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SUMMARY

A surveillance inspection of this Active Pharmaceutical Ingredient (API) and finished dosage form manufacturer of commercial and investigational drug products was conducted as part of the NWJ-DO FY2011 drug workplan. The FACTS assignment number is 1101507 and OP ID number is 4405699. Compliance Programs 7256.002 and 7356.002F provided inspectional guidance. An investigational drug product was covered during the inspection based on a request from CDER's Office of Compliance, Division of Manufacturing and Product Quality.

The previous inspection of this firm was conducted by NWJ-DO in July 2008 as part of NWJ-DO's FY2008 drug workplan. The inspection covered the Quality, Production, Packaging and Labeling, and Laboratory Control Systems. An FDA 483, Inspectional Observations, was issued for the following: the firm failed to assure that a drug met the requirements of the FD&C Act based on an investigation that confirmed finding metallic particles; changes to written procedures were not drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality control unit (the firm changed manufacturing equipment and master batch records without prior and formal QC review); procedures designed to prevent objectionable microorganisms in drug products not required to be sterile were not established and/or followed with respect to managing the quality of the [redacted] (b) (4) used in [redacted] (b) (4). A discussion with management was also conducted regarding additional deficiencies. The inspection was ultimately classified as VAI. The firm submitted a written response regarding its corrective actions to the FDA; these corrections were reviewed and verified during the current inspection.

The current inspection covered the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Control Systems. An FDA 483 was issued for the failure to:

- establish a stability-indicating method to monitor potential impurities for Dapsone 25 mg and 100 mg tablets;
- evaluate the Dapsone drug substance for impurities during stability testing of this API;
- address temperature excursions from the controlled room temperature stability chamber, in-process cold room, and transport;
- investigate mishandling of PASER granules;
- review deviations during the production of Aminosalicylic Acid (PAS) within [redacted] (b) (4) as required by firm's procedure;
- review complaints and investigations related to finished drug products when conducting annual reviews;
- establish a procedure for evaluating drug products at least annually that would include a review of complaints and investigations;
- establish appropriate controls for computerized systems in the quality control laboratory to prevent unauthorized access, changes, or omission of data;
- clean powder-like residues and leaking water observed in the sampling area;
- calibrate and ensure the proper performance of a [redacted] (b) (4) used to monitor the [redacted] (b) (4) during [redacted] (b) (4);
- implement sound process validation for a [redacted] (b) (4) increase in the batch size of PAS;
- ensure the procedure for sampling [redacted] (b) (4) is consistent with actual practice for valve [redacted] (b) (4); and
- store drums of in-process lots of PASER granules at the same stage of manufacture with its status to prevent mix-ups.

Additional deficiencies were discussed with the firm's management throughout the inspection and at the closeout meeting. The firm decided to [redacted] (b) (4) until corrective actions are implemented and stated that they would respond in writing to the observations cited on the FDA 483 to NWJ-DO.

Although the firm established a stability test method for the Dapsone API in response to the October 1997 WL issued to the firm, it was never implemented over its expiration or re-test period.

The firm was cooperative and made no refusals. No samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	Jacobus Pharmaceutical Company Inc.
Location:	Industrial Research Laboratory Building Schalks Crossing Road Plainsboro, NJ 08536
Phone:	609-799-8221, 609-921-7447
FAX:	609-799-1176
Mailing address:	PO Box 5290 37 Cleveland Lane Princeton, NJ 08590
Dates of inspection:	1/24/2011, 1/25/2011, 1/26/2011, 1/28/2011, 2/3/2011, 2/4/2011, 2/7/2011, 2/9/2011, 2/10/2011, 2/11/2011, 2/15/2011, 2/18/2011
Days in the facility:	12
Participants:	Atul J. Agrawal, Consumer Safety Officer Rebeca Rodriguez, Consumer Safety Officer

On 1/24/11, CSO Rebeca Rodriguez and I, CSO Atul J. Agrawal, issued an FDA 482, Notice of Inspection, and presented our credentials, to Ms. Laura R. Jacobus, Vice-President of Quality Assurance. Ms. Jacobus stated that she was the most responsible person onsite at the time and was authorized to accept the FDA 482 on behalf of Dr. David P. Jacobus, who is the firm's president and most responsible individual. I explained to Ms. Jacobus the purpose of the inspection and that CSO Rodriguez was present for auditing purposes and would not be participating in the inspection.

The FDA 483 was issued to Dr. Jacobus during the closeout meeting on 2/18/2011. Dr. Jacobus and Ms. Jacobus stated that they would respond in writing to NWJ-DO within 15 days.

Relevant Inspectional History

The inspectional history of the firm for the past 3 inspections is as follows:

a. Inspection: 6/26/2008 – 7/9/2008

- Comprehensive GMP Inspection covering the Quality, Production, Packaging and Labeling, and Laboratory Control systems
- FDA 483 issued for the following:
  1. The firm failed to assure that a drug met the requirements of the FD&C Act based on an investigation that confirmed finding metallic particles.
  2. Changes to written procedures were not drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality control unit (the firm changed manufacturing equipment and master batch records without prior and formal QC review).
  3. Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile were not established and/or followed with respect to managing the quality of the [redacted] (b) (4) used in [redacted] (b) (4).
- Final Classification: VAI Firm's response: 10/3/2008

b. Inspection: 5/16/2006 – 5/23/2006

- Limited GMP Inspection covering the Quality and Materials systems
- No FDA 483 issued Final Classification: NAI

c. Inspection: 10/12/2004 – 10/26/2004

- Comprehensive GMP inspection covering the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Control systems
- No FDA 483 issued Final Classification: NAI

The firm received a warning letter in 1997 for GMP deficiencies related to APIs and finished products.

Dr. Jacobus requested that all correspondence be addressed to either himself or Ms. Jacobus as follows:

Dr. David P. Jacobus, President/Ms. Laura R. Jacobus, Vice-President of Quality Assurance

Jacobus Pharmaceutical Co., Inc.

37 Cleveland Lane

P. O. Box 5290

Princeton, NJ 08540.

