen during NOE 11-12-008-SL. This NOE report describes an event concerning the (b) (4) System. When an event occurs with the (b) (4) System, management is notified immediately. NOE 11-12-008-SL occurred on 12/01/11 but the report was initiated on 11/18/11, see **Exhibit SAH-4**. No explanation as to the delay was documented.

Laboratory Investigation of Out-of-Specification (OOS) Results

SOP/Document #	Title	Dated
SOP-QLA-MQA-00001-SL	Laboratory Investigation of Out-of-Specification (OOS) Results	09/01/11
LIR10-08-004-SL	LIR report	08/10/10
LIR11-10-002-SL	LIR report	10/06/11
LIR11-10-007-SL	LIR report	10/24/11
LIR11-11-005-SL	LIR report	11/14/11
LIR11-12-001-SL	LIR report	12/02/11

I (SAH) found issues with the following investigation:

- LIR-10-002-SL discusses an OOS result for (b) (4) during the running of test method SOP-LAB-RDL-00233-SL on a (b) (4) month stability sample for EpiPen batch 0EM101, see **Exhibit SAH-5**. The investigation concluded that the high OOS (b) (4) result for the EU specification was not caused by any laboratory error. The investigation does not discuss whether this product was originally distributed to the EU or to the US.

Miscellaneous Documents

SOP/Document #	Title	Dated
SOP-QLA-MQA-00718-SL	Deviation Reports	01/03/12
SOP-QLA-MQA-00720-SL	Quality Assurance Reports (QAR)	01/03/12
SOP-QLA-MQA-00721-SL	Good Practices for an Effective CAPA System	01/03/12

These documents were all recently issued so their efficacy was not determined.

(written by SJB)

I reviewed NOE 11-10-010-SL for Diazepam lots 1D1664 and 1D1665, NOE 11-12-013-SL for lot 1PT711 Atropen, NOE 11-11-017-SL for lot 1PT709 Atropen, NOE 11-11-012-SL for lot 1PT710 Atropen and CFI 11-11-002-SL relating to five DOD products: Atropen, ATNAA, Pralidoxime Chloride, Diazepam and Morphine. No concerns were noted.

Annual Product Reviews

(Written by MHH)

Annual product reviews are compiled for each product line. I reviewed the annual product reviews for EpiPen (12/09–11/10), Atropen (5/10–4/11), Diazepam (12/09–11/10), and ATNAA/DuoDote (1/10–12/10). The reviews included a listing of manufactured batches, manufacturing changes, validation change control documentation, agency-approved changes to the production processes, media fill summaries and conclusions, stability reports including a summary of stability data and master stability protocols, complaint analysis, ADE summaries, annual product reserve reviews, field alerts and recalls, environmental monitoring summaries for production areas and personnel, and qualifications/re-qualifications of equipment or component suppliers. No objections were found during the review of these annual product reviews.

Facilities and Equipment System

(Written by SAH)

I observed the Clean and Prep Room during the tour of the facilities on 01/30/12. I reviewed SOP-PRO-CLP-00050-SL – Preparation of (b) (4) Needles procedure, effective 05/21/10, see **Exhibit SAH-6**. This procedure specifies how all ATNAA and ATOX needles will be processed, including a submergence time for approximately (b) (4) minutes, with shaking every (b) (4) minutes to ensure all needles are saturated. Henry Slodkowski – Director of Validation confirmed that the validation of cleaning procedure SOP-PRO-CLP-00050-SL was conducted with a (b) (4) minute submergence time. This procedure references (b) (4) additional procedures prior to washing of the needles from cleaning of the sinks (SOP-PRO-CLP-00012-SL), changing filters (if needed) on the (b) (4) and sink (b) (4) (SOP-PRO-CLP-00026-SL and SOP-PRO-CLP-00027-SL), and prepping the (b) (4) (SOP-PRO-CLP-00014-SL). During the review of batch 1M1726, Multichambered Autoinjector 2.1mg Atropine/0.7 mL dose, 600mg Pralidoxime Chloride/2.0 mL dose, I noted that batch record states only to record the initials of the person who washed the needles per SOP-PRO-CLP-00050-SL, see **Exhibit SAH-7**. (b) (6), (b) (7)(C) – Supervisor of Clean and Prep confirmed that no times are documented for when the needles were washed and no other paperwork exists to document start and stop times of the submergence step. Not documenting this information at the time of performance was listed in **Observation 4** on the FDA-483, see OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE section for additional information on these issues.

I (SAH) reviewed SOP-LAB-ALM-00105-SL – Maintenance and Calibration of the (b) (4) (b) (4) Chromatography, effective 10/Nov/2011. No discrepancies were noted.

I (SAH) reviewed CRI Investigation #311 – Adding Time Delays for Pressures Report dated 11/18/03. This report established how long the doors of the controlled areas can be open and how long areas can be out of specifications before additional cleaning or monitoring should occur. I reviewed CRI Investigation #311 Addendum; dated 07/27/06, which addressed the addition of the (b) (4) system. I also reviewed the Facility Cleanroom Recovery Testing Services Final

Report, dated 04/25/11. This evaluation of the cleanrooms was performed by (b) (4) (b) (4) of (b) (4) This testing was accomplished during an "at rest" facility mode at the end of a routine facility shutdown period. Acceptability of the test data was determined by Meridian Medical.

HEPA Filters

(Written by JAB)

HEPA filters are recertified in house every (b) (4) months. Certification includes filter integrity testing with the (b) (4) HEPA filters can be repaired up to (b) (4) % of the surface area with a (b) (4) before they are replaced. Also performed is velocity testing at the filter face and work levels and particle counts. Uniformity of the class 100 areas is calculated with a specification of (b) (4) %. We reviewed the most recent HEPA certifications for rooms #(b) (4) (portion with the filling hood for the AtroPen fill line), #(b) (4), #(b) (4) and #(b) (4) No deficiencies were noted.

Smoke studies were viewed for the hood in room #(b) (4) where AtroPen is filled. This is a new process since the last inspection. We also viewed smoke studies for room #(b) (4) where aseptically assembly of the (b) (4) sheath and the (b) (4) occur. No deficiencies were noted in the smoke studies for either room.

Equipment Qualifications

(Written by MHH)

During the inspection, I reviewed the qualification for the (b) (4) Washer, which is used to wash the Atropen plastic cartridges, and was designed, manufactured, and assembled in (b) (4) I also reviewed QP 10-113, Performance Qualification of the (b) (4) (b) (4) Washing Increased Batch Size of AtroPen Plastic Cartridges. QP 10-113 increased the washing batch size of (b) (4) cartridges from a (b) (4) unit batch size to a (b) (4) unit batch size. No objections were found during the reviews.

While taken a tour of the Brentwood sterile product manufacturing process, the inspection team noticed, what appeared to be a, "dark mold like substance", inside or outside the plastic water vapor tube clamped to the top of the washer then to the ceiling. Water was also running down the tube into what appeared to be the washing area. Mr. Michael A. Rapisardo, Director, Engineering, stated there was a condensation drain that directs the water running down the tube into the facility site drain. Mr. Rapisardo showed the inspection team where the small condensation drain was located and stated the water running down the tube was not going into the washing area. I reviewed the specification drawings for the (b) (4) Washer, which showed the condensation drain, located inside the machine washing station and that the water passing through the condensation drain is direct to the facility regular site drain. Mr. Rapisardo stated the firm replaced the plastic water vapor tube, which appeared to have "dark mold like substance", with a new plastic water vapor tube and this was verified by the inspection team. He also stated he was going to update the maintenance procedures to include a (b) (4) inspection of the water vapor tube

since there was currently no maintenance schedule for the part. Investigator Hughes asked if the firm was going to analyze the substance to identify exactly what the substance was. (b) (5) (b) (5)

Materials System

Limited coverage was give to the Materials System. Vendor qualification for Glycerin was covered. See Additional Information section for objections noted with the Materials System.

(Written by SAH)

I reviewed SOP-MDP-GEN-00013-SL – In-process Product Transfer procedure. This procedure is applicable to in-process product transfers between departments, production centers and buildings. This procedure was not followed during the transfer of Atropine, batch (b) (4) from the Brentwood facility to the Westport facility; see **Observation 1** on the FDA-483 and OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE section for additional information on these issues.

(b) (4)

(Written by MHH)

During the inspection, the (b) (4) system, (b) (4) was reviewed. The (b) (4) room was located in the Brentwood sterile product manufacturing facility and consisted of (b) (4) generators and (b) (4) (b) (4). One person is always on shift in the (b) (4) room. The firm's (b) (4) system used (b) (4) for its (b) (4) A waterline connects (b) (4) to (b) (4), since (b) (4) is used to fill (b) (4) (b) (4) connects to the waterline that leads to the (b) (4) area and the (b) (4) area. The '(b) (4)' area and '(b) (4) area have a return waterline, which carries any excess water back to the (b) (4) room to be reused.

On the (b) (4) system, there are (b) (4) monitors, which monitor temperature and pressure, in varies locations. A monitor is located on (b) (4) A monitor is placed on the waterline from (b) (4) A monitor is located on both the waterline from (b) (4) (b) (4)' area and from (b) (4) area.

(Written by SAH)

I reviewed Dec. 2011 Water – (b) (4) Report. No discrepancies were noted. I also reviewed RQ 11-004 – Requalification of the Stability Chamber, Chamber (b) (4), dated 06/20/11, no discrepancies were noted.

Production System

The production system was covered through review of procedures, data, and observing employees. The areas we covered included: training, critical activities and operations, equipment identification, batch production records and equipment cleaning and use logs. The firm no longer performs manual fills in room (b) (4) They have qualified a hooded Class 100 area and several aspects of this were covered during the inspection. They plan to eventually remove the long section of hoods where the manual fills occurred in the past. During the inspection we observed manufacturing operations, cleaning/sanitization in room (b) (4) set-up in room (b) (4) for EpiPen Jr lot 2GK080, (b) (4) assembly, packaging of EpiPen Jr 2 Pak NGA and sterility testing. See list of manufacture/packaged schedule during the inspection attached as **Exhibit SJB-4**.

