DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| U.S. Food and Drug Administration, New Jersey District Office<br>10 Waterview Boulevard, 3rd Floor<br>Parsippany, NJ 07054<br>P: (973)-331-4900, F: (973)-331-4969<br>Industry Information: www.fda.gov/oc/industry | 1/24, 1/25, 1/26, 1/28, 2/3, 2/4, 2/7, 2/9, 2/10, 2/11, 2/15, 2/18/2011 |
| | FEI NUMBER<br>2243092 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dr. David P. Jacobus, President

| FIRM NAME | STREET ADDRESS |
|---|---|
| Jacobus Pharmaceutical Co., Inc. | Industrial Research Building, Schalks Crossing Road |
| CITY, STATE AND ZIP CODE<br>Plainsboro, NJ 08536 | TYPE OF ESTABLISHMENT INSPECTED<br>Active Pharmaceutical Ingredient and Finished Dosage Form Mfr. |

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:

***AMENDED THE FDA 483 TO ORGANIZE THE OBJECTIONABLE CONDITIONS ACCORDING TO THE GMP SYSTEMS AND TO AMEND OBSERVATION 4 FOR A TYPOGRAPHICAL ERROR.***

LABORATORY CONTROL SYSTEM

OBSERVATION 1

The written stability program for drug products does not include reliable, meaningful, and specific test methods.

Specifically, your stability program for Dapsone 25 mg and 100 mg tablets does not include a stability-indicating method to monitor potential impurities.

OBSERVATION 2

Your stability testing program is not designed to monitor the stability characteristics of APIs.

Specifically, you do not evaluate the Dapsone drug substance for any impurities during stability testing of this API.

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| | Atul Agrawal | Atul J. Agrawal, Consumer Safety Officer | 2/24/2011 |

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## QUALITY SYSTEM

### OBSERVATION 3

Your firm's quality unit is not involved in quality-related matters; the unit fails to review deviations from established specifications or procedures and does not adequately assess the need for corrective actions for deviations it is made aware of.

Specifically,

1. Excursions dated back to June 2009 for your controlled room temperature (CRT) stability chamber, in-process cold room, and transport and handling of in-process lots of your PASER granules product were not investigated. These include the following examples:

a. For the CRT chamber used for long-term stability samples for APIs and finished drug products (e.g. Dapsone, Sulfapyridine, 3,4 Diaminopyridine):

| Dates | # of Excursion Events | Humidity | Temperature | Total Length of Time |
|---|---|---|---|---|
| 8/26-10/1/09 | (b) (4) | low & high | N/A | >14 days |
| 12/7/09-1/11/10 | | low | low | >2 days |
| 3/13-4/19/10 | | high | N/A | >19 hours |
| 8/19-9/28/10 | | low | high | >1 day |
| 12/28/10-1/26/11 | | low | low | >1 day |

For the in-process cold room used to store in-process PASER granule lots (storage requirement of less than (b) (4) °F):

| Dates | # of Excursion Events | Humidity | Temperature | Total Length of Time |
|---|---|---|---|---|
| 3/18-4/9/10 | (b) (4) | N/A | high | >14 hours |
| 7/8-8/9/10 | | N/A | high | >2 days |

You have no SOP that defines the monitoring and maintenance of your stability chambers and cold room. The stability chamber is not monitored on a frequent basis and has not been reviewed for adequacy since the sole

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qualification of the chamber in 1999.

b. For the transport and handling of in-process PASER granule lots, I found the following high temperature excursions:

| Dates | # of Lots | # of Excursion Events | Total Time | Extreme Temp Recorded |
|---|---|---|---|---|
| 6/12-7/22/09 | (b) (4) | (b) (4) | >25 days (1 event= (b) (4) ays) | 82.9 °F |
| 2/19-3/8/10 | | | >20 hours | 74.8 °F |
| 6/4-7/21/10 | | | 1 day | 73.7 °F |

This product is transported to a contract coating facility and then to a contract packaging company. Your employees informed me that this product is to be maintained at less than (b) (4) F between manufacturing steps and that data loggers are included during the transport and handling of in-process lots of PASER granules to ensure adequate storage and handling.

No follow-up or investigations were conducted for the excursions listed above to determine root cause and potential impacts on the products and stability studies.