INTERSTATE COMMERCE/JURISDICTION

The firm continues to manufacture APIs which are used to manufacture finished drug products into tablet or granular dosage form. This includes:

Commercial Drug Products:

- **Dapsone USP (4,4'-diaminodiphenylsulfone) 25 & 100 mg Tablets:**
  A technical grade of Dapsone, USP is acquired from [redacted] (b) (4) and then purified at this facility by [redacted] (b) (4) steps; this purified bulk/API is then used to manufacture Dapsone 25 mg and 100 mg tablets. The tablets, after [redacted] (b) (4) at this facility, are shipped to [redacted] (b) (4) for blister packaging. After packaging, the finished product is shipped to [redacted] (b) (4) . for distribution to customers.

  Therapeutic Use: Used most commonly for the treatment of leprosy and to control the dermatological symptoms of Dermatitis hepetiformis; it has been known to have an off-label use at times in preventing pneumonia in HIV patients

- **Paser (Aminosalicylic Acid) Delayed-Release Granules (4 grams per packet):**
  The API, Aminosalicylic Acid, is manufactured by [redacted] (b) (4) at the Plainsboro, NJ facility. It is then used in the production of PASER granules by [redacted] (b) (4) . The [redacted] (b) (4) granules are then shipped to [redacted] (b) (4) for enteric coating and then shipped to [redacted] (b) (4) for packaging into individual pouches (4 grams per pouch). After packaging, the finished product is shipped to [redacted] (b) (4) for distribution to customers.

  Therapeutic Use: Used in the treatment of tuberculosis

[redacted] (b) (4)

The firm ceased the production and distribution of the [redacted] (b) (4) in 2009; the API was manufactured exclusively for [redacted] (b) (4) The firm continues to support distributed lots still within expiry. The API was manufactured for further processing into [redacted] (b) (4) tablets.

Ms. Jacobus stated that greater than [redacted] (b) of the firm's commercial products enter interstate commerce. The firm distributes its commercial products for the US through the third-party logistics provider [redacted] (b) (4) [redacted] (b) (4) distributes Jacobus' products primarily to pharmaceutical distributors, examples of which are given in the History section of this EIR. The firm's products are ultimately used domestically and internationally. The firm distributes [redacted] (b) (4) [redacted] (b) (4).

Ms. Jacobus stated that since the previous inspection in July 2008, the firm has manufactured and distributed more than [redacted] (b) (4) batches of PASER Delayed-Release Granules, [redacted] (b) (4) batches of Dapsone 25 mg tablets, and [redacted] (b) (4) batches of Dapsone 100 mg tablets.

Exhibit 1 is a copy of information that is provided with each [redacted] (b) (4); **Exhibit 2** is a copy of labeling associated with US marketed lots of PASER granules and Dapsone 25 mg and 100 mg tablets.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Dr. David P. Jacobus stated that, as President, he is the firm's majority owner and most responsible individual. He stated that he is aware of all day-to-day matters. He maintains an office at his home and at the firm's manufacturing facility in Plainsboro, NJ and makes frequent visits to this site. Dr. Jacobus was present on most days of the inspection and participated in the closeout meeting and most of the discussions of issues that occurred.

Ms. Laura R. Jacobus, Vice-President of Quality Assurance, reports directly to Dr. Jacobus and is the firm's most responsible individual on a day-to-day basis. Dr. Jacobus informed me that Ms. Jacobus has the authority to make all decisions and implement corrective actions in his absence. Ms. Jacobus' responsibilities include: serving as the firm's most responsible person for quality-related matters; coordinating production, internal audits, and regulatory filings; designating priorities among departments; compliance review of all batches before release to market; review of SOPs; and managing and coordinating outside medical data.

Mr. Richard W. Pursell, Plant Manager and Pharmaceutical Manufacturing and Shipping Coordinator, reports directly to Ms. Jacobus. His responsibilities include: production schedules for dosage forms; assisting in the design and execution of validating or re-validating processes; production record review; new dosage form development; oversight of equipment cleaning and use logs; oversight of returned and salvaged drug products; coordinating product transfer and shipping; and assisting engineering employees in equipment maintenance and repair.

Mr. Raju Shah, Director of Quality Control, joined the firm in January 2010 and reports directly to Ms. Jacobus. Mr. Shah's responsibilities include: approval and rejection of all drug components, packaging, in-process materials, and all drug products; maintenance of QC equipment and laboratory reagents; maintenance of laboratory records; calibration and qualification of QC equipment; maintenance of reserve samples and the firm's stability program; conducting QC-related training; and working with the chemistry department on the analytical testing of the firm's [redacted] (b) (4)

Guy A. Shiehser, Ph. D, Director of Chemistry, reports directly to Ms. Jacobus. Dr. Shiehser's responsibilities include: API manufacturing; design of validation experiments; production schedules for API production; research on new chemical entities; conducting training, overseeing analytical research and development; production record review; and reviewing API records and initiating investigations as needed.

Mr. Robert J. Warman, Sr., Director of Engineering, reports directly to Ms. Jacobus. Mr. Warman, Sr.'s responsibilities include: overseeing the maintenance and monitoring of all mechanical systems (which include the [redacted] (b) (4)); coordinating with production and lab personnel for equipment installation, maintenance, and repair; and maintaining the areas used to store in-process materials (e.g. cold room for in-process lots of PASER granules).

Dr. Kathy Ales, Medical Officer, reports directly to Ms. Jacobus. Her responsibilities include: designing, writing, and submitting reports for clinical trials and on-going medical surveillance; reviewing and analyzing Med-Watch complaints; and coordinating with clinical research organizations. Dr. Ales was not present during the current inspection.

Most questions during the current inspection were answered by Dr. Jacobus, Ms. Jacobus, Mr. Pursell, Mr. Shah, Dr. Shiehser, and Mr. Warman, Sr. These individuals were also present for discussions of issues and concerns that occurred periodically.

Ms. Jacobus was my primary contact at the firm, provided documents, and made employees available as needed. Mr. Pursell and Mr. Shah escorted me on inspectional walk-throughs of the warehousing and manufacturing areas of the facility and the QC labs.