(Written by SAH)
I reviewed the following batch records:

2M1030	Multichambered Autoinjector 2.1mg Atropine/0.7 mL dose, 600mg Pralidoxime Chloride/2.0 mL dose
1M1726	Multichambered Autoinjector 2.1mg Atropine/0.7 mL dose, 600mg Pralidoxime Chloride/2.0 mL dose
1GH804	EpiPen with Carrier

2M1030 and 1M1726 batch records state to pull a sample of (b) (4) basic units and check for proper plunger placement per SOP-PRO-FIL-00109-SL. If the plunger depth is out of range, the batch record allows for a retest. If the retest is out of range, an operator would segregate to the last good test and perform 100% inspection. Only the final result of the rework inspection is documented on the observation sheet and not the raw data obtained from the 100% inspection. This rework is not reviewed or approved by the Quality Unit; see **Observation 1** on the FDA-483 and OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE section for additional information.

I observed that SOP-PRO-FIL-00001-SL - General Aseptic Procedure states, *"***EVENTS CAN OCCUR WHICH ARE NOT COVERED BY THE BATCH RECORD**IF PERSONNEL ARE UNSURE IF A COMMENT IS REQUIRED OR HOW TO DOCUMENT AN EVENT, NOTIFY SPM SUPERVISOR OR QUALITY ASSURANCE BEFORE MAKING THE COMMENT IN THE BATCH RECORD***"*, see **Exhibit SAH-24**. I discussed this statement with management as this statement is contrary to current GMP thinking where if there is doubt about whether or not something should be documented, the operator should document it in the batch record instead of waiting to discuss with QA or a supervisor, who are not always present in the filling room. Information should be documented at the time it occurs. This was listed as the **third verbal recommendation** in the GENERAL DISCUSSION WITH MANAGEMENT section of this report.

Media Fill Review

(written by SJB)

I requested a list of all the media fills conducted since the previous inspection of August 2010 (copy attached as **Exhibit SJB-5**). Several media fills were reviewed during the current inspection. I reviewed SOP-QLA-VAL-00020-SL, Media Challenge of Aseptic Processes. We reviewed media fill qualifying batches for the new (b) (4) Filling machine in Room (b) (4) for Atropen. We reviewed portions of batch numbers QP 11-802, QP 11-803, QP-816, QP 11-807 and QP 11-808.

The Media Fill for Atropen Type Container/Closure Group using (b) (4) Atropen Filler in SPM Room (b) (4) was reviewed for QP 11-802, QP 11-803 and QP 11-816. This qualification emulated the process for producing Atropen basic units using sterile microbial growth media, (b) (4) (b) (4), included the (b) (4) activities in the SPM Room (b) (4) and filled in the new (b) (4) Filler in SPM Room (b) (4) The media fills were designed to include the (b) (4) of employees and at least (b) (4) with the minimum duration of (b) (4) hours. After incubation the units were expelled and inspected for growth. No growth was noted with the three batches. I reviewed the three batches to verify all interventions were performed as required. Copies of the summary of the Media Fill Reports are attached as **Exhibit SJB-6**. The chart below shows the number units filled, incubated, and all reported no growth. I had no concerns with the three media fill batches I reviewed.

Media Fill in Room (b) (4)	**QP 11-802**	**QP 11-803**	**QP 11-816**
Fill Date	(b) (4)	(b) (4)	(b) (4)
Units Filled (target (b) (4)	(b) (4)	(b) (4)	(b) (4)
Units Incubated ((b) (4)	(b) (4)	(b) (4)	(b) (4)
Contaminated	0	0	0

The firm reported media fill failures in Room (b) (4) related to the manual fill. The firm no longer performs manual fills in Room (b) (4) Cross Functional Investigation Report (CFI) 11-06-001-SL (**Exhibit SJB-7**) discusses the failed media fills in Room (b) (4) After the media fill failure of QP 11-807 (fille (b) (4) results 2 positives) an investigation was conducted and covered data back to 2005. Their investigation indicated the media fill QP 11-807 failure was an isolated incident. They report no confirmed sterility failures reported for any Meridian product in the last five years. Once corrective actions were implemented three additional media fills were conducted and two of the three failed (QP 11-809 filled (b) (4) - 1 positive, QP 11-810 filled (b) (4) – 1 positive and QP 11-811 filled (b) (4) – no growth). A risk analysis was performed for all lots produced using the (b) (4) pump in Room (b) (4) since the last media fill. Their review back to the last successful media fill QP 10-812 filled (b) (4) found no growth) to the QP 11-807 filled (b) (4) show the same aseptic interventions with the exception of one during the pump change. With the fill of QP 10-812 no aseptic activities were performed until the pan was closed and wiped with (b) (4). QP 11-807 was not performed the same. From the (b) (4) lots of product produced during this period (b) (4) lots were released (b) (4) that were manufactured within (b) (4)

months of the last successful media fill. No filling interventions were noted with these (b) (4) lots. This is not a (b) (4) and due to filling interaction performed on Lot 1N3379 and the proximity of filling of Lots 1N3379 and 1N3413 (both manufactured in (b) (4)) the firm rejected both lots. KAN-DO plans further contact with the firm regarding this matter.

The firm has aborted one media fill since the August 2010 inspection due to a small amount of water discovered dripping from around the frame for a HEPA filter into clean room (b) (4). A NOE was initiated 8/3/11 relating to this media fill QP 11-801 in Room (b) (4) in the new hood (b) (4). An inventory was performed in room (b) (4) All equipment and materials from this were passed out of the APA and re-sterilized back in or disinfected and passed back in to room (b) (4) The media fill QP 11-801 was discontinued and cancelled. All units were rejected along with the remaining plastic bodies for this media. Environmental Data Review reported in the NOE data is within limited from 8/3/11 – 8/9/11 with the exception of an (b) (4) for (b) (4) with (b) (4) This leak was repaired on (b) (4) during the (b) (4) facility shutdown. A copy of the NOE is attached as **Exhibit SJB-8**.

(written by SAH)
I reviewed Media Fill OP-11-808, dated (b) (4) . This media fill is inadequate to qualify personnel in that it does not adequately document the process manipulations that simulate the routine filling operations and exposure that the product itself would undergo. According to Attachment 5.12A: List of Filling Events, several operators (b) (7) (C) were qualified during media fill OP-11-808 without performing any filling events; see **Observation 2** on the FDA-483 and OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE section for additional information.

Packaging and Labeling System

On 2/6/2012 Investigator Hunt and I (Investigator Berryman) initiated the inspection at the packaging and labeling at the Westport facility. We observed the firm's packaging and labeling operations and found them to be satisfactory with no objections. The firm has a challenge standard roll of labels that is run each time before counting incoming rolls of labels. We visited the controlled label storage area which has limited access. We verified the count on two different labels. Labeling and packaging areas appeared clean and adequately managed. We observed individuals performing visual checks on vials against both a black and white background. We observed the packaging and labeling of EpiPen Jr. 2 Pack NGA lot 2GN084. I reviewed one complaint regarding packaging and labeling.

Laboratory Control System

(Written by SAH)

I reviewed the active lots on stability along with SOP-QLA-MQA-00739-SL – Stability Programs for Finished Product procedure, effective 11-10-11, and RP-386 – Report on the Analytical Method Validation of a Stability Indicating (b) (4) for Epinephrine and Related Impurities, dated 03/03/03. No discrepancies were noted. I reviewed the final report for the Revalidation of Analytical Method SOP-LAB-RDL-00251-SL – (b) (4) of Sodium Metabisulfite in Epinephrine Drug Products using the (b) (4), dated March 02, 2011. I reviewed the analytical data from batch 1GH804 – Epinephrine Injection 1:1000; 0.3 mL/Dose including the following procedures:

SOP #	Title
SOP-LAB-RDL-00194-SL	(b) (4) Test for Epinephrine Solutions
SOP-LAB-RDL-00233-SL	Determination of Epinephrine and Related Impurities by (b) (4)
SOP-LAB-ALM-00105-SL	Maintenance and Calibration of the (b) (4)
SOP-LAB-RDL-00251-SL	(b) (4) of Sodium Metabisulfite in Epinephrine Drug Products

No discrepancies were noted in the above procedures.

During the tour of the stability chambers, I observed finish product stability samples being stored in hard plastic containers with lids that are closed snuggly, but were not air tight. Some containers were observed as being taped shut. Stability samples should be stored in the same manner as they are packaged for distribution. Management discussed drilling holes in the plastic containers to enhance air flow through the container.

Microbiology

(Written by JAB)

The firm's laboratory building at the Brentwood site houses the microbiology laboratories. The microbiology laboratory consists of (b) (4). (b) (4) is used for sterility and endotoxin testing and the (b) (4) is the "culture" side of the lab where microbial identification, water testing, bioburden, and growth promotion testing occurs. The firm uses a (b) (4) identification and is in the process of validating (b) (4)

Sterility testing is performed per SOP-LAB-MIC-00406-SL Sterility Test Procedure, see **Exhibit JAB-1.** There have been no sterility failure investigations since the previous inspection. Media used in the microbiology laboratory is purchased. Growth promotion of the (b) (4) and (b) (4) broth mediums used for sterility testing is performed upon receipt and every (b) (4) months after receipt until it is completely consumed or reaches the manufacturers expiration date. The firm uses the specified USP organisms and an in-house environmental isolate. Growth promotion of sterility test media was reviewed and no deficiencies were noted.

Sterility testing occurs inside of an isolator, which is (b) (4) On 1/30/12 we observed sterility testing for EpiPen lot 2GH051 which occurs using the isolator. The isolator has one size of gloves, which were reported to be too large for some analysts and too small for others. They were too large for the analysts we observed. Integrity testing of the gloves is performed with each use.

The test units contain a needle and during the performance of the test on 1/30/12 we noted a needle stuck into the isolator glove near the left wrist of the analyst. The analyst tried to shake the needle and brush the needle off, but it was firmly stuck in the glove. After a few tries the analyst was able to remove the needle.

