DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
550 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 (312) 353-5863 Fax:(312) 596-4187 Industry Information: www.fda.gov/oc/industry	08/25/2010 - 09/17/2010* FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kimberly J. Wasserkrug, Executive Director, Quality Control and Assurance

FIRM NAME	STREET ADDRESS
Akorn, Inc.	1222 W Grand Ave
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Decatur, IL 62522-1412	Pharmaceutical Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Drug products failing to meet established standards, specifications, and quality control criteria are not rejected.

Specifically,

- Product Code 566, Myochrysine is a light sensitive injectable product. It is labeled as a light sensitive product. The firm manufactured batch #031170 consisting of (b) (4) units . This batch was exposed to 119 hours and 57 minutes of light. The validated light exposure time was no more than (b) hours. The excursion was discovered on 4/16/2010, after the process step had been completed. This batch was released and distributed.

- Product Code 547, Labetalol Hydrochloride Injection, USP, 5 mg/mL, 40 mL/50mL vial. This is a light sensitive injectable product. It is labeled as a light sensitive product. The firm manufactured batch #031280 consisting of (b) (4) units. The validated light exposure hold time is calculated from the time the API is added to the compounding vessel through the end of packaging. The actual light exposure time for this batch was 264 hours and 18 minutes which exceeds the validated light exposure time of not more than (b) (4) hours. This was discovered on 03/24/2010. This batch was released and distributed.

- Fluorescein Injection USP 10% (100ml/mL as Fluorescien Sodium) product code 5010, has a validated hold time for no more than (b) hours. This batch was formulated on 03/22/2010. The actual hold time on batch #031320 was 192 hours. This batch consisted of (b) (4) units which was released and distributed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Phung Thien Nguyen, Investigator Carl A. Huffman III, Investigator	09/17/2010

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OBSERVATION 2

Failure to reject any lot of components that did not meet the appropriate written specifications for identity, strength, quality, and purity.

Specifically,

The firm used expired 25% Benzalkonium Chloride Solution, NF Lot #81149, expiration date of "02/2010 or 02/28/10" in the manufacturing of two drug product. The two drug products are:

- Brimonidine Tartrate Opthalmic Solution, Code #5135 Lot #031030 formulated on 03/01/10 and released by the quality unit on 03/20/10
- Tobramycin Opthalmic Solution, Code #5021 Lot #031040 formulated on 03/02/10 and released on 04/07/2010

OBSERVATION 3

Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use.

Specifically,

The firm currently has the following products on the market without appropriate stability data to support the expiration dating:

- Myochrysine (Gold Sodium Thiomalate) Code 566, Lot # 031170.
- Labetalol Hydrochloride Injection, Code 547, Lot # 031280.
- Fluorescein Injection, USP, Code 5010 Lot #031320.
- Brimonidine Tartrate Opthalmic Solution, Code #5135 Lot #031030.
- Tobramycin Opthalmic Solution, Code #5021 Lot #031040.

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OBSERVATION 4

Each lot of components, drug product containers, and closures is not withheld from use until the lot has been sampled, tested, examined, and released by the quality control unit.

Specifically,

The firm released raw materials and components into manufacturing prior to the completion of testing, the firm calls this "conditional release". The following are the "conditional release" raw materials and components from 06/2009 to 09/2010:

- Dev 2009 09-99-3-0045: Stoppers, item #310079
- Dev 2009 09-10-3-0072: API, Tyloxapol, USP Lot #19090021
- Dev 2009 09-10-3-0089: Excipient raw material, Sodium Chloride, USP Lot #E34435
- Dev 2009 09-11-3-0103: API, Ephedrine raw material Lot #017173AX10
- Dev 2009 09-22-9-0110: (b) (4) stoppers lot #(b) (4)
- Dev 2009 10-10-3-0041: 1ml treated amber ampule, customer batch no. 68658
- Dev 2010 10-11-3-0033: API, Phenylephrine HCL raw material lot #1043185
- Dev 2010 10-10-3-0069: API, Phenylephrine HCL lot #1045452

OBSERVATION 5

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

- The last six consecutive batches of Atropine (product code 5058, batches (b) (4) (b) (4)) failed to meet the solution yield criteria of (b) (4) %. The following are the corresponding Non-Laboratory Out of Specifications (NL-OOS) and yield results for these batches:
  - 10-15-00064, 96%
  - 10-15-00092, 93%
  - 10-15-00117, 93%

- 10-15-00325, 95%
- 10-15-00354, 96%
- 10-15-00395, 94%

The firm has not taken follow-up actions to address the continued failures of actual vs. theoretical yields of these products.