Additional information was provided by:

[redacted] (b) (6), Deputy Director of Quality Control, answered questions related to the firm's sampling and testing of raw materials and packaging components, in-process QC testing, finished product testing, and temperature and humidity data loggers.

[redacted] (b) (6), Jr., Engineer, answered questions related to the firm's temperature and humidity data for the controlled room temperature stability chamber, in-process cold room, and transport and storage of in-process lots of PASER granules.

[redacted] (b) (6) Chemist, answered questions related to the firm's sampling and testing of the [redacted] (b) (4).

[redacted] (b) (6) Production Supervisor, answered questions related to the firm's production of PASER granules and to the [redacted] (b) (4) and [redacted] (b) (4) of Dapsone 25 mg and 100 mg tablets.

Exhibit 3 is a copy of an organizational chart provided by Ms. Jacobus and a list of all of the firm's employees.

FIRM'S TRAINING PROGRAM

I reviewed the firm's SOP # G-0008-001 titled "Training"; the firm's program calls for GMP training to be provided to employees on a regular basis along with training related to the employee's job functions; training is also to be provided when a procedure is revised. I reviewed the training records for four employees, two of whom joined the firm after the last inspection. Based on the training records I reviewed and Ms. Jacobus' explanation of the firm's training policies, I found no deficiencies in the firm's training program.

MANUFACTURING/DESIGN OPERATIONS

As previously stated, I provided coverage of the Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory Control Systems. I covered the commercial products (PASER granules and Dapsone tablets) along with the [redacted] (b) (4) tablets.

The inspection included walk-throughs of areas on 1/24/11, 1/25/11, 1/26/11, 2/3/11, 2/4/11, 2/10/11, 2/11/11 and 2/15/11. **Exhibit 4** includes maps of the firm's facility in Plainsboro, NJ.

A. QUALITY SYSTEM

Ms. Jacobus provided me with a list of the firm's SOPs. I selected and reviewed SOPs from the list based on areas that I covered during the inspection. Ms. Jacobus and Mr. Shah informed me employees access SOPs from binders that are located in each area. I discussed several deficiencies related to the adequacy and adherence to firm's SOPs during the inspection and at the closeout meeting. Refer to item # 6 in the General Discussion with Management section of this EIR.

I began reviewing the firm's change control forms, which are reduced in size and pasted into log books. I asked the firm to create a list of all change controls; I reviewed the list and selected certain ones for further review. I observed that the firm conducted a (b) (4) increase in batch scale for the production of the API Aminosalicylic Acid in 2010 based on one of the change controls I selected for further review (**Exhibit 5**). Refer to the Production System section of this EIR.

Ms. Jacobus informed me that her firm has reprocessing procedures for APIs; however, reprocessing is not allowed for finished drug products. I reviewed one manufacturing investigation (MF071409) for Lot # 11752 of Dapsone 25 mg tablets in which an (b) (4) was performed based on the presence of white residues in the (b) (4); Ms. Jacobus stated that the batch was (b) (4) for informative purposes only and was ultimately rejected because a validated and approved reprocessing procedure did not exist. I stated that I found no justification for (b) (4) the batch, even for informative purposes.

I reviewed out-of-specification (OOS) investigations with Mr. Pursell and Mr. Shah. I entered the manufacturing investigations into an Excel spreadsheet and then sorted them by problem. I observed that there were 3 investigations for PASER granules for the presence of metallic particles and 5 investigations for moisture content failures during manufacturing. I reviewed the firm's handling of these investigations with Mr. Pursell. For the metallic particle issue, I found that the firm implemented additional controls and checks during the manufacture of the API and finished dosage form as corrective actions. For the moisture content investigations, the cause of the deviations appeared to be a combination of mechanical and operator issues. The firm ultimately implemented a setting equipment correction; I found that the batch record was not updated with clear instructions for this setting. Refer to item # 3 in the General Discussion with Management section of this EIR. I also discussed deficiencies in the firm's SOP titled "Deviations." Refer to item # 8 in the General Discussion with Management section of this EIR. I selected and reviewed OOS investigations with Mr. Shah, which included 2 OOS investigations for Dapsone stability samples; I found deficiencies with the firm's SOP titled "Laboratory Investigations." Refer to items # 5 in the General Discussion with Management section of this EIR.

On 2/4/11, I encountered a list of deviations that occurred during the production of the API Aminosalicylic Acid. I reviewed these deviations and observed that the firm's QA unit was not involved in their review at the time of occurrence, as required by the firm's SOP # G-0023-01. On 2/4/11 and 2/10/11, I reviewed temperature and humidity data and observed that the quality unit did not investigate and determine the impact of temperature and humidity excursions in the controlled room temperature (CRT) stability chamber, in-process cold room, and during PASER granule shipments. Both of these observations were cited on the FDA 483. **Refer to Observation 3 in the Objectionable Conditions and Management's Response section of this EIR.**

When I asked for a list of rejected batches, I was informed that this would need to be determined based on the investigations. A list of rejected batches was not available. I informed the firm's management that this information should be readily available.

Mr. Pursell informed me that, since the previous inspection, no lots of products have been returned.

Refer to the Complaints section of this EIR for my review of complaints.

I reviewed annual product reviews (APRs) for the following APIs and finished drug products manufactured at this location in the calendar year 2009:

- Aminosalicylic Acid (aka PAS) – API
- Dapsone drug substance – API
- PASER Delayed-Release Granules – Finished Drug Product
- Dapsone 25 mg and 100 mg tablets – Finished Drug Product

I observed that the APRs for finished drug products did not include a review of all complaints received and investigations conducted during 2009. I also found that the firm's SOP # G-0025-1 titled "Product Quality Review" does not address annual reviews for finished drug products. This observation was cited on the FDA 483. **Refer to Observation 4 in the Objectionable Conditions and Management's Response section of this EIR.**

I reviewed a re-validation that was conducted between 2003 and 2006 for the firm's [redacted] steps for Dapsone 25 mg and 100 mg tablets. I found and discussed deficiencies with the manner in which this re-validation was conducted. Refer to item # 7 in the General Discussion with Management section of this EIR.