The microbiology supervisor, Mr. (b) (7) (C) was watching the testing with us and also noted the needle in the isolator glove. He informed us the testing should stop if the integrity of the glove is compromised. The analyst continued her testing after the needle was removed. At that time Mr. (b) (7) (C) entered the room and told her to abort the test and new samples would be tested after new isolator gloves had been installed. It was reported that the analyst did not know what to do when the needle punctured the glove. **See General Discussion with Management #2.**

A (b) (4) laboratory is located in the (b) (4) building. This lab is used to incubate and read environmental monitoring samples and media fill units. This room has (b) (4) incubators, (b) (4) at (b) (4)-(b) (4)°C and (b) (4) at (b) (4)(b) (4)°C. The incubators are on the firm's (b) (4) system. A note on each incubator indicated they were qualified at both (b) (4)-(b) (4)°C and (b) (4)(b) (4)°C. The qualification for the Incubator # (b) (4) which was observed to be set for (b) (4)-(b) (4)°C on (b) (4), was reviewed. The initial qualification was performed at (b) (4)-(b) (4)°C, but the requalification, including temperature mapping, was completed at (b) (4)-(b) (4)°C. The firm had written a justification that (b) (4)-(b) (4)°C were more difficult conditions for the compressor to maintain and therefore this one temperature range was used to qualify both sets of temperature ranges.

There were no logs for these incubators indicating what samples were in them and the incubator identification is not recorded on the raw data sheets. The firm also does not record the times samples are placed in the incubator. The raw data forms indicate the date samples were collected, and the firm's procedures require samples to be incubated immediately, but they do not document the time the samples are placed in the incubator to ensure they were promptly incubated. The date the plates were read is recorded as well, but without specific times a quality reviewer could not determine if plates were incubated for the proper amount of time. See **Observation #3.**

Environmental Monitoring

(Written by JAB)

SOP-LAB-ENV-00805-SL Environmental Sampling of the Sterile Manufacturing Area is included as **Exhibit JAB-2.** The firm performs (b) (4) monitoring in the class 100 areas on a (b) (4) basis during aseptic operations including filling and component assembly. They also

perform (b) (4) monitoring on a [redacted] basis during filling operations. This is completed with (b) (4) that are changed (b) (4)

Personnel monitoring is performed using (b) (4) plates. Operators are plated upon exiting the aseptic area (b) (4) in association with (b) (4) they are working on. If the operator exits the area and re-gowns later in the day, they (b) (4) if they return to work on the same batch. Supervisors, environmental control personnel, and "floaters" which are not assigned to a particular batch, but enter the aseptic area, are plated (b) (4) The plating is done on the (b) (4) Plating is performed by a trained environmental control person upon exiting the aseptic area. The only exception is during media fills, when some individuals will plate themselves.

Action and alert levels are found on page #17 of **Exhibit JAB-2.** It was found that the firm did not base their specifications on historical data. The alert and actions limits are based on USP guidance, but did not consider their historical results. See **Observation #2E.**

MANUFACTURING CODES
(written by MHH)

The firm's manufacturing codes are generated in the order listed below:

(b) (4)

Next, (b) (4)

Finally, (b) (4)

An example of the firm's manufacturing code is "1PT716", for an (b) (4) lot produced in (b) (4)

COMPLAINTS
(written by SJB)

We reviewed the Complaint Procedure, no. SOP-QLC-QLE-00702-SL, Product Complaint Handling. ADE's were filed by King Pharmaceuticals, Inc. and are now filed by Pfizer. I reviewed a list of all complaints from August 2010 through January 2012. Investigator Hunt and I reviewed approximately 30 complaints selected for review identified as: Adverse drug events, particles in solution, spontaneous activation, no effect, failure to activate, discolored solution, dissatisfied with product features, other, unit damaged, and leakage. Our review also included NGA EpiPen lot numbers 0GU196 and 0GU629 which had the most complaints, 7 complaints each. I also reviewed a complaint for (b) (4) which had a missing lot number on the carton but the lot number was on the blister pack and vial.

Review of complaint 1106-104381 for NGA EpiPen Jr. lot 0GR591 reported particles in the solution. The distributor, (b) (4) was not able to obtain the complainants sample. MMT did not look at reserve samples to see if there was any visual change in the product for this lot. I asked Mr. Coerver about looking at the reserve samples and he stated he guessed they could have looked at reserve samples. I did not see a trend of failure to look at reserve samples during complaint investigations. Other than this example, all other complaints reviewed appeared properly documented, evaluated and investigated in a timely manner.

The complaints that covered the DQRS for the firm can be located in **Exhibit MHH-3**.

Health Canada Public Notice of December 22, 2011

(Written by SJB)

Mr. Lawson notified SCSO Warren Lopicka of the Health Canada Public Notice issued in December 2011 (copy attachment to the report **Exhibit SJB-9**). MMT manufactures EpiPen and EpiPen Jr as Legacy (currently distributed outside the US and Canada) and the Next Generation Autoinjector (NGA) (currently distributed to US and Canada). The NGS has a new design making the autoinjector pen oval instead of round which MMT believe assists in patients using the pen properly. The first NGA EpiPen Jr was shipped 9/17/2009 and the first NGA EpiPen Sr was shipped 9/22/2009 in the US. EpiPen Jr has a 19 month expiry and EpiPen Sr has a 20 month expiry.

MMT informed KAN-DO in letter of 12/28/2011 of a Health Canada (HC) consumer complaint concerning the NGA EpiPen Auto-injector blue safe pin and stem breaking and remaining in the power pack preventing activation. (Mr. Lawson reports no safe pin breakage in the US except for two trainer units). HC requested and obtained samples from Pfizer HC distribution center and tested them. HC reported observing spontaneous activation "in which it appears that the units activated after the safe pin was manipulated by HC testing personnel." MMT reported HC did not share nor discuss its EpiPen testing methods with them. See MMT letter to KAN-DO dated 12/28/2011 for full details. MMT's examination of returned HC units found no manufacturing related issues and "observed indications the spontaneous activation appeared to have been caused by intentionally pulling and reinserting the blue safe pin in a manner not shown in the product labeling picture." MMT reports they were "able to replicate the spontaneous activation by performing an extreme, hard sideways pull on the blue safety release of the EpiPen Auto-Injector or by reinserting the blue safety release back into the EpiPen***". MMT reports no spontaneous activation when the safe pin was removed as shown in the instructions for use (see copies of labeling including patient and physician insert attached as **Exhibit SJB-10**). The US labels and patient insert show a picture removing the blue safe pin directly above the pen.

MMT believe this spontaneous activation is not an issue in the US for several reasons:

- Since June 2011, all EpiPen products sold in the US have been distributed as a 2-pack including the trainer. The trainer is a similar unit with a different main color label – blue. The EpiPen main color label is yellow and the EpiPen Jr mail color is green. Both EpiPen

and EpiPen Jr have "NEEDLE END" with an arrow pointing down with a background of orange. The trainer does not have a needle or the drug but does have the blue safety release pin. All EpiPens sold in Canada are sold as a single pack unit and trainers only per request.

- MMT reports when directions are followed the product performs as expected.
- MMT re-examined (b) (4) returned NGA samples from the US and Canada with reported spontaneous activation from 2010 and 2011. They reported 8 units appeared to have any damage similar to the extreme sideways pull of safe pins and 3 reported activated at the time the safe pin was pulled similar to what HC reported in their testing.
- Subassemblies (power-Paks) and finished auto-injectors tests have been performed since 2009 for the NGA. They report (b) (4) samples tested with no spontaneous activation.
- MMT reports with the initiation of the NGA complaint history for NGA compared to the Legacy shows a reduction in reported number of spontaneous activation complaints. EpiPen complaints per (b) (4) units sold dropped by (b) (4)% from (b) (4) complaints per (b) (4) n 2008/2009 to (b) (4) in 2010/2011. The actual number reported complaints dropped by (b) (4)%: (b) (4) in 2008/2009 to (b) (4) in 2010/2011. I was provided with several charts (**Exhibit SJB-11**) including: USA vs Non-US complaints showing the decline in EpiPen complaints per (b) (4) since 2008; Spontaneous Activation Legacy vs NGA EpiPen since 2006 (Please note the increase in 2010 includes the Legacy version still in the market place.) Charts for the Top EpiPen Complaints (**Exhibit SJB-12**) shows Spontaneous Activation went from the 2nd most complaints in 2009 to the 3rd most complaints in 2010 and 2011.
- MMT plans to (b) (4) and feels it would further reduce the likelihood of misuse. In MMT Memo to File dated 12/14/2011 (copy attached as **Exhibit SJB-13**) Re: Corrective action for spontaneous activation issue reports (b) (4) and (b) (4) of use. Mr. Lawson stated labeling improvements might be (b) (4) (b) (4)
- MMT Memo to File dated 1/26/2012 (copy attached as **Exhibit SJB-14**) Re: Answer to Health Canada request on modification to Safe Pin Cap dated Jan 11, 2012 reports the firm has (b) (4) the Safe Pin (b) (4) from (b) (4)' to (b) (4)' to minimize the reported breaking. The new production began on (b) (4) at the supplier. A drawing of the Safe Pin and change is attached to the Memo.

Mr. Lawson stated there should be no legacy EpiPens in the US or Canada within expiration date.

RECALL PROCEDURES

(written by MHH)

The firm has a supply agreement with (b) (4) which states Meridian Medical owns the NDAs and is responsible for the any recalls of the NDAs. Currently, Meridian Medical and (b) (4) are in the process of establishing (b) (4)

During the inspection, the firm's standard operating procedure was reviewed and no issues were noted. The firm has not initiated a recall since the previous 2010 inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

The observations listed on this FDA 483 relate to conditions and practices observed at the manufacturing facility located at 2555 Hermelin Dr., St. Louis, MO 63144 referred to as the Brentwood facility and at the corporate office located at 1945 Craig Rd., St. Louis, MO 63146, registered under CFN/FEI 1937280.

