DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE Kalamazoo, MI 49001	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

The ATNAA (Atropine 2.1mg/0.7mL and Pralidoxime Chloride 600mg/2.0mL Injection) auto-injector remediation process was not validated to consistently detect and remove all ATNAA units with atropine (b) (4) [redacted]

Specifically,

SOP 27283, Kalamazoo Site Validation Master Plan, states that validation is defined as "established documented evidence that provides a high degree of assurance that a specific method, process, or system will consistently perform as intended." According to the MMT Remediation Plan dated 5/20/13, the intent "of the remediation is to use a robust, validated process to check units of ATNAA… [and] detect and remove units that do not have either atropine (b) (4) [redacted] or pralidoxim (b) (4) [redacted] as described…".

However, the acceptance criteria for executed Process Validation Protocols QP 13-136 and QP 13-130 do not require evidence that the remediation process will perform as intended. The acceptance criteria requires that 100% reconciliation of units is maintained, all batch record steps are completed as specified, and that copies of all documentation are included.

For example, for Process Validation Protocol QP 13-136, lot 2M1030 was remediated. During post-remediation testing for lot 2M1030, 5 units from the (b) (4) [redacted] unit sample failed due to atropine levels below (b) (4) [redacted] including 1 unit with (b) (4) [redacted] g of atropine. In spite of these failed units, the results summary for QP 13-136 states that the acceptance criteria were met and that the remediation process is validated.

Overall, in 22 out of (b) (4) [redacted] remediated lots, 1 to 13 units from each lot's (b) (4) [redacted] unit sample failed the atropine fill volume requirement of (b) (4) [redacted] demonstrating that the remediation process does not perform consistently as

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Emily J. Orban	Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013

intended.

OBSERVATION 2

The design of the ATNAA remediation process did not adequately evaluate all variables to consistently detect and remove all ATNAA units with atropine (b) (4) and/or pralidoxime (b) (4) g (b) (4) % of target).

Specifically,

A. The occurrence rate and impact of ATNAA unit separation plunger dislodgement on the atropine fill volume visual inspection process was not evaluated. In several of the ATNAA Fill Volume Weight Check reports used to document the post-remediation testing of a (b) (4) unit sample from a lot, the presence of ATNAA units found with atropine (b) (4) was explained by referencing MTR 13-038. This report dated 7/9/13 states that ATNAA units can pass the visual inspection process, but have atropine fill weights of (b) (4) due to separation plunger dislodgement and documents several instances where this occurred. In total, 22 out of (b) (4) remediated batches contained units from th (b) (4) sample that failed the atropine fill volume requirement of (b) (4) g

B. The weight check limit o (b) (4) g used to evaluate pralidoxime fill weight is inadequate to assure that the remediation process will remove all ATNAA units with a pralidoxime fill of (b) (4) % (b) (4) g) of the target. MTR 13-003 and MTR 13-012 document that the limit of (b) (4) g was derived, in part, by calculating the maximum weight of an empty ATNAA unit (b) (4) g) with (b) (4) % confidence. During remediation of lot 1M1738, ATNAA unit weights of up to (b) (4) were recorded, which indicate a greater empty unit weight than previously assumed possible. Management stated this was likely due to component weight variability not represented in the MTRs. Due to these higher than expected weights, the calculated weight check limit of (b) (4) g does not ensure that all units with a pralidoxime fill of (b) (4) g (b) (4) % of target) are removed with (b) (4) % confidence, as stated in the Remediation Plan dated 5/20/13.

OBSERVATION 3

The ATNAA remediation process and visual inspection operators were not qualified to consistently detect and remove all ATNAA units with atropin (b) (4) g.

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE Kalamazoo, MI 49001	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

Specifically,

The MMT Remediation Plan dated 5/20/13 states the validity of the Visual Examination of Atropine process will be demonstrated, in part, by Qualification Protocol QP-13-129. This QP states that the process will be qualified by seeding (b) (4) marked ATNAA units with (b) (4) g of atropine into a population of (b) (4) units and that the successful removal of all (b) units during remediation would result in a successful qualification. This proposed draft qualification protocol QP 13-129 to qualify the atropine fill volume visual examination process was never performed and no equivalent qualification protocol was executed prior to the remediation of all ATNAA lots including 2M1257, 2M1513, 1M1738 and 1M1512.