B. FACILITIES AND EQUIPMENT SYSTEM

The firm's sole manufacturing facility is divided between areas for API and finished dosage form manufacturing, Quality Control, Microbiology, R&D, warehousing, and offices.

The [redacted] source is [redacted] Pest monitoring and control is handled in-house based on a [redacted] schedule. Trash and recycling is collected [redacted], respectively, by [redacted] The firm contracts [redacted] for the destruction of rejected batches of APIs or finished drug products.

The firm has designed specific areas for manufacturing operations. For example, various steps in the manufacture of PASER granules [redacted] (b) (4)) are performed in dedicated areas.

Equipment identification practices appeared to be adequate. Equipment for the production of APIs is dedicated for each product; the equipment used to produce PASER granules is also dedicated. Equipment for the [redacted] (b) (4) of Dapsone, [redacted] (b) (4) tablets is non-dedicated; the same [redacted] (b) (4) is used for these products. I selected and reviewed equipment cleaning and swab testing procedures after the manufacture of Dapsone and [redacted] (b) (4) tablets. I found 2 instances in which equipment was not cleaned according to the firm's SOPs; I discussed these deficiencies with the firm's management. Refer to item # 6a in the General Discussion with Management section of this EIR.

I observed that there is excess equipment and clutter throughout the facility. I discussed this with Ms. Jacobus; she stated that she agreed with my comment, and her firm will work to remove unneeded equipment. I also observed that areas of the facility are not maintained in a clean and sanitary manner. For example, I observed the sampling area (room) to have powder-like residues and leaking water on its floors and walls. This observation was cited on the FDA 483. **Refer to Observation 6 in the Objectionable Conditions and Management's Response section of this EIR.**

I reviewed 3 equipment qualifications; one currently being conducted for a [redacted] (b) (4) to be used after tablet [redacted] (b) (4) one conducted in 2010 for an [redacted] (b) (4) chamber, and one conducted in 2010 for a new [redacted] (b) (4) system.

I reviewed the calibration status of equipment during walk-throughs. Calibration of equipment is performed by external vendors. I found that a [redacted] (b) (4) [redacted] (b) (4) used to monitor the [redacted] (b) (4) [redacted] (b) (4) for the [redacted] (b) (4) was not calibrated since 6/30/10 and found another [redacted] (b) (4) connected to a [redacted] (b) (4) without a tag or sticker to indicate its calibration status. This observation was cited on the FDA 483. **Refer to Observation 7 in the Objectionable Conditions and Management's Response section of this EIR.**

On 1/25/11 and 2/10/11, I reviewed the firm's storage and security of raw data files and folders on QC workstations. I found that computerized systems do not have adequate controls to prevent unauthorized access, changes, or omission of data. **Refer to Observation 5 in the Objectionable Conditions and Management's Response section of this EIR.**

As mentioned in the Quality System section, I found and cited the firm (under FDA 483 Observation 3) for temperature and humidity excursions for the CRT stability chamber and in-process cold room that were not investigated.

C. MATERIALS SYSTEM

Raw materials and components are received at the site and held in a quarantine area until approved for use. After approval, raw materials are moved to other areas based on use. I found appropriate status stickers on raw materials containers. I observed that, because of space constraints, approved raw materials are held in many different areas of the facility. I discussed this with Mr. Pursell and Ms. Jacobus, who stated that they are working towards creating space in the facility.

I reviewed the firm's inspection, quarantine, sampling, and testing procedures for raw materials and components. I also reviewed SOPs for retesting of raw materials, which is performed based on manufacturer retest dates.

According to Mr. Shah and [redacted] (b) (6) y, all incoming raw materials and components are tested to the full CofA. No reduced testing is performed for acceptance. I selected and reviewed the QC testing for 3 raw material lots and verified that full testing is performed.

Raw material, API, and finished product inventory is maintained manually through the use of log books. I selected and reviewed the distribution records for 2 lots of finished products. I found that the firm keeps thorough records of all distributed lots of drug products.

The [redacted] (b) (4) system qualification was reviewed during the previous inspection. On 2/3/11, I briefly reviewed a re-qualification that was performed after the last inspection based on an expansion of the [redacted] (b) (4); this re-qualification included rigorous and continued testing based on seasonal variations. I reviewed microbial and chemical testing results for the firm's [redacted] (b) (4) [redacted]. The [redacted] (b) (4) is sampled and tested according to a schedule that involves the rotation of sampling and testing of the valves.

D. PRODUCTION SYSTEM

I reviewed master batch records for the APIs Aminosalicylic Acid, Dapsone, and [redacted] (b) (4). I also reviewed the master batch records for the finished drug products PASER granules, Dapsone tablets, and [redacted] (b) (4) tablets. My review of master batch records included a review of the SOP that governs their preparation and control. I observed several deficiencies with the manufacture of Dapsone tablets that I discussed with the firm's management; refer to item # 2 in the General Discussion with Management section of this EIR.

I reviewed executed batch records; this included a review of charge-in practices for components, completion and documentation of in-process sampling and testing, calculations of actual yields and percentages of theoretical yields, and first and second person sign-offs.

During a walk-through on 1/24/11, I observed that information in a batch record was not being entered contemporaneously during production. I discussed this deficiency with the firm's management; refer to item # 4 in the General Discussion with Management section of this EIR.