OBSERVATION 1

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically,

A. **Supervisor (b)(7)(C) reported times recorded for specific steps in the batch record are not the actual times steps started and stopped, but rather theoretical times. For example, step (b)(4) for the filling batch record of AtroPen lot #1PT716 on (b)(4) is documented with a start time of (b)(4) and stop time of (b)(4). However, (b)(7)(C) stated the start time is recorded and the stop time is immediately written for when the step should theoretically end. In step (b)(4) this is (b)(4) minutes later. It is not recorded when the step actually ended.**

B. **During the filling of lot #1PT716 of AtroPen on (b)(4) operator (b)(7)(C) exited the aseptic area at (b)(4) and did not return that day. Operator (b)(7)(C) signed off that they verified step (b)(4) and performed step (b)(4) f the batch record, both of which occurred after (b)(4) Step (b)(4) could not have been performed until at least (b)(4) minutes after the (b)(7)(C) exited for the day. Supervisor (b)(7)(C) reported the batch record would have been pre-filled out by (b)(7)(C) before (b)(7)(C) exited the aseptic area.**

C. **The "performed by/date" was not recorded for the inspection of the gasket on the active air sampling forms for (b)(4) and (b)(4) on (b)(4) at the time of performance.**

D. **Batch 1M1726 - Multichambered Autoinjector 2.1 mg Atropine/0.7 mL dose 600 mg Pralidoxime Chloride/2.0 mL Dose states to pull a sample of (b)(4) basic units and check for proper plunger placement per SOP-PRO-FIL-00109-SL. If the plunger depth is out of range, the batch record allows for a retest. If the retest is out of range, an operator would segregate to the last**

good test and perform 100% inspection. Only the final result of the rework inspection is documented on the observation sheet and not the raw data obtained from the 100% inspection. This rework is not reviewed or approved by the Quality Unit.

E. Batch 1M1726 - Multichambered Autoinjector 2.1 mg Atropine/0.7 mL dose 600 mg Pralidoxime Chloride/2.0 mL Dose states in step (b) (4) *"*Prior to inspecting each bag/container, verify the count of each container using a weight counting scale per SOP-MAN-PKG-00103-SL. Notify SPM if weight count quantity varies more than -/+ (b) (4) % of the transfer sheet quantity***".* The weights from this verification are not documented.**

F. SOP-MDP-GEN-00013-SL - In-process Product Transfer procedure was not followed during the transfer of Atropine, batch 1M1726. The Product Transfer Form for 1M1726 states that (b) (4) tubs were transferred to Westport on (b) (4), but the Carrier signed off on the transfer on (b) (4)

G. The annual review of product reserves for AtroPens were not approved by the statistical quality control supervisor or designee by the (b) (4) reserve report due date, (b) (4) listed in SOP-QLC-SQC-00384-SL. The listed lot numbers were approved by the statistical quality control supervisor or designee on 6-27-2011.

- **AtroPen, 2 mg, Lot Number: 954408**
- **AtroPen, 2 mg, Lot Number: 954821**
- **AtroPen, 2 mg, Lot Number: 954409**
- **AtroPen, 1.0 mg, Lot Number: 95L847**
- **AtroPen, 0.5 mg, Lot Number: 75M749**
- **AtroPen, 1.0 mg, Lot Number: 05L214**

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

A&B. (JAB) The firm does not record actual end times of steps, but rather theoretical times that a step should end. Therefore, it can not be determined if critical times were met for any of the timed steps in any of their batch records. The processes are validated for specific times, but due to their practice of not recording actual time, they can not assure the times are being met. I also discussed that if employees pre-fill out the batch records we can not ensure the data recorded is accurate and it makes us question all of the data they generate.

SOP-QLA-MQA-00603-SL Proper Documentation Version 9.0 was effective at the time lot #1PT716 was manufactured and is included as **Exhibit JAB-3.** Section [redacted] states: *"***All entries, operator and verification signatures must be completed at the time process is performed and that the entries must be made by the same person performing the work.***"*

This batch record was initially reviewed during a FDA St. Louis Resident Post review of this batch record as it is for a military contract product. An FDA memo dated 12/22/11 discussed concerns that the initial time for step [redacted] was changed. Step [redacted] is for [redacted] tubing for a minimum of [redacted] minutes with the [redacted] It was reported that the tubing [redacted] removing it from the product. If the tubing isn't [redacted] and therefore [redacted] with [redacted] it will absorb the [redacted] from product at the beginning of the fill resulting in low [redacted] concentrations in the finished product.

I spoke with supervisor [redacted] overseeing this fill area and he explained the initial time identifying the [redacted] step as occurring from [redacted] to [redacted] was incorrectly written because the operator was recording the time for steps prior to the [redacted]. The times were changed to [redacted] and [redacted], which would meet the requirement of [redacted] minutes for [redacted] Pages from the filling record are included as **Exhibit JAB-4.**

The individual making the changes and then verifying step [redacted] was operator [redacted], identified as [redacted] The environmental monitoring data shows that employee [redacted] was plated for personnel monitoring at [redacted], see **Exhibit JAB-5**. Mrs. Santangelo explained to me that plating always occurs after the operator has exited the filling areas. Once the employee is plated, they can not return until they have re-gowned. I reviewed the entrance log to the aseptic area and found that employee [redacted] did not re-enter the aseptic area for the remainder of the day on [redacted]. The employee's supervisor, [redacted], verbally confirmed to me that the employee left the facility for the day after exiting the aseptic area at [redacted].

I then asked the supervisor how [redacted] could have verified and recorded their signature for a stop time of [redacted] if the employee had exited the area [redacted] minutes earlier. The supervisor told me this was because the end times are not the actual time. The start time is recorded and they immediately record the theoretical end time for when the step should end based on the batch record requirements. The operator's signature and verifying signature are recorded at the start time. They do not record when the step actually ended. The supervisor told me this is their normal practice.

Step [redacted] of this record includes a [redacted] therefore this could not have occurred until at least [redacted] if step [redacted] was done correctly. Step [redacted] is a sign-off that steps [redacted] have been completed and operators are authorized to begin the filling operation, see **Exhibit JAB-4**. Operator [redacted] who left the aseptic area at [redacted], performed this step in the batch record, authorizing filling, though it shouldn't have been

authorized until at least (b) (4) Supervisor (b) (6), (b) (7) old me the operator pre-filled out the batch record before exiting the filling room.

Lot #1PT716 also had NOE 11-12-016-SL associated with it due to a failed (b) (4) during calculation of (b) (4), see **Exhibit JAB-6**. All results met specification for (b) (4) with at least (b) (4) ng/ml. The beginning sample had a result of (b) (4) ng/ml while the middle and end had a result of (b) (4) mg/ml. This resulted in a (b) (4) of (b) (4) %, beyond the limit of (b) (4) %. (b) (4) of the samples confirmed the result with the beginning samples being the lowest and having a (b) (4) % (b) (4) for all samples. The investigation concludes there was no product impact because the (b) (4) for beginning, middle, and end all met the specifications. The root cause states *"***there is still an effect at the beginning of the fill with (b) (4) into the tubing.***"* The investigation concludes that the proper steps were taken to (b) (4) the tubing, but because the operators were not recording actual times and were pre-filling the records, it can not be verified that the batch record steps were properly performed.

C. (JAB) On 1/31/12 we toured the environmental control laboratory. Paperwork for active air sampling for locations (b) (4) and (b) (4) during production of lot 2GH052 on (b) (4) was present. For each form a gasket inspection was to be performed and is checked off as occurring, but the operator did not sign the record as completing the gasket inspection. These forms, as we observed them on 1/31/12, are included as **Exhibit JAB-7.**

D. (SAH) Batch 1M1726 – Multichambered Autoinjector 2.1 mg Atropine/0.7 mL dose 600 mg Pralidoxime Chlorie/2.0 mL Dose states to pull a sample of (b) (5) basic units and check for proper plunger placement per SOP-PRO-FIL-00109-SL, see **Exhibit SAH-8**. If the plunger depth is out of range, the batch record allows for a retest. If the retest is out of range, an operator would segregate to the last good test and perform 100% inspection. Only the final result of the rework inspection is documented on the Observation Sheet and not the raw data obtained from the 100% inspection, see **Exhibit SAH-9**. The Observation Sheet for batch 1M1726 states, *"***100% Inspected bags (b) (4) for plunger depth placement. (b) (4) rejects found**After review of the batch record, bag (b) (4) was 100% inspected for plunger depth as well. (b) (4) rejects were found***"*. On the accountability sheet of the batch record, the individual counts of bags (b) (4) were changed to read as follows; see **Exhibit SAH-10**:

Bag	Original QTY	QTY After Rework
(b) (4)		

This rework is not initiated, reviewed or approved by the Quality Unit.

E. (SAH) Batch 1M1726 – Multichambered Autoinjector 2.1 mg Atropine/0.7 mL dose 600 mg Pralidoxime Chlorie/2.0 mL Dose states in step (b) (4) *"***Prior to inspecting each bag/container, verify the count of each container using a weight counting scale per SOP-MAN-PKG-00103-SL. Notify SPM if weight count quantity varies more than -/+ (b) (4)% of the transfer sheet quantity***"*, see **Exhibit SAH-11**. The weights from this verification are not documented, nor whether a discrepancy of less that ± (b) (4)% occurred during the weight count.

F. (SAH) SOP-MDP-GEN-00013-SL – In-process Product Transfer procedure states to *"***Prepare a Product Transfer Form (FRM-MDP-004) or a Controlled Drug Product Transfer form (FRM-MDP-001) for the lot to be transferred***"*, see **Exhibit SAH-12 pg 4**. FRM-MDP-004 has a space to document the "date transferred" along with the "carrier/signature". The Product Transfer Form for batch 1M1726 documents the transfer of (b) (4) tubs of (b) (4) from the sterile facility to Westport on (b) (4), but the Carrier signed off on the transfer on (b) (4) see **Exhibit SAH-13**. Likewise, Product Transfer Form for batch 1PT716 states that (b) (4) containers were transferred from SPM to Westport on (b) (4), but the Carrier signed off on the transfer on (b) (4), see **Exhibit SAH-14**. Management stated the SPM (sterile facility) is located approximately (b) (4) minutes from the Westport facility.