- Six of the last 23 batches of Hydralazine HCL (product code 563, batches (b) (4) (b) (4)) failed to meet the solution yield criteria of (b) (4) %. The following are the corresponding NL-OOSs and yield results for these batches:

  - 10-15-00066, 96%
  - 10-15-00126, 96%
  - 10-15-00263, 96%
  - 10-15-00335, 96%
  - 10-15-00345, 95%
  - 10-15-00396, 95%

The firm has not taken follow-up actions to address the continued failures of actual vs. theoretical yields of these products.

- The following light-sensitive injectable product batches exceeded their validated light exposure time:

  - Myochrysine (Gold Sodium Thiomalate), USP 50mg/ml, 1ml in a 2ml vial, Product Code 566 batch #031170. Exposure time: 119hrs, 57min, Validated Maximum hold time: (b) (4)
  - Labetalol Hydrochloride Injection, USP, 5 mg/mL, 40 mL/50mL vial, product Code 547 batch #031280. Exposure time: 264hr, 18min, Validated Maximum hold time: (b) (4) hrs.

The firm implemented Protocol P2609-08-01, Protocol for Evaluation of Commercial Batches for Excursion in Validated Process Hold Times, to address the products being exposed to light longer than the validated maximum light exposure time. The firm did not conduct an investigation which addressed root cause. The investigation conclusion did not result in a corrective action or preventive

action plan.

- The following injectable product batch exceeded its validated hold time:

    - Fluorescein Injection, USP 10% (100ml/mL as Fluorescien Sodium), product code 5010, batch #031320

  The firm implemented Protocol P2609-08-01, Protocol for Evaluation of Commercial Batches for Excursion in Validated Process Hold Times, to address the product being held longer than the validated maximum hold time. The firm did not conduct an investigation which addressed root cause. The investigation conclusion did not result in a corrective action or preventive action plan.

OBSERVATION 6

Written procedures are lacking which describe in sufficient detail the testing, approval, and rejection of components, drug product containers, and closures.

Specifically,

- Protocol P2609-08-01, Protocol for evaluation of commercial batches for excursions in validated process hold time. This protocol was used on the following batches:

    - Myochrysine (Gold Sodium Thiomalate), USP 50mg/ml, 1ml in a 2ml vial, product code 566 batch #031170
    - Labetalol Hydrochloride Injection, USP, 5 mg/mL, 40 mL/50mL vial, product code 547 batch #031280
    - Fluorescein Injection, USP 10% (100ml/mL as Fluorescien Sodium), product code 5010, batch #031320

  These batches were released and distributed. This protocol is not initiated until after manufacturing and is used to approve product that has been processed outside of validated parameters. The protocol does not require an investigation that addresses root cause, corrective/preventative actions.

- The firm uses SOP QA106, Revision 9, Dated 01/14/2010, titled Review and Approval of Raw Materials. The SOP states under section 5.4:

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"Any planned use of incoming material in Production, prior to completion of incoming testing, must be considered only in the most extreme and unusual circumstances documented with a planned deviation that defines the reason and justification for the deviation. Such deviaitons must have the prior written approval or the Akorn VP of Global Quality and Regulatory Compliance. This will be referred to as a conditional release."

The firm uses this SOP to allow "conditional release" of raw materials, components, and closures into manufacturing before testing has been completed.