During walk-throughs, I reviewed equipment cleaning and use logs; these appeared to be adequate. The firm was producing (b)(4) lots of PASER granules each day when I conducted a walk-through on 1/24/11 and 1/26/11. I observed that the containers holding these different in-process lots are held in the production areas and hallways; usually, these different in-process lots end up being at the same stage of manufacture during QC testing steps. I found no control system to identify these containers so as to prevent potential mix-ups. **Refer to Observation 10 in the Objectionable Conditions and Management's Response section of this EIR.**

The PASER granules product is manufactured via (b)(4). (b)(4) from valve (b)(4) of the (b)(4) is used. A plastic hose approximately (b)(4) feet long is attached to valve (b)(4) and is used to acquire (b)(4) into drums. I observed that the firm's procedure for acquiring (b)(4) from this valve is not the same as its procedure for sampling the valve for microbial testing. **Refer to Observation 9 in the Objectionable Conditions and Management's Response section of this EIR.**

As stated previously, the firm performed a validation in 2010 for a (b)(4) increase in scale for the production of the API Aminosalicylic Acid. Dr. Shiehser provided me with a copy of the validation protocol and report. I found deficiencies in this validation which were cited on the FDA 483 issued to the firm. **Refer to Observation 8 in the Objectionable Conditions and Management's Response section of this EIR.**

E. PACKAGING AND LABELING SYSTEM

The firm's commercial lots that are marketed within the US are packaged by (b)(4) (b)(4) is an alternate packaging site. The firm packages into bottles Dapsone tablets that are sold for external markets (e.g. New Zealand). On 1/24/11 and 1/26/11, I reviewed the line used to fill Dapsone tablets into bottles located in the packaging room.

I reviewed the firm's procedures for the receipt, inspection, sampling, and testing of incoming labels, inserts, and components; I reviewed the storage of labels and labeling, which I found were stored in a locked cabinet in the locked quarantine area in the warehouse.

I reviewed the firm's packaging procedures for Dapsone tablets that are packaged at this facility; this included a review of line clearance, label reconciliation and controls, examination of the finished product, and use of lot numbers. Lot numbers on batches that were being packaged during the

inspection appeared to be adequate. I observed that a specimen of the label is included in the packaging batch record.

The firm's management stated that they receive and review all packaging batch records for batches that are packaged at [redacted] (b) (4). I reviewed the packaging batch record for lot 12735 of PASER Granules that was packaged at [redacted] (b) (4) and found no deficiencies.

F. LABORATORY CONTROL SYSTEM

I conducted a walk-through of the QC lab areas on 1/25/11 and on additional days based on items covered. I reviewed the firm's procedures for receiving and holding samples for QC testing. I also reviewed the calibration and maintenance status of equipment and expiration dates on reagents. Mr. Shah informed me that calibration and preventative maintenance for equipment is either performed in-house or by a third-party vendor. The program for equipment calibration and maintenance appeared to be adequate. I reviewed QC data packets for raw material testing on 1/28/11 and raw data chromatograms on 2/15/11 for finished product release and stability testing. The firm appeared to have adequate practices for system suitability checks for chromatography. All raw data appeared to be adequately retained as part of QC data packets.

Mr. Shah informed me that the firm has not developed new methods since the last inspection. He stated that many of the methods used by the firm for commercial products are the same as when the products were first developed and launched.

I reviewed the firm's program for maintaining reference and working standards and found no deficiencies. Working standards are qualified [redacted] (b) (4) actives and [redacted] (b) (4) for impurities.

I reviewed the firm's stability program with Mr. Shah. This included a review of SOP # G-0001-006 titled "Stability Testing Program." I found that the SOP did not define timeframes for beginning stability studies and completing analyses. I discussed this with the firm's management at the closeout meeting; refer to item # 9 in the General Discussion with Management section of this EIR. I also reviewed stability pulls and data with Mr. Shah and the firm's program for maintaining and checking reserve samples.

During my review of stability data, I found that the firm is not testing both Dapsone finished drug products for impurities; the test methods currently used for these finished drug products are not stability indicating. For the Dapsone drug substance, I found that the firm has developed and validated a stability indicating test method; however, the method is not being used to monitor impurities during stability testing of the API. **Refer to Observations 1 and 2 in the Objectionable Conditions and Management's Response section of this EIR.** I also found that the firm does not

have a range defined for its thickness specification for Dapsone tablets; refer to discussion item # 2c in the General Discussion with Management section of this EIR.

As previously mentioned, the computerized systems used in the lab do not have sufficient controls to prevent unauthorized access, changes, and deletions (refer to FDA 483 Observation 5).

I reviewed laboratory notebooks on 2/10/11 and found that testing information regarding the methods, equipment, instruments, and reagents was adequately documented. Raw data and calculations were also included, as was first and second person sign-offs.

MANUFACTURING CODES

The firm continues to assign codes as follows:

- [redacted] (b) (4)
- [redacted]
- [redacted]
- [redacted] (b) (4)

COMPLAINTS

I reviewed the firm's SOP # G-0032-001 titled "Procedure for the Handling of Product Related Complaints" and SOP # G-0006-2 titled "Standard Operating Procedure for the Handling of Complaints and the Post Marketing Safety Reporting for Human Drugs" (**Exhibits 6 - 7**). SOP G-0032-001 ends abruptly at section 4.3 in the middle of a sentence. I discussed with the firm's management that this indicates that documents are not being reviewed adequately.

The firm monitors product-related complaints and complaints related to adverse events. Of the complaints I reviewed, 3 complaints were for crushed tablets received in November and December 2010. I discussed deficiencies with the firm's management in their handling of these complaints. Refer to item # 1 in the General Discussion with Management section of this EIR.

Drug Quality Reporting System (DQRS):

I found 2 DQRS reports for the firm (MSB # 2009-06986 and 2010-05372). Both reports are for complaints that the product Dapsone 100 mg tablets has bar codes only on the outer box, not on the unit dose tablets (i.e. on every blister). Ms. Jacobus informed me that her firm received and corresponded with FDA regarding these reports; she provided copies of the correspondence. Each

carton is considered to be a "Unit of Use" for the product and the product is not intended to be distributed as individual tablets; based on this, the firm has met its requirement to have a bar code on every unit. Ms. Jacobus informed me that her firm still decided to implement bar codes for every blistered tablet. She provided a copy of the letter and attachments her firm sent to the FDA noting this modification (**Exhibit 8**).