G. I (MHH) reviewed the firm's Annual Review of Product Reserves procedure (Version 4.0, effective 9/17/2010, attached as **Exhibit MHH-4**). On page 3 in item (b) (4) the procedure states "Review reserves in the following order by product. Assure to begin at any time up to (b) (4) days prior to the end of the month the report is due below." The anniversary date for Atropen is (b) (4) and the (b) (4) reserve report due date is (b) (4) As stated above the annual review of the product reserves were not approved by the statistical quality control (SQC) supervisor or designee before the established date, (b) (4), required by their procedure. The Annual Review of Product Reserves for the lot numbers listed above included Adult Atropen, Atropen DOD, and Pep Atropen products and can be viewed in **Exhibit MHH-5**.

Discussion with Management:

A&B. The firm provided me an updated procedure SOP-QLA-MQA-00603-SL Proper Documentation Version 10.0 effective 12/28/11, see **Exhibit JAB-8**. They also provided a training presentation titled Documentation Practices which occurred (b) (4), see **Exhibit JAB-9.** I was provided a list of individuals attending the training, which included operator (b) (6), (b) I was told this training showed the issue had been corrected. Point C of this observation documents an example of operators not properly documenting their performance after this training had occurred.

I was provided an updated batch record that requires signatures for the start and stop times for the (b) (4) separately. It also puts a time on the (b) (4) step and (b) (4)

(b) (4) when the (b) (4) occurs, see **Exhibit JAB-10**. I explained that this was a specific example that they were correcting because it was discussed extensively during the inspection. However, they need to evaluate every batch record and every step and determine what changes to the batch record needed to be made to assure information gets properly documented.

C. (JAB) No comment.

D. (SAH) Management showed me SOP-QLA-MQA-00719-SL – Notice of Event Reports (NOE) and SOP-QLA-MQA-00720-SL – Quality Assurance Reports (QAR). Both procedures define rework as, *"Rework/reclaim is any labeled or packaged units/lot declared in writing an approved by Regulatory and Quality Assurance to be re-workable or reclaimable by following a specified approved procedure"*, see **Exhibit SAH-3 pg 4** and **Exhibit SAH-15 pg 4**. Ms. Santangelo also provided FRM-QLA-431 - Request to Perform Rework form, see **Exhibit SAH-16**. She stated that the rework procedure is used at the Westport packaging and labeling facility but that it is not followed at Brentwood for material undergoing production. We discussed the importance of documenting the original data during these reworks and involving Quality in the rework process.

E. (SAH) No comment.

F. (SAH) Management confirmed that they were not documenting the counts obtained during the verification.

(MHH) Carolina Santangelo, Director, Quality Assurance & Microbiological Services, stated the SOP-MDP-GEN-00013-SL - In-process Product Transfer procedure was effective 12/1/11 and another procedure was used at the time of the transfer. Ms. Santangelo explained that at the time of the transfer, the FRM-MDP-004, Product Transfer Form, was used and the Carrier signs and dates the document, beside "CARRIER/SIGNATURE", when the Westport warehouse receives the product shipment. She also stated the Packaging and Inspection division documents the date, on the bottom section of the Product Transfer Form by the "DATE RECEIVED", when the product shipment is transferred from the Westport warehouse to the Westport packaging and inspection area. Ms. Santangelo stated the shipment of (b) (4) ubs were transferred the Westport warehouse on (b) (4) but the Packaging and Inspection division documented the date received, (b) (4), as the date they transferred the shipment from the Westport warehouse to the Westport packing and inspection division.

I (MHH) showed Ms. Santangelo the Product Transfer Form stating that Atropine, batch 1PT716, was transferred from the Brentwood SPM on (b) (4) and received by the Brentwood SPS/Westport facility on (b) (4) She explained the Atropine shipment was transferred to the Brentwood SPS facility on (b) (4), then to the Westport warehouse on (b) (4), then to the Westport packaging and inspection division on (b) (4).

G. (MHH) Charles Coerver, Senior Manager, Quality Engineering and Statistical Quality Control, stated the product reserves review/examination was conducted before the due date and the document review was completed after the due date. I agreed with Mr. Coerver that the reserves review/examination was conducted before the due date, but informed him that the report wasn't completed and the SQC supervisor or designee had not checked "Acceptable" by the due date. I also stated since the report isn't complete until it is reviewed, found acceptable, and signed which means the report was completed pass the due date. Mr. Coerver read the item [(b) (4)] on page 3 of the procedure and stated that item needs to be written more clearly.

During the close-out meeting, Mr. Coerver wanted to clarify that the observation was not a repeat observation from the 2010 inspection, since the product reserves review/examination was conducted before the due date and the document review was completed after the due date. I stated to Mr. Coerver the procedure stated the Annual Reserve Report Due Date was (b) (4) and the report was reviewed and found acceptable which completes the report after the due date. Mr. Coerver stated he just wanted to reiterate that the actually product reserves review/examination was conducted before the due date.

OBSERVATION 2

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

Specifically,

A. "SOP-PRO-FIL-00001-SL General Aseptic Procedure" was not followed. The (b) (4) (b) (4) is a component of the finished product. During aseptic assembly of (b) (4) lot (b) (4) in room #[(b) (4)] on (b) (4) the following was observed:

1) **Operator [(b) (6), (b) (7)(C)] was observed to pick (b) (4) components off the assembling turret and toss them back in the (b) (4) bowl. Section [(b) (4)] of the procedure states "***To clear a component, use sterile forceps to remove the item(s) from the area***".**
2) **Operator [(b) (6), (b) (7)(C)] was observed to shake a bag of (b) (4) and allow the bag to touch the inside of the (b) (4) bowl while adding (b) (4) Section [(b) (4)] of the procedure states "***When adding components, one smooth motion is used to pour components into the bowl***".**
3) **Operator [(b) (6), (b) (7)(C)] was observed to make unnecessary hand movements and reach over the assembling turret area. Section [(b) (4)] of the procedure states"***Personnel will eliminate**unnecessary hand or arm movements***".**

B. On (b) (4) , "SOP-PRO-FIL-00001-SL General Aseptic Procedure" was not followed. Supervisor [(b) (6), (b) (7)(C)] was present in the class 100 area and performing batch record step [(b) (4)] and

weight checks during the filling of AtroPen lot #1PT716, but did not sign the filling operation sign in sheet. Section (b) (4) of the procedure states "*Any person entering a class 100 area while production is in progress must sign the batch record***" and section (b) (4) of the filling batch record states "***All APA personnel entering this filling area must sign the appropriate table below***".**

C. SOP-PRO-FIL-00002-SL Aseptic Processing Area Gowning was not followed in that:

1) **On 2/3/2012 two of the (b) (4) individuals observed aseptically gowning placed their foot on the bench while putting their boots on. After 8:50am on 2/3/2012 an additional two of (b) (4) individuals were observed to also don sterile boots by placing them on the bench and then proceed to enter the Aseptic Processing Area. Under (b) (4) of the procedure it states "***don boots one at a time over the shoe covers, allowing only the boots to touch the floor on the other side of the bench.***"**
2) **One employee was observed to don the sterile coveralls and then reach across the boot cart allowing the coveralls to rub against the cart while retrieving boots.**

D. During the cleaning / sanitization in Room (b) (4) on 2/2/2012 one individual was observed cleaning from the ceiling to and including the return air vent and the second employee was observed cleaning the floor. Neither individual cleaned the "Cove Base", the portion between the return air vent and the floor.

E. The microbial alert and action levels established to initiate investigations of environmental monitoring results are not based on historical environmental monitoring sampling data.

F. Media Fill OP-11-808 is inadequate to qualify personnel in that it does not adequately document the process manipulations that simulate the routine filling operations and exposure that the product itself would undergo. According to Attachment 5.12A: List of Filling Events, several operators ((b) (6), (b) (7)(C) and (b) (6), (b) (7)) were qualified during media fill OP-11-808 without performing any filling events.

Reference: 21 CFR 211.113(b)

Supporting Evidence and Relevance/ Discussion with Management:

A. Investigators Boyd and Hughes watched the aseptic assembly of (b) (4) lot # (b) (4) in room # (b) (4) on (b) (4) The (b) (4) is a component of the finished product. The parts, the (b) (4) sheath and (b) (4) , are sterilized in (b) (4) and brought into room # (b) (4) for aseptically assembly in a class 100 assembly area. The finished (b) (4) are placed in sterilized bags that are transferred on carts to the filling room where

they are added to the fill lines. SOP-PRO-FIL-00001-SL General Aseptic Procedure is included as **Exhibit JAB-11.**

1. The procedure states in section (b) (4): *"***To clear a component, use sterile forceps to remove the item(s) from the area***"*. We observed operator (b) (6), (b) to use sterile forceps to pick out (b) (4) ((b) (4) Sheath) components that had not been combined with (b) (4) at the assembly turret and using the forceps toss the (b) (4) back into the (b) (4) bowl instead of removing the rejected component from the area. We saw (b) (6), (b) toss two (b) (4) back into the bowl. A third was tossed toward the bowl, but missed.
2. The procedure states in section (b) (4) *"***When adding components, one smooth motion is used to pour components into the bowl***"*. We observed operator (b) (7) (C) pour (b) (4) into the (b) (4) bowl. They did not pour out right away, so he shook the bag over the (b) (4) bowl. When they did start coming out, the shifting weight of the pouring (b) (4) dropped the level of the bag and the bag touched the inside of the (b) (4) bowl.
3. The procedure states in section (b) (4) *"***Personnel will eliminate...unnecessary hand or arm movements***"*. We observed there to be a mechanical problem near the turret of the assembling area. Operator (b) (6), (b) used her hands to reach over and point problem areas out to a mechanic while the machine was running. The machine was then stopped and operator (b) (6), (b) talked while making excessive and unnecessary movements with her hands over the components in the track and in the turret area. These components were not rejected.