Instead, to be qualified for the ATNAA atropine fill volume visual inspection process, personnel were required to complete a single skill check demonstration by successfully removing (b) (4) seeded units with (b) (4) g of atropine from a (b) (4) unit qualification kit. No objective data was provided to support that operators could successfully identify and remove ATNAA units with an atropine fill weights between (b) (4) g and (b) (4) g. In 22 of (b) (4) remediated lots, 1 to 13 units from each lot's (b) (4) unit post-remediation test sample were found with atropine weights ranging between (b) (4)

OBSERVATION 4

Written process validation protocols for the remediation of ATNAA units were not followed.

Specifically,

Operators were not qualified according to the remediation plan and process validation protocol requirements for the atropine visual examination step of the ATNAA remediation process. The MMT Remediation Plan dated 5/20/13 states that the validity of the remediation process will be demonstrated by several documents, including an OJT protocol. The qualification criteria for this OJT states that the "Inspector must successfully complete (b) (4) consecutive Skill Check Demonstrations" which consists of removing all (b) (4) (b) (4) Additionally, both Process Validation Protocol QP 13-136 and Process Validation Protocol QP 13-130 state: "Only trained personnel can participate in QP 13-136 [QP 13-130] and future production requiring this

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Kalamazoo, MI 49001	Drug Manufacturer

additional rework step. Each inspector qualified must have successfully completed (b) (4) consecutive skill check demonstrations utilizing this qualification test kit. At the completion of each skill check, the trainer verified the defects were the seeded units. This was repeated with each inspector qualified, demonstrating consistent, reproducible results." Protocol QP 13-136 was used for PV lot 2M1030; Protocol QP 13-130 was used for PV lot 2M1257.

No documentation was provided to support that employees listed as able to perform the fill volume checks (FVC) on the Sign-In Forms for PV lots 2M1030 and 2M1257 completed (b) (4) test kit qualifications. Management confirmed every employee only completed one kit. (b) (4) employees were listed as able to perform FVC on lot 2M1030 and (b) (4) were listed for lot 2M1257.

OBSERVATION 5

Investigations related to ATNAA product discrepancies were inadequate.

Specifically,

A study used to justify particulate matter found in the rear grooves of the plunger failed to adequately address the issue. Three units in ATNAA lot 1M1512 and two units in lot 1M1738 were found with particulate matter in the grooves during the testing of each lot's (b) (4) unit post-remediation sample. The analyst familiar with this stated it was partially liquid. Finding moisture in the grooves of the rear plunger could be considered a potential sterility breach. A brief footnote was written at the bottom of the pages of the ATNAA Fill Volume Weight Check records stating particulate matter was found and referenced a MMT Memo dated September 3, 2013 for justification. This three paragraph memo stated particulate matter found on remediated units from batch 1M1426 appears to be dried pralidoxime chloride. The referenced memo does not address particulate matter being found in the grooves of the rear plunger but rather dried material found on a unit.

OBSERVATION 6

Employees performing the ATNAA remediation process were not trained according to written procedures.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Kalamazoo, MI 49001	Drug Manufacturer

Specifically,

SOP 29173, Kalamazoo Curricula Management, states employees are to complete the training items in their job specific curricula prior to performing job-related tasks. Example discrepancies are noted as follows:

a. Employee (b) (6) worked on ATNAA remediation batch 2M1257 which ran from 6/8-6/11/13 (b) (6) did not complete training on the written SOP for the 100% manual check of assembled and labeled units for low upper chamber fill volume until 6/15/13 (training item PGM-KZO-TEO8002223 and SOP-MAN-INS-00002). This training item is part of the curricula for operators working on the remediation process. It is a prerequisite for completing the OJT training item (PGM-KZO-OJ08001802) which qualifies the employee to work independently on the fill volume check.

b. Contract employee (b) (6) was signed in to work on remediation batch 2M1257 on 6/10/13 without any restriction from performing the upper chamber low fill inspection. (b) (6) had not completed the OJT training (PGM-KZO-OJ08001802) for this task. Management stated that employees were frequently rotated through different tasks throughout their shifts. (b) (6) was enrolled in the ATNAA Operator Remediation curricula PGM-KZO-0000105520 which requires the upper chamber low fill inspection OJT training. If such training could not be completed, it was to be noted on the sign in sheet of the batch record.

c. Employee (b) (6) signed in to work on batch 2M1257 on 6/10/13. (b) (6) performed line operator duties by signing off on two items on this batch record. (b) (6) was enrolled in the line coordinator curriculum (PGM-KZO-0000105519) which includes record training item PGM-KZO-TE0800221 which required review of the batch record. (b) (6) did not complete this training item until 7/31/13.