RECALL PROCEDURES

During the write-up of this EIR, I reviewed the firm's SOP # G-0015-01 titled "Recall Policy" (**Exhibit 9**) and found that the procedure does not define timeframes for notifying FDA if a recall is considered. This issue should be addressed during the next inspection. During the inspection, I reviewed distribution records and found that the firm kept adequate records of lots distributed. It appears that the firm could execute a recall successfully if needed.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

*****REVISED THE FDA 483 TO ORGANIZE THE OBJECTIONABLE CONDITIONS ACCORDING TO THE GMP SYSTEMS*****

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.

Supporting Evidence and Relevance:

While reviewing stability data on 2/9/11, I observed that the firm is not testing Dapsone 25 mg tablets and Dapsone 100 mg tablets for impurities. **Exhibit 10** is a copy of stability data sheets for Dapsone 25 mg and Dapsone 100 mg tablets showing that the Dapsone tablets are not tested for impurities. No test method has been developed or validated for this purpose.

Mr. Shah provided me with the specifications (**Exhibits 11-12**), stability protocol (**Exhibit 13**) and laboratory methods for the Dapsone 25 mg and 100 mg tablets. I reviewed these documents and

found that there are no requirements to evaluate these finished products for impurities and do not include specifications for allowable levels of impurities. There has been no evaluation to determine the potential for any interactions between the drug substance, excipients, and container-closure system. I asked if any forced degradation studies were ever conducted on the finished product to identify potential impurities that may form and whether these co-elute with the Dapsone peak. Mr. Shah stated that forced degradation studies were never conducted on the Dapsone 25 mg or 100 mg tablets.

Ms. Jacobus and Mr. Shah stated that the test method used to assay the finished drug product, DF-DAP-LC-1, is the only method that was developed and validated (**Exhibit 14**). Ms. Jacobus stated that this method may allow for the identification and measurement for (b) known impurities. She provided me with a copy of a revalidation performed for the method in 2003. I reviewed the protocol and report for this revalidation (**Exhibit 15**). The revalidation is for the assay method to determine the level of the active ingredient, not for a related substances test. According to the protocol and report, the retention times of known impurities were measured using (b) (4) (b) (4) (b) (4) A known impurity, was found to interfere with the Dapsone peak; it would therefore interfere with an accurate measurement of Dapsone. No further evaluation was performed. One of the firm's requirements in the protocol was to provide an interference free measurement of Dapsone. The information regarding the co-elution of the (b) (4) peak with the Dapsone peak demonstrates that the method validation failed. In addition, since a forced degradation study was not performed, there are no data to demonstrate the lack of interference between known and unknown impurities and between unknown impurities and the Dapsone peak.

Prior to closing out, I asked the firm to provide a list of lots that are stored in the controlled room temperature stability chamber (**Exhibit 16**). I reviewed the list while writing this EIR and found that it includes the following US marketed lots of Dapsone finished products that are within expiry.

Dapsone 25 mg Tablets: 11198, 11199, 11252, 11903, 11904, 12093, 12339
Dapsone 100 mg Tablets: 11172, 11303, 11304, 11307, 11319, 11754, 11970, 11971, 12296

Discussion with Management:

Mr. Shah did not know why the firm is not evaluating the Dapsone finished products for impurities. He stated that he realized this issue after joining the firm in 2010 and considered developing and validating a method for this purpose, but he has not had the chance to do so. I also spoke with Dr. Jacobus and Ms. Jacobus regarding this issue on 2/11 and 2/15. Both individuals stated that the Dapsone drug substance goes through (b) (4) purification steps that should remove impurities. I stated that the drug substance is used in further manufacturing steps (b) (4)) using non-dedicated equipment and that the firm does not check the finished product for known and unknown impurities (e.g. process-related impurities). I also

reiterated that the firm has never conducted forced degradation studies on the finished product to evaluate whether any degradation products can form and interfere with the Dapsone peak. The packaging configuration for US marketed lots of Dapsone 25 mg and 100 mg tablets was changed in 2008 from bottles to blister packs. I stated that a stability-indicating method has not been developed and validated for this finished drug product.

At the closeout meeting, Ms. Jacobus stated that her firm's management accepts and agrees with the observation and that they are in the process of developing and validating an appropriate stability-indicating test method for Dapsone 25 mg and 100 mg tablets. She stated that she would provide further details in her written response to the FDA 483.

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.

Supporting Evidence and Relevance:

The firm's management stated that a crude form of the Dapsone drug substance (aka technical grade) is acquired from an (b) (4) API supplier. The crude form is purified in-house by (b) (4) These (b) (4) reduce or remove (b) (4) known impurities in the crude drug substance. Dr. Jacobus and Ms. Jacobus stated that the test method, RM-DAP-LC-4, for evaluating the Dapsone drug substance for impurities was developed and validated using forced degradation studies; this correction was in response to the October 1997 Warning Letter issued to the firm. This test method is currently used to evaluate 1 lot of purified Dapsone drug substance (b) (4) (b) (4) it is not used to test every lot of the drug substance prior to its release for use or for stability testing. A copy of the test method is included as **Exhibit 17**. Mr. Shah provided an example of the latest evaluation of impurities conducted on a lot of the Dapsone drug substance purified at Jacobus (**Exhibit 18**). I reviewed this document along with associated raw data; I found that the firm evaluates a lot of the technical grade of the Dapsone drug substance that it receives (b) (4) for impurities and then evaluates the same lot for impurities after it has been purified (through the (b)) at Jacobus. I asked if the lot that is chosen for this evaluation is the same lot that is placed on stability; Mr. Shah stated that the lot evaluated is not necessarily the stability lot. I asked if the firm evaluates the Dapsone drug substance for known and unknown impurities during release and stability testing. Mr. Shah stated that the drug substance is not evaluated for known and unknown impurities during release and stability testing using method RM-DAP-LC-4 that was developed and validated for this purpose. He stated that the drug substance is evaluated for assay using test method RM-DAP-LC-1 (**Exhibit 19**). He stated that the crude substance is evaluated using a (b) (4) (RM-DAP-TLC-1) for the presence of any of the known (b) impurities (**Exhibit 20**).