B. The procedure states in section (b) (4) *"***Any person entering a class 100 area while production is in progress must sign the batch record***"*. Supervisor (b) (6), (b) (7) performed step (b) (4) in the batch record, (b) (4) , see page #1 of **Exhibit JAB-4**. He also performed in process weight checks prior to fill and verified the weight checks at (b) (4), see page #5 of **Exhibit JAB-4.** The batch record sign-in sheet is included as page #3 of **Exhibit JAB-4.** The sign-in sheet is used to determine who participated in filling a batch in the case of an investigation.

C. SOP-PRO-FIL-00002-SL Aseptic Processing Area Gowning is included as **Exhibit JAB-12.**

1. On 2/3/12 Investigators Boyd and Hughes watched (b) (4) individuals aseptically gown. Section (b) (4) of the procedure states: *"...don boots one boot at a time over the shoe covers, allowing only the boots to touch the floor on the other side of the bench...You may utilize the bench to be seated while donning boots."* We observed two of the (b) (4) individuals place their foot up on the bench to put their boots on. The other (b) (4) we observed sat on the bench and put their boots on only allowing them to touch the floor on the clean side of the room.

   Again on 2/3/12, Investigators Berryman and Hunt observed (b) (4) employees gown and also observed two employees ("(b) (6), (b)" and "(b) (6), (b) (7)") place their sterile boots up on the bench

to don their boots. **Exhibit SJB-15** is a copy of the APA S12540 Entry Log pages 6-9. The batch/ purpose for employee [redacted] was listed as "(b) (4)" and for [redacted] "[redacted].

2. We also observed one employee don her sterile coveralls. She then went to get her boots and she reached for boots on the far part of the cart. This caused her to walk between the bench and the boot cart. This space was tight and while she did this the front of her overalls rubbed against the boot cart.

D. On 2/2/2012, Investigator Hunt and I (SJB) observed cleaning/sanitization of the walls and floors in room (b) (4) starting about (b) (4) m. Employee [redacted] was observed cleaning the walls and (b) (4) after the manufacture of (b) (4) The firm's procedure for cleaning and sanitization does not specifically address the cleaning of the "Cove Base". However, SOP-PRO-FIL-00047-SL, Cleaning and Sanitization of Aseptic Processing Areas (APA) (**Exhibit SJB-16**) states under [redacted] Walls Sanitizing, (b) (4) "*Proceed around the room until all wall surfaces have been sanitized.*"

During the close-out meeting Mr. Sitts stated he was updating the procedure.

E. Review of NOE 11-11-009SL reported results of 4 cfu's (alert 2/action 3) collected at the end of the fill at (b) (4) The sample was collected from on top of the Machine (b) (4) (See Diagram **Exhibit SJB-17**, page 27 for the location) in the class 100 area. The investigation indicates the contamination may have occurred from a (b) (4) made at (b) (4) Samples of (b) (4) were also collected and found negative at (b) (4) (b) (4) and both were negative for growth. No growth was found with other samples collected that day. Their review of the trends for this location determined this was an isolated incident. Sterility testing performed (b) (4) found no growth. I asked how they determined the Action of ≥ [redacted] for Machine Top (see page 17 **Exhibit SJB-18**). Ms. Santangelo showed me in USP 34 under <1116>. I stated over 1000 in the USP was for informational purposes and they should determine their limits based on their historical environmental monitoring trend data. I reviewed trend data reported in Air, Surface, Temperature, and Pressure Monitoring for 2011 for Room (b) (4) where this occurred and Room (b) (4) which is the other Class 100 room. I found no other reported growth for this Room (b) (4) I reviewed SOP-LAB-ENV-00800-SL, Environmental Monitoring and Control Program and SOP-LAB-ENV-00805-SL, Environmental Sampling of the Sterile Manufacturing Area, effective 30-Jan-2012 (**Exhibit SJB-18**).

F. (SAH) Specifically, Media Fill OP-11-808 is inadequate to qualify personnel in that it does not adequately document the process manipulations that simulate the routine filling operations and exposure that the product itself would undergo. Attachment 5.12A: List of Filling Events documents the operations performed by the operators, see **Exhibit SAH-17**. This data is then summarized in a microbial trends report for QP11-808, see **Exhibit SAH-18**. According to the Summary of (b) (4) Environmental Sampling in the Aseptic Processing Area sheet, dated 06/10/11, the environmental monitoring results entered into the microbial

trends report is entered and verified by the same person, see **Exhibit SAH-19**. In order to pass a media fill, the operator must be successfully plated [redacted] times. According to the list of filling events for OP 11-808, several operators ((b) (6), (b) (7)(C), and [redacted]) were qualified during media fill without performing any filling events. I was told by management that personnel activities would also be record on the plate during plating by the EC personnel. Therefore a person could be recorded as a Loader, even though this information was not documented in Attachment 5.12A: List of Filling Events, nor does the EC personnel document these activities at the time of occurrence instead, the EC personnel goes off of memory.

(SAH) Management provided SOP-PRO-FIL-00104-SL – Training and Qualification of Aseptic Processing Personnel procedure states, *"***Initial Certification of new clean room employees shall be completed when the following steps have been performed**New employees have demonstrated acceptable gowning technique by passing [redacted] consecutive gowning cycles and successfully completing a media fill**The new employee is able to demonstrate competency in his or her job by successfully passing the Training Checklist designed for each job function. New employees must demonstrate competency by independently performing each job function on [redacted] separate occasions***"*, see **Exhibit SAH-20 pg. 5**. The (b) (4) Certification of Aseptic Technique lists the tasks performed per job classification the employees would have to perform for Quality prior to being certified, see **Exhibit SAH-21** along with Attachment 1 from SOP-LAB-ENV-00807-SL – Monitoring Aseptic Processing Area Personnel for Microbial Contamination which lists a guideline of activities, stating whom would perform said activity and whether that activity would be considered a level [redacted] interaction, see **Exhibit SAH-22**. Management also provided SOP-QLA-MQA-00600 – Quality Assurance Batch Record Audit and Product Disposition states, *"*** (b) (4) an audit will be performed to ensure that the interventions performed in the media fill activities reflect the interventions performed in the respective commercial batch records***"*, see **Exhibit SAH-23, pg 16**. Although interventions performed in the media fill reflect the interventions performed in the respective commercial batch, the intervention are not being performed by the same individuals who are being qualified by attending that media fill. I discussed with the firm that if certain activities are critical enough to be reviewed and certified by Quality, maybe those activities should be reviewed and qualified during a media fill.

(SAH) In addition, although it is not documented in a procedure, Neil Nelson – Manager, QA & Microbiological Services stated that Environmental Control personnel do not plate themselves unless they absolutely have to. During Media Fill OP-11-808, it was observed that the EC personnel plated themselves [redacted] times; see **Exhibit SAH-18**.

OBSERVATION 3

Established laboratory control mechanisms are not followed.

Specifically,

The identity of the incubator used to store environmental monitoring plates is not recorded. There are (b) (4) incubators at (b) (4) °C and (b) (4) at (b) (4) °C for environmental monitoring samples. Records do not indicate which incubator was used for environmental monitoring plates. Therefore, quality personnel reviewing results can not verify the correct temperature conditions were used.

The times environmental monitoring microbial plates are placed into the incubator is not recorded. Therefore, quality personnel reviewing results can not verify the plates were incubated for the specified period of time.

Reference: 21 CFR 211.160(a)

Supporting Evidence and Relevance:

(written by JAB)
The incubators for environmental monitoring samples and media fill units are located in the environmental control laboratory in the SPM building. There are (b) (4) incubators, (b) (4) each for the conditions of (b) (4) °C and (b) (4) °C. They are qualified for both temperature ranges and can be changed if extra capacity is needed.

There are no log books describing the contents of the incubator and the raw data forms for environmental monitoring samples do not reference the incubator used, see **Exhibit JAB-5**. I asked Mr. (b) (6), (b) (7)(C) if he could tell me where specific samples had been incubated and he could not. Reviewers of the results can not verify the correct temperature conditions were used.

The records show the date samples were collected, but they do not show when the samples were placed in the incubator. They also show the date plates are read, but do not show the time. For this reason, the personnel reviewing the raw data can not assure that samples were incubated for the proper amount of time.

(written by SJB)

In addition, review of Media Fills QP 11-803, QP 11-807, and QP 11-808 found they do not record the time incubated only the date of incubation. The firm does record the incubator I.D. (see **Exhibit SJB-19**.

OBSERVATION 4

Written procedures are not followed for the handling of components.

Specifically, batch records call for the washing of needles per SOP-PRO-CLP-00050-SL - Preparation of (b) (4) Needles. The firm does not document to assure the validated soak time is met during the preparation of the needles.

Reference: 21 CFR 211.80(a)

Supporting Evidence and Relevance:

(SAH) I observed the Clean and Prep Room during the tour of the facilities on 01/30/12. I reviewed SOP-PRO-CLP-00050-SL – Preparation of (b) (4) Needles procedure, effective 05/21/10, see **Exhibit SAH-6**. This procedure specifies how all ATNAA and ATOX needles will be processed, including a submergence time for approximately (b) (4) minutes, with (b) (4) minutes to ensure all needles are saturated. This procedure references (b) (4) additional procedures prior to washing of the needles from cleaning of the sinks (SOP-PRO-CLP-00012-SL), changing filters (if needed) on the (b) (4) and sink # (b) (4) SOP-PRO-CLP-00026-SL and SOP-PRO-CLP-00027-SL), and prepping the (b) (4) (SOP-PRO-CLP-00014-SL). During the review of batch 1M1726, Multichambered Autoinjector 2.1mg Atropine/0.7 mL dose, 600mg Pralidoxime Chloride/2.0 mL dose, I noted that batch record states only to record the initials of the person who washed the needles per SOP-PRO-CLP-00050-SL, see **Exhibit SAH-7**. No times are documented for when the needles were washed or the start and stop times of the submergence steps.