2. Deviations during the production of 4-Aminosalicylic Acid (aka PAS) are not reviewed by your firm's quality unit at the time of occurrence. According to your firm's SOP # G-0023-01 titled "Deviations," your quality assurance department is responsible for reviewing and approving all proposed actions and corrective actions following deviations within (b) (4) hours of the event. Examples of deviations not reviewed by your QA unit within (b) (4) hours include:

| Lot | Deviation | Date of Deviation | QA Review Date of Deviation |
|---|---|---|---|
| 1163 | pH drop during precipitation | 2/15/09 | 3/19/09 |
| 1171 | pH drop during precipitation | 3/10/09 | 4/8/09 |
| 1219 | flow meter malfunction* | 7/31/09 | 8/21/09 |
| 1364 | acid valve malfunction** | 10/20/10 | 12/13/10 |

* This flow meter malfunction also occurred during the 8 subsequent lots (1220-1227) of PAS manufactured after

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Lot 1219. Your QA unit did no assessment to determine appropriate corrective and preventative actions after the flow meter problems associated with lots 1219-1227.
** Production indicated that this may affect the API particle size. The [redacted] (b) (4) and the production of the batch was continued.

I observed that there is no written program that identifies and defines your quality unit's roles and responsibilities related to the manufacture, processing, packaging, holding, and distribution of drug products.

OBSERVATION 4

Written procedures are not established for evaluations done at least annually and including provisions for a review of complaints and investigations conducted for each drug product.

Specifically,
a. Your quality unit failed to review all complaints and investigations related to finished drug products when conducting annual reviews. For example, the 2009 annual review for PASER Granules did not include a review of [redacted] (b) (4) 9 manufacturing investigations conducted for the product. Three of these investigations were for the same issue (moisture content failures during manufacturing).
b. You do not have an established procedure for evaluating finished drug products on at least an annual basis that would include a review of complaints and investigations. Your SOP titled "Product Quality Review" addresses annual reviews for APIs but not finished drug products.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

Appropriate controls are not established over computerized systems.

Specifically, computerized systems in your Quality Control laboratory do not have sufficient controls to prevent unauthorized access to, changes to, or omission of data. Electronic data can be deleted from computerized systems connected to your HPLC and UV-VIS instruments with no audit trail to document such an event.

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Additionally, one general account and password for QC managers and analysts is used for the operating systems installed on these systems, and no computer lock mechanism has been configured to prevent unauthorized access to data.

OBSERVATION 6

Buildings used in the manufacture, processing, or holding of drug products are not maintained in a clean and sanitary condition.

Specifically, I observed powder-like residues covering approximately half of the floors and walls of your firm's sampling area for raw materials and components. I also observed leaking water from the outside of your facility onto the floors and walls of this sampling area.

OBSERVATION 7

Routine calibration of electronic equipment is not performed according to a written program designed to assure proper performance.

Specifically, you failed to calibrate and ensure the proper performance of a digital thermometer (serial # 99560022) used during the production of the finished drug product PASER granules to monitor the inlet air temperature, a critical parameter of the fluid bed dryer. The thermometer was due for calibration on June 30, 2010. Based on your firm's records, the fluid bed dryer has been used on a daily basis in the manufacturing process of more than (b) (4) batches of PASER granules since June 30, 2010. In addition, I observed another thermometer that is connected to your "Unit 2" spheronizer with no tag or sticker to indicate its calibration status.

PRODUCTION SYSTEM

OBSERVATION 8

The process validation for a 50% increase in the batch size (b) (4) of the active pharmaceutical ingredient PAS is inadequate.

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For example:
a. The validation did not define or specify the critical process parameters that need to be monitored and controlled.
b. There were no pre-defined acceptance criteria to determine the reproducibility of the process.
c. The protocol and report noted changes in the steps (e.g. size of the precipitations and centrifuge loads) and the times required. These specific changes were not outlined and justified in the protocol or report.
d. There was no provision for increased sampling to demonstrate the robustness of the process.
e. There was no provision for placing validation batches on stability.

OBSERVATION 9

Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not established and followed.

Specifically, your procedure for sampling purified water is inconsistent with actual practice. I observed employees acquiring purified water for use at valve 11 by using a plastic hose that is approximately 5 feet long. The hose is stored (hung) in several loops and routinely connected to the port in between uses, thus increasing the risk for bio-film buildup. Sampling is conducted by disconnecting the hose and directly sampling the port. This point of use is used to acquire purified water during the production of PASER granules.

OBSERVATION 10

All compounding and storage containers used during the production of a batch of drug product is not properly identified at all times to indicate the phase of processing of the batch.

Specifically, I observed that drums of in-process lots of PASER granules at the same stage of manufacture are stored together in your manufacturing areas and hallways during manufacturing and QC testing without being adequately identified as to its status. You have no controls in place to prevent mix-ups of in-process material for further manufacture.

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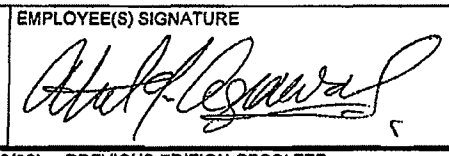
| |  | Atul J. Agrawal, Consumer Safety Officer | 2/24/2011 |