Mr. Shah provided me with the specifications for Dapsone technical grade and purified (**Exhibits 21-22**), stability protocol (**Exhibit 23**) and laboratory methods for the Dapsone drug substance. I reviewed these documents and found that test method RM-DAP-LC-4 for impurities is not performed during stability testing and is not part of the firm's release testing for the API. **Exhibit 24** is a copy of stability data sheets for the Dapsone drug substance; this is included as examples to show that the Dapsone drug substance is not evaluated for impurities.

Discussion with Management:

I asked Dr. Jacobus and Ms. Jacobus on 2/10 why the Dapsone drug substance is not evaluated for impurities during stability testing. They stated that the purification of the crude Dapsone should significantly reduce or remove all impurities and that the [redacted] (b) (4) test on 1 purified lot demonstrates this. They stated that the impurity levels, if any, are at very low levels after purification. I stated that the firm still needs to evaluate and monitor for any impurities or degradation products during release and long-term stability testing of the API. The test method RM-DAP-LC-4, which was developed and validated for the purpose of identifying and measuring impurities as part of the response to the October 1997 Warning Letter issued to the firm, is not performed.

At the closeout meeting, Ms. Jacobus stated that her firm's management accepts and agrees with the observation and that they are in the process of instituting a change so that test method RM-DAP-LC-4 will be performed on [redacted] (b) (4) for use and during testing of stability lots. She stated that she would provide further details in her written response to the FDA 483.

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, [redacted] (b) (4)):

Dates	# of Excursion Events	Humidity	Temperature	Total Length of Time
8/26-10/1/09	11	low & high	N/A	>14 days
12/7/09-1/11/10	5	low	low	>2 days
3/13-4/19/10	10	high	N/A	>19 hours
8/19-9/28/10	4	low	high	>1 day
12/28/10-1/26/11	4	low	low	>1 day

For the in-process cold room used to store in-process PASER granule lots (storage requirement of [redacted] (b) (4)):

Dates	# of Excursion Events	Humidity	Temperature	Total Length of Time
3/18-4/9/10	4	N/A	high	>14 hours
7/8-8/9/10	16	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 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	8	7	>25 days (1 event=23 days)	82.9 °F
2/19-3/8/10	8	5	>20 hours	74.8 °F
6/4-7/21/10	8	8	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 [redacted] (b) (4) 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 [redacted] (b) (4) of the event. Examples of deviations not reviewed by your QA unit within [redacted] (b) (4) include:

Lot	Deviation	Date of Deviation	QA Review Date of Deviation
1163	pH drop during [redacted] (b) (4)	2/15/09	3/19/09
1171	pH drop during [redacted] (b) (4)	3/10/09	4/8/09
1219	[redacted] (b) (4) malfunction*	7/31/09	8/21/09
1364	[redacted] (b) (4) malfunction**	10/20/10	12/13/10

* This [redacted] (b) (4) malfunction also occurred during the 8 subsequent lots (1220-1227) of PAS manufactured after Lot 1219. Your QA unit did no assessment to determine appropriate corrective and preventative actions after the [redacted] (b) (4) problems associated with lots 1219-1227.

** Production indicated that this may affect the [redacted] (b) (4). The [redacted] (b) (4) was [redacted] (b) (4) d 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.

Supporting Evidence and Relevance:

1. I selected three sets of data loggers to review for temperature and humidity data. The first data logger I reviewed is for the controlled room temperature (CRT) stability chamber; this chamber has been in use at this facility since 1999; the chamber is a room in the basement of approximate size [redacted] (b) (4) (**Exhibit 25**). The chamber has one data logger located in the southeast corner. Stability lots are stored on steel shelves located along the east wall (**Exhibit 25**). Mr. Warman, Sr. stated that the room was qualified in 1999 using empty drums as "placeholders" to help maintain the temperature and humidity of the room. I briefly reviewed the qualification report (from 1999) for the room; I asked if the room has been re-qualified since 1999 or re-assessed . Mr. Warman, Sr. stated it has not.

   The second and third set of data loggers I reviewed is for the monitoring of in-process and shipped lots of PASER granules; the product has a storage requirement of [redacted] (b) (4) I reviewed the data logger for the cold room used to store in-process lots of PASER granules (during manufacturing at this facility); I also reviewed the data logger used to monitor the shipment and handling of in-process PASER granule lots sent to the firm's contract coating and packaging facilities.

   On 2/4/11 and 2/10/11, I reviewed temperature and humidity data with Mr. Warman, Sr. for these three sets of data loggers. Mr. Warman, Sr. informed me that he is responsible for downloading the temperature and humidity data on a [redacted] (b) (4) basis. I reviewed data for the time period from June 2009 through January 2011. The data is downloaded [redacted] (b) (4) for the CRT stability chamber and cold room; for shipped lots of PASER granules, the data is downloaded after finished product retain samples are received at Jacobus (sent from [redacted] (b) (4).). I assigned set numbers for each group of data in which I observed excursions.

   For the CRT stability chamber, I found the following excursions.

Set #	Time Period	# EE	Total Temperature Excursion Time(s)	Total Humidity Excursion Time(s)	Extreme(s) Recorded in this time period	References (Exhibit #)
1	6/8/09-7/23/09	1	- N/A	- Low (3 hrs)	RH: 45.9%	26
2	8/26/09-10/1/09	11	- N/A	- Low (14 days, 7 hrs)	RH: 33.7 %, 66.3 %	27

				- High (2 hrs)		
3	10/1/09-11/10/09	3	- N/A	- Low (8 days, 1 hr)	RH: 21.3%	28
4	12/7/09-1/11/10	5	- Low (1 day, 21 hrs)	- Low (2 days, 23 hrs)	T: 21.3 °C RH: 6.8 %	29
5	1/11/10-2/23/10	1	- Low (22 hrs)	- Low (23 hrs)	T: 21.2 °C RH: 10 %	30
6	2/23/10-3/13/10	2	- Low (5 hrs)	- Low (7 hrs) -High (1 hr)	T: 17.1 °C RH: 35.7 %, 66.3 %	31
7	3/13/10-4/19/10	10	- N/A	- High (19 hrs)	RH: 66.6 %	32
8	4/19/10-5/21/10	1	- N/A	- Low (6 hrs)	RH: 39.1 %	33
9	5/21/10-6/22/10	2	- N/A	- Low (8 hrs) - High (7 hrs)	RH: 43.7 %, 69.4 %	34
10	6/22/10-7/21/10	2	- N/A	- High (4 hrs)	RH: 69.1 %	35
11	8/19/10-9/28/10	4	- High (8 hrs)	- Low (1 day, 10 hrs)	T: 29.2 °C RH: 36.9 %	36
12	12/28/10-1/26/11	4	- Low (22 hrs)	- Low (1 day, 1hr)	T: 19.4 °C RH: 11.2 %	37

 # EE = Number of Excursion Events recorded by data logger

For the in-process cold room, I found the following excursions.