Discussion with Management:

(SAH) Henry Slodkowski – Director of Validation confirmed that the validation of cleaning procedure SOP-PRO-CLP-00050-SL was conducted with a (b) (4) minute submergence time. (b) (6), (b) (7)(C) – Supervisor of Clean and Prep confirmed that no times are documented for when the needles were washed and no other paperwork exists to document start and stop times of the submergence step.

REFUSALS

The firm refused to allow photographs. An FDA 463a, Affidavit, was prepared for interstate documentation for Clint R. Lawson, Senior Director Quality. Mr. Lawson refused to read or sign per corporate policy.

GENERAL DISCUSSION WITH MANAGEMENT

During the inspection there were daily wrap-up meetings as needed with firm management regarding the inspection progress and findings. At the conclusion of the inspection a close-out meeting was held. Personnel who attended the final discussion are listed in **Exhibit SJB-20**. The FDA 483, Inspectional Observations, was issued to Stephen C. Natsch, Vice President & General Manager.

Several issues encountered during the inspection were not cited on the FDA 483. These items were discussed with management during the inspection and at the close-out meeting.

Discussion Items

(written by JAB)

1. **Individuals verifying calculations and reviewing batch records did not note that no value was entered for step (b) (4) during the accountability calculations of the filling for lot # 1D1796 of Diazepam.**

The accountability sheet for the filling of lot #1D1796 is included as **Exhibit JAB-13.** The actual result for step (b) (4) is blank. I performed the calculations on the form and found the end yield result is correct if step (b) (4) had been performed correctly. Mr. Nelson told me there should be a value in this field and that the results were missed.

SOP-QLA-MQA-00603-SL Proper Documentation version 9.0 is included as **Exhibit JAB-3.** Section (b) (4) states: *"To verify a calculation the verifier must independently perform the calculation."*

I explained that my biggest concern was that the calculations had been performed by one individual, verified by a second, and a third individual had signed off as a final batch record review for this page, yet no one noticed that a calculation result had not been recorded. I explained that it made me question whether the reviewers were actually performing the calculations.

(written by JAB)

2. **SOP-LAB-MIC-00406-SL Sterility Test Procedure does not address actions to take if the integrity of the isolator gloves is compromised and analysts are not properly trained.**

On 1/30/12 an analyst performing sterility testing in the isolator was observed to continue working after a needle punctured the isolator glove. The microbiology supervisor stopped the testing and stated the analyst was unsure of what to do.

On 1/30/12 we observed sterility testing occur using an isolator for EpiPen lot 2GH051. The test units contain a needle and during the performance of the test we noted a needle stuck into the isolator glove near the wrist. The analyst tried to shake the needle and brush the needle off, but it was firmly stuck in the glove. After a few tries the analyst was able to remove the needle.

The microbiology supervisor, Mr. (b) (6), (b) (7)(C) was watching the testing with us and also noted the needle in the isolator glove. He informed us the testing should stop if the integrity of the glove is compromised. The analyst continued her testing after the needle was removed. At that time Mr. (b) (6), (b) (7)(C) entered the room and told her to stop and new samples would be tested after new isolator gloves had been installed. Mr. (b) (6), (b) (7)(C) told us the analyst was unsure whether or not to continue. SOP-LAB-MIC-00406-SL Sterility Test Procedure does not address what to do if the integrity of the isolator gloves is compromised during testing, see **Exhibit JAB-1.**

We discussed with Mr. (b) (6), (b) (7)(C) that compromised integrity of an isolator glove could lead to contamination of the isolator environment and a false positive during sterility testing. Routine leak testing of the isolator gloves is part of the firm's procedures and should identify any hole in the case it would be unnoticed at the time by the analyst. Our concern was that the analyst did not know what to do. We explained that analysts should be trained and understand why environment integrity is important for aseptic activities.

(Written by SAH)

3. **SOP-PRO-FIL-00001-SL "General Aseptic Procedure" states: "***EVENTS CAN OCCUR WHICH ARE NOT COVERED BY THE BATCH RECORD**_IF PERSONNEL ARE UNSURE IF A COMMENT IS REQUIRED OR HOW TO DOCUMENT AN EVENT, NOTIFY SPM SUPERVISOR OR QUALITY ASSURANCE BEFORE MAKING THE COMMENT IN THE BATCH RECORD_***". This is contrary to current GMP thinking where if there is a doubt about whether or not something should be documented, the operator should document it in the batch record instead of waiting to discuss with QA or a supervisor, who are not always present in the filling room. Information should be documented at the time it occurs.**

(written by SJB)

4. **NDA-Field Alert Report (FAR) for OOS for (b) (4) lot (b) (4) was submitted to the FDA one day late - at day four instead of day three. The date when notified about the problem first became know was 4/8/2011. It was reported to the FDA on 4/13/2011. This was the only initial FAR reported since the previous inspection.**

Mr. Lawson stated they always try to meet the time frames for field alerts. He did not recall missing this time frame. I said I could show him the FAR and he declined and stated he would look later.

On Page 4 of SOP-QLA-MQA-00723-SL, NDA Field Alert and Product Recall (**Exhibit SJB-21**) states submit two copies of the NDA-Field Alert Report to the FDA District Office within three business days. A copy of the Initial and Final Field Alert is attached as **Exhibit SJB-22**.

No specific commitments regarding corrective actions were made during the closing meeting except Mr. Sitts did state on a couple of the items he was working on updating procedures (FDA 483 2.D. and Verbal item 3). Mr. Lawson stated the firm would respond in writing to the FDA 483 within 15 working days. At the end of the discussion, management was reminded of their responsibilities under the FD&C Act and sanctions available to the FDA for non-compliance were outlined for them.

ADDITIONAL INFORMATION

DFI Field Alert 22

Per DFI Field Alert #22, I (Investigator Berryman) and Investigator Hughes reviewed vendor qualification for Glycerin USP used in Atro DOD 2mg 144L 4/D/M, ATNAA DOD Atro 2mg 90L , Ped Atro 0.5mg/ml & 1.0mg/ml and 0.1mg/ml & 0.5mg/ml, and Atro DOD 2mg 144L 4/D/M. SOP-QLA-COM-00005-SL, Supplier Evaluation/Approval Process (**Exhibit SJB-23**), procedure classifies suppliers of products that may come in contact with the drug as a High Risk Supplier and the excipients supplier of Glycerin would be in that category. Three Certificate of Analysis (COAs) (**Exhibit SJB-24**) for Glycerin (b) (4) ot numbers (b) (4) released 5/11/2010), (b) (4) (released 3/22/2011) and (b) (4) released 4/18/2009) along with the Raw Material testing by MMT for (b) (4) (MMT Control No) and (b) (4) batches (**Exhibit SJB-25**) were reviewed. The (b) (4) COA identifies the Country of Origin as the (b) (4) for the USP (b) (4) (b) (4) glycerol). Ms. Santangelo stated they perform full testing on (b) (4) batch per year. I did not review the test procedure. The Raw Material Test Report states for reduced testing perform identification testing and any additional testing that is not listed on the manufacturer's certificate of analysis. Testing appeared acceptable for the lots listed above.

(b) (7) (C) Quality Compliance Auditor informed me (b) (4) repacks and tests Glycerin. She said the Glycerin is distributed by (b) (4) and may be manufactured by (b) (4) or other manufacturers. I was not supplied with any other manufacturer names other than (b) (4) related to the (b) (4) COAs. I was provided with a document (**Exhibit SJB-26**) on (b) (4) letterhead (formerly (b) (4) that lists the Manufacturing Reference Code of (b) (4) with the name and address of (b) (4) (b) (4) which does not appear to be a MMT document or a controlled document. I asked for documentation of the audit of the manufacturer – (b) (4) I was provided with a (b) (4) (b) (4) (**Exhibit SJB-27**). (b) (4) is related to Pfizer and MMT became part of Pfizer in March of 2011. I asked for documentation of (b) (4) prior to March 2011. She provided King Pharmaceuticals audit of (b) (4) (b) (4) performed (b) (4) and prior to that, King Pharmaceuticals and MMT audit of (b) (4) on (b) (4) (**Exhibit SJB-28**). I was not

provided with any documentation the manufacturer of the glycerin was audited prior to Pfizer ownership. They received at least the (b) (4) batches of Glycerin prior to Pfizer ownership. According to the glycerin specification change summary, they have not had a change of manufacturer since the effective date of 3/12/2008 (see page 3 of **Exhibit SJB-29**). SOP-QAL-COM-00010-SL, Supplier Audit Procedure **(Exhibit SJB-30)** under 8.1.4. allows use of the distributor or repackager audit of the manufacturer of the material, provided they have been accepted through their audit program. It also states they audit raw material excipients every (b) (4) years. This procedure allows the use of another King facility audit performed within the last (b) (4) years. The firm is in the process of updating all procedures since they became part of Pfizer. We were informed Pfizer would replace the King references in procedures.

Ms. (b) (6), (b) (7)(C) also provided me an audit procedure or template **(Exhibit SJB-31)** with the following headings: Audit Date, Purpose, Auditors, Scope, Inspectional Tour, Obtain Copy of Regulatory and Company Information, lists all the systems and time of audit/closeout meeting. She stated coverage may vary per firm. She also provided a copy of a 10/28/11 King Pharmaceuticals Purchase Order (PO) **(Exhibit SJB-32)**, ordered from (b) (4) Ms. (b) (6), (b) (7)(C) pointed out on page 2 of the PO under item "(4) NO MATERIAL OR PROCESS CHANGES MAY BE MADE BY SUPPLIER WITHOUT PRIOR APPROVAL OF MMT."

The Raw Materials Specifications for Glycerin, USP/EP shows the Manufacturer as (b) (4) Just prior to close-out meeting I informed Mr. Lawson the documents received shows (b) (4) in (b) (4) as the manufacturer. I believe listing (b) (4) as the manufacturing on the raw material specification is incorrect. (b) (4) is the distributor; (b) (4) (manufacturer # (b) (4)) should be listed as the manufacture if applicable. I stated the manufacturer block on the Raw Material Specification for Glycerin, USP/EP should list the manufacturer or the Manufacturer Reference Code: (b) (4) if (b) (4) is the manufacturer (see page 1 of **Exhibit SJB-29**). This was discussed with Mr. Lawson prior to the close-out meeting with the firm.