OBSERVATION 7

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

Specifically,

- SOP *QSP 13.1 Supplier Qualification, effective date March 15, 2006* requires the review and evaluation of all suppliers. This SOP states that quality history along with several other criteria may be reviewed. Documentation for approval of four active pharmaceutical ingredient suppliers were requested, two of the four had a supplier questionnaire and the other two were approved through a quality history review. The firm provided the questionnaires, but was unable to provide the documentation for the quality history approvals. The following firms were approved through Quality History (QH) review:

  - (b) (4) Phenylepherine HCL, USP, (QH)
  - (b) (4) Tyloxapol, USP, (QH)

  The firm stated that they currently do not have documentation for suppliers approved through a QH review. The firm has a total of (b) suppliers they have qualified in this manner.

- The firm's SOP QA153 Procedures for Processing and Issuing SOPs, describes the process of document control for SOPs. During the walkthrough seven SOPs were randomly selected from rooms A and B:

  - Room A, SOPs:

- QA115 Revision 12 was found; current version is 18
- QA133 Revision 4 was found; current version is 9

o Room B, SOP:

- FL133 Revision 8 was found; current version is 9

- The firm's validation for Atropine, product code 5058 consisted of three batch runs. The process parameters established for step 24 in the validation has atropine warming up to (b) (4) °C, but was later altered to (b) (4) °C because the room temperature is kept a (b) (4) °C. There was no justification in writing for this change.

- The firm's SOP, QA 162 revision 0, Quality Assurance Certification of Daily Water Testing and Preformulation USP/EP Testing states that the firm will keep an electronic log for daily water testing. This log was not kept from April to June 2010.

- The firm uses SOP QA106, Revision 9, Dated 01/14/2010, titled Review and Approval of Raw Materials. The SOP states under section 5.4:

> *"Any planned use of incoming material in Production, prior to completion of incoming testing, must be considered only in the most extreme and unusual circumstances..."*

The following are deviations and reasons for why incoming material was released into production prior to completion of incoming testing:

Deviations	Item	Description of Root Cause
Dev 2009 09-99-3-0045	Stoppers, item #310079	Scheduling conflict.
Dev 2009 09-10-3-0072	API, Tyloxapol, USP Lot #19090021	Not enough reagents in-house to complete incoming testing prior to production.
Dev 2009 09-10-3-0089	Excipient raw material, Sodium Chloride, USP Lot #E34435	Not enough of previous lot to complete formualtion.
Dev 2009 09-11-3-0103	API, Ephedrine raw material Lot #017173AX10	Validation for bioburden testing was not completed prior to the testing of the incoming lot of API.
Dev 2009 09-22-9-0110	(b) (4) stoppers lot # (b) (4)	Production and Laboratory scheduling of this lot did not provide adequate timing for

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		release prior to manufacturing.
Dev 2009 10-10-3-0041	1ml treated amber ampule, customer batch no. 68658	Production demand immediate upon receipt.
Dev 2010 10-11-3-0033	API, Phenylephrine HCL raw material lot #1043185	Microlaboratory scheduling.
Dev 2010 10-10-3-0069	API, Phenylephrine HCL lot #1045452	Production demand.

OBSERVATION 8

The master production and control records are deficient in that they do not include complete instructions and specifications.

Specifically,

Thermocouples are placed in trays of Bentyl Injectable 10mg/ml code 2479 batch 081450 for b(4) [redacted] sterilization. The batch record states, "All LP's are to be placed in the center of the trays". However, the load probes (LP) are too long to be placed directly into the center of the tray except on the top layer. Therefore, personnel directly responsible for the validation needed to be present in order to clarify the set up. It was described by the validation personnel that during validation the top layer probe was placed directly in the center and the additional probes for the lower shelves were placed on the side of the trays. This information was not clearly stated within the batch records and the validation documentation was also not clear.

*** DATES OF INSPECTION:**
08/25/2010(Wed), 08/26/2010(Thu), 08/27/2010(Fri), 08/30/2010(Mon), 08/31/2010(Tue), 09/01/2010(Wed), 09/02/2010(Thu), 09/03/2010(Fri), 09/07/2010(Tue), 09/08/2010(Wed), 09/09/2010(Thu), 09/13/2010(Mon), 09/14/2010(Tue), 09/16/2010(Thu), 09/17/2010(Fri)

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