OBSERVATION 7

The ATNAA batch records are deficient in that they do not include identification of the persons performing each significant step in the operation.

Specifically,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE Kalamazoo, MI 49001	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

The batch records for the remediation of all ATNAA lots do not always identify which tasks an operator performed during processing (e.g. the ATNAA upper chamber visual inspection, the unit weight checks, and/or the re-packaging steps). There is no documentation that individuals did not perform the visual fill volume checks (FVCs) when they were not trained to do so.

The Following Additional Contract Non-Conformances Were Observed:

OBSERVATION 8

The switching rules in the ISO-2859-1 standard, which require tightened inspection and discontinuance when the appropriate thresholds for failed lots are met, were not applied. Management stated the switching rules were not used for the remediated lots. Section 9.3.1 of ISO 2859-1 requires the sampling to go to tightened inspection when (b) (4) out of (b) (4) consecutive lots have been non-accepted. The results from AQL sampling of the remediated lots found the first two lots of ATNAA (2M1257 and 2M1513) met the criteria of zero low atropine fills, yet the next 8 batches failed. The (b) (4) lot should have been under tightened inspection if the switching rules in ISO-2859-1 were followed.

ISO 2859-1 Section 12.6.1 "Use of individual plans" reads "Occasionally, specific individual plans are selected from this part of ISO 2859 and used without the switching rules. For example, a purchaser may be using the plans for verification purposes only. This is not the intended application of the system given in this part of ISO 2859 and its use in this way shall not be referred to as "inspection in compliance with ISO 2859-1"."

The Modified Contract section 2.c signed 9/19/13 states that a sample size of (b) (4) units from each lot shall be evaluated in accordance with ISO 2859-1 and that the sample will meet an Acceptable Quality Level (AQL) of (b) (4)

OBSERVATION 9

Documentation was not provided to support that AQL samples were collected at random. The modified contract

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 (313) 393-8100 Industry Information: www.fda.gov/oc/industry	9/30/13, 10/1/13, 10/2/13, 10/3/13, 10/9/13
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Road
CITY, STATE AND ZIP CODE Kalamazoo, MI 49001	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

section 2c states in part, "remaining ATNAA units from each lot/batch shall include an additional inspection whereby a sample size of (b) (4) units in accordance with ISO 2859-1…". ISO 2859-1 states in section 8.1: "The items selected for the sample shall be drawn from the lot by simple random sampling…". No evidence was provided that AQL samples were drawn at random for ATNAA lots 1M1512, 2M1257, 2M1513, or 1M1738. The batch records and written procedures do not include instructions and documentation on where and how samples were collected. The Process Technology Manager stated there are no specific instructions on how to collect random samples.

The Modified Contract signed 9/19/13 states "Remaining ATNAA units from each lot/batch shall include an additional inspection whereby a sample size of (b) (4) units in accordance with ISO 2859-1 [is evaluated]".

OBSERVATION 10

On 10/1/13, during FDA review of remediated pouches from 10 of (b) (4) outer shipping boxes from ATNAA lot 2M1257, 3 pouches out of (b) (4) were observed to be missing the "R" used to denote they had been remediated. Two of the (b) (4) lots presented for review used the same pouch material item number which was susceptible to this defect. Batch records used at the Kalamazoo site during the remediation of ATNAA did not state to review sealed pouches for the presence of an "R" until revision 7, dated 7/15/13. One of the four ATNAA lots presented for review (lot 2M1257) did not have the written requirement in the batch record to review sealed pouches for the presence of an "R", as required in MMT batch record FP-M-1. Management stated the review for an "R" was only verbally stated to employees at the time of remediation for this lot.

The MMT Remediation Plan dated 5/20/13 states that "The overall remediation process will be documented in a batch record FP-M-1". Batch Record FP-M-1 states under Repackaging Step 5 to "100% inspect each sealed pouch for absence of wrinkles, creases, gaps, folds, and printed "R"."

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Emily J. Orban	Jeffrey D. Meng, Investigator Emily J. Orban, Investigator Danial S. Hutchison, Compliance Officer Dawn C. Olenjack, Investigator	10/09/2013