Also reviewed were SOP-QLA-COM-00005-SL, Supplier Evaluation/Approval Process, SOP-QAL-COM-00010-SL, Supplier Audit Procedure and the supplier audit of (b) (4) in (b) (4) for the supplier of Epinephrine and Atropine. Ms. (b) (6), (b) (7)(C) and Su Ghosh, Director, Chemistry Testing, performed the (b) (4) audit.

DFI Bulletin 31

Rejected Imported Components, APIs, Container/Closures and Products discovered during domestic inspections: Mr. Lawson reports no rejected components or APIs from a foreign source since the previous inspection.

DFI Field Bulletin 36

Coverage of Drug Program Area Use of Wooden Pallets in Drug Manufacturing Operations found the firm does not allow the use of wooden pallets in controlled areas. I reviewed their pallet supplier document from (b) (4) stating they provide (b) (4) certification of

(b) (4)F for (b) (4)minutes to (b) (4) standards. MMT also provided an 8/5/10 King letter to suppliers for my review that requests only to send product on heat treated pallets. In addition the warehouse SOP includes the warehouse employees to check for the '(b) (4)' on products received in on wooden pallets.

SAMPLES COLLECTED
(written by MHH)

DOC 730681 was collected to document interstate commerce of Atropine, USP, Lot# (b) (4) received by the firm, used as the main component in the AtroPen Auto-Injector, Lot# 1PT716, and distributed into interstate commerce. An FDA 463a, Affidavit, was prepared for interstate documentation for Clint R. Lawson, Senior Director Quality. Mr. Lawson refused to read or sign per corporate policy.

VOLUNTARY CORRECTIONS
(written by SJB)

Corrections made to observations made during the previous inspection of 8/9-18/2010 were evaluated and appeared adequate. I observed there was no longer a rust-like appearance on the bottom of the stainless steel plate located on the window in Room (b) (4) I reviewed the gowning requalification of (b) (4) that was observed to have his sterile mask on incorrectly.

EXHIBITS COLLECTED

Exhibits are identified by the investigators initials and sequential exhibit number.

SJB

1. MMT Organizational charts (17 pages)
2. Pfizer Organizational chart reporting to Allan Larsen, VP, Established Products QO (9 pages)
3. Pfizer Organizational chart reporting to William C. Kennally III, Regional President N America-EP (6 pages)
4. SPM and Packaging-Shipping schedule for 1/30-2/10/2012 (2 pages)
5. Media Fill Tracking History (1 page)
6. Copies of Media Fill for Atropen Type Container/Closure Group Using (b) (4) – SPM Room (b) (4) for QP 11-802, QP 11-803 and QP 11-816 (22 pages)
7. Copy of CFI 11-06-001-SL Re: Media fill failures (21 pages)
8. Copy of NOE 11-08-002-SL, initiated 8/3/11 for Media Fill QP 11-801 (4 pages)
9. Copy of Pfizer 12/22/2011 Public Communication and Dear Healthcare Professional with Subject: Important Safety Information on the Correct Use of EpiPen and EpiPen Jr Auto-Injector (6 pages)

10. EpiPen NGA labeling for US and leaflets for Canada EpiPen NGA (10 pages)
11. Charts re: Spontaneous Activation (3 pages)
12. 2009, 2010, & 2011 Top 10 EpiPen Complaints (3 pages)
13. Copy of 12/14/2011 Memo to File Re: Corrective action for spontaneous activation issue (2 pages)
14. Copy of 1/26/2012 Memo to File Re: Answer to Health Canada request on modification to Safe Pin Cap dated 1/11/12 (2 pages)
15. Copies of APA Entry Log S12540 pages 6-9 (4 pages)
16. Copy of SOP-PRO-FIL-00047-SL Cleaning and Sanitization of Aseptic Processing Areas (APA) (10 pages)
17. Copy of NOE dated 11/14/11 re: ATNNA 1M1726 and attachments (27 pages)
18. Copy of SOP-LAB-ENV-00805-SL Environmental Sampling of the Sterile Manufacturing Area (19 pages)
19. Copies of Media Fill (b) (4) Test Report 6 pages each for batch no. QP 11-803, 11-807, and 11-808 (18 pages)
20. List of attendees to the close-out meeting (1 page)
21. Copy of SOP-QLA-MQA-00723-SL, NDA Field Alert and Product Recall (7 pages)
22. NDA-Field Alert Report initial date notified of problem 4/8/2011 submitted 4/13/2011 and final report (4 page)
23. Copy of SOP-QLA-COM-00005-SL, Supplier Evaluation/Approval Process (12 pages)
24. (b) (4) COA for Glycerin, USP (6 pages)
25. Copies of Raw Material Test Report for control no. (b) (4) and (b) (4) (4 pages)
26. Copy of (b) (4) document showing (b) (4) as the manufacture with a reference code: (b) (4) (page 1)
27. Copy of (b) (4) audit of (b) (4) dated (b) (4) (1 page)
28. Copy of King supplier Audit of (b) (4) and (b) (4) (2 pages)
29. Copy of MMT Raw Material Specification for Glycerin, USP/EP (5 pages)
30. Copy of SOP-QLA-COM-00010-SL, Supplier Audit Procedure (11 pages)
31. Copy of MMT template for Audit (2 pages)
32. Copy of King PI for Glycerin dated (b) (4) with attachments (5 pages)
33. Copy of NDA 19-430/S-051 FDA Approval Letter signed 11/7/2011 and MMT 10/3/2011 request (3 pages)

JAB

1. SOP-LAB-MIC-00406-SL, Sterility Test Procedure. (13 Pages)
2. SOP-LAB-ENV-00805-SL Environmental Sampling of the Sterile Manufacturing Area. (19 pages)
3. SOP-QLA-MQA-00603-SL Proper Documentation, Version 9.0. (8 Pages)
4. Selected pages from 1PT716 filling record. (5 Pages)
5. 1PT716 Personnel Monitoring form. (1 Page)
6. NOE 11-12-016-SL. (28 Pages)
7. Active air sampling forms for (b) (4) and (b) (4) (2 Pages)
8. OP-QLA-MQA-00603-SL Proper Documentation, Version 9.0. (10 Pages)
9. Documentation Practices Presentation. (9 Pages)

10. Updated filling record for AtroPen page. (2 Pages)
11. SOP-PRO-FIL-00001-SL General Aseptic Procedure. (8 Pages)
12. SOP-PRO-FIL-00002-SL Aseptic Processing Area Gowning. (8 Pages)
13. Diazepam #1D1796 filling accountability. (1 Page)

SAH

1. NOE #11-11-008-SL, dated 11/08/11 (6 pages)
2. SOP-QLA-MQA-00720-SL – Notice of Event (NOE) and Cross Functional Investigation (CFI) Reports, RETIRED (20 pages)
3. SOP-QLA-MQA-00719-SL – Notice of Event (NOE), dated 01/03/12 (15 pages)
4. NOE #11-12-008-SL, dated 12/13/11 (24 pages)
5. LIR #11-10-002-SL, dated 10/06/11 (9 pages)
6. SOP-PRO-CLP-00050-SL – Preparation of (b) (4) Needles, dated 05/21/10 (4 pages)
7. Batch 1M1726, dated (b) (4), pg 3 (1 page)
8. Batch 1M1726, dated (b) (4) pg 15 (1 page)
9. Batch 1M1726, dated (b) (4) pg 19 (1 page)
10. Batch 1M1726, dated (b) (4) pg 23 (1 page)
11. Batch 1M1726, dated (b) (4) pg 4 (1 page)
12. SOP-MDP-GEN-00013-SL – In-Process Product Transfer, dated 12/01/11 (10 pages)
13. Product Transfer Form for 1M1726, dated (b) (4) 1 page)
14. Product Transfer Form for 1PT716, dated (b) (4) 1 page)
15. SOP-QLA-MQA-00720-SL – Quality Assurance Reports (QAR), dated 01/03/12 (22 pages)
16. FRM-QLA-431 - Request to Perform Rework form (1 page)
17. OP 11-808 Attachment 5.12A: List of Filling Events (32 pages)
18. Microbial Trends for OP 11-808 (4 pages)
19. Summary of (b) (4) Environmental Sampling of the Aseptic Processing Area, dated 06/10/11 (1 page)
20. SOP-PRO-CLP-00104-SL – Training and Qualification of Aseptic Processing Personnel (7 pages)
21. FRM-PRO-034 – (b) (4) Certification of Aseptic Technique form (1 page)
22. SOP-LAB-ENV-00807-SL – Monitoring Aseptic Processing Area for Microbial Contamination, pg 9 (1 page)
23. SOP-QLA-MQA-00600-SL – Quality Assurance Batch Record Audit and Product Disposition (18 pages)
24. FRM-PRO-403 – Guidance Form for Adding Comments to the Master Batch Record (1 page)

MHH

1. Top 5 Current Product List (1 page)
2. Meridian Medical Job Descriptions (23 pages)
3. Complaints from DQRS (9 pages)
4. SOP-QLC-SQC-00384-SL (Annual Review of Product Reserves Procedure) (6 pages)
5. Annual Review of Product Reserves (6 pages)

ATTACHMENTS

FDA 482, Notice of Inspection, issued to Clint R. Lawson, Senior Director Quality at the Brentwood facility on 1/30/2012

FDA 483, Inspectional Observations, issued to Stephen C. Natsch, Vice President and General Manager issued at the Brentwood facility on 2/13/2012

FDA 463a, Affidavit, dated 2/13/2012 for Clint R. Lawson, Senior Director Quality (unsigned)

Shirley J. Berryman, Investigator

Sandra A. Hughes, Investigator

Justin A. Boyd, Investigator

Matthew H. Hunt, Investigator