Set #	Time Period	# EE	Total Temp Excursion Time(s)	Extreme(s) Recorded in this time period	References (Exhibit #)
13	3/18/10-4/9/10	4	14 hrs	64.7 °F	38
14	7/8/10-8/9/10	16	2 days, 14 hrs	62.9 °F	39
15	8/9/10-9/10/10	5	19 hrs	62.6 °F	40

 # EE = Number of Excursion Events recorded by data logger

For the monitoring of lots of PASER granules shipped to and handled by the firm's contracted coating facility and packaging site, I found the following excursions:

Set #	Time Period	# EE	Total Temp Excursion Time(s)	Extreme(s) Recorded in this time period	Lots monitored	References (Exhibit #)
16	6/12/09-7/22/09	7	25 days	82.9 °F	(b) (4) [redacted]	41
17	2/19/10-3/8/10	5	20 hrs	74.8 °F		42
18	6/4/10-7/21/10	8	1 day, 1 hr	73.7 °F		43
19	6/11/10-7/7/10	5	1 day, 8 hrs	76.9 °F		44
20	6/19/10-7/6/10	10	1 day, 2 hrs	80.9 °F		45

 # EE = Number of Excursion Events recorded by data logger

The exhibits referenced for each time period include the summary page. The following information is included on the summary page:

- The period of time monitored (begins with "First Point" and ends with "Stop Time")
- Total time(s) of excursions – this is reported for 4 categories (low temperature, high temperature, low humidity, high humidity); the total time in each category is the sum total of all excursion events in that category; for example, for the CRT stability chamber for the time period 8/26/09-10/1/09, there were 8 excursions for low humidity (aka excursion events) (**Exhibit 27**); the sum total of these 8 excursion events is 14 days, 7 hrs; there was one excursion that lasted 6 days, 12 hrs.
- Extreme(s) recorded for each of the 4 categories
- Any comments of significance

For the excursions cited above, there is no documented deviation; an investigation has not been conducted to determine the root cause and effects on the quality of the product and on the stability study. I observed that 5 summary pages (set #s 6, 8, 11, 12, 13) have comments citing mechanical issues either with the [redacted] (b) (4) (for the CRT stability chamber) or the cold room [redacted] (b) (4) (for the in-process cold room); Mr. Warman, Sr. stated that he entered these comments. I asked Mr. Warman, Sr. if he reviews the data when he conducts his downloads; he stated he does not review the data; however, if he knows of an issue that occurred, then he will enter a note in the Comments field. I asked if he informs the firm's quality unit if any issue has occurred; he stated that he addresses the issue (e.g. [redacted] (b) (4) failure) and may verbally mention it to Mr. Pursell, Ms. Jacobus, etc. but does not inform the quality unit through any formal procedure.

For the excursions that occurred in set # 16, I found one excursion reported to last 23 days. Mr. Warman, Sr. speculated that this may be an issue in which the data logger was shipped back with the retain samples, and then the data logger sat in the QC area for 23 days until the data was downloaded. I asked if there is any record of this incident; Mr. Warman, Sr. stated that there is no record.

There is no program to routinely monitor the CRT stability chamber and cold room; the only time at which monitoring is conducted, if at all, is when data is downloaded from the data loggers. Additionally, the data loggers are not alarmed; therefore, if there are excursions, no one is notified or made aware. Mr. Warman, Sr. stated that even though the data loggers are not alarmed, the boilers and air conditioning units that supply the air for the CRT stability chamber and cold room are alarmed and are programmed to notify individuals if mechanical failures occur. I asked for alarm notification records for the boiler issues noted in sets 6, 8, 11, and 12. Mr. Warman, Sr. checked and found that the alarm was not always activated; for example, no alarm was triggered for the boiler failure noted in set 8 above.

I observed that the excursion set points for the CRT long-term stability chamber are at [redacted] (b) (4). I asked Mr. Warman, Sr. for the reason for these set points. He was not sure and referred me to Mr. Shah. I asked Mr. Shah, who informed me that the set points were instituted before he began working at the firm but are supposed to be based on ICH guidelines; I pointed out to Mr. Shah that the ICH guidelines for controlled room temperature are 25±2°C/60±5%RH. Mr. Shah stated that he agreed and would ask Mr. Warman, Sr. to correct the set points to match ICH guidelines.

I reviewed the firm's SOP # G-0023-01 titled "Deviations" (**Exhibit 46**). The firm's management informed me that this is the only SOP that governs all types of deviations (except for laboratory out-of-specification results) for the facility. I observed that this SOP calls for the following:

- Deviations to be recorded on deviations sheets in the batch record.
  However, it does not state if deviations that are not related to production should be documented using the same form.
- It calls for Production, QA, and QC to review the immediate action after a deviation is recorded within [redacted] (b) (4)
  In the case of these excursions, no deviation was recorded, and no action was taken.
- The impact of the deviation on the quality of the material should be assessed.
  This was not conducted for any of the excursions previously listed.

2. **Exhibit 47** is a list of deviations I encountered on 2/10/11; these deviations occurred during the production of the API Aminosalicylic Acid (PAS). I reviewed the list and selected deviations for further review. In each instance, I found that the firm's quality unit did not review the deviation at the time of occurrence. The firm's SOP # G-0023-01 titled "Deviations" (**Exhibit 46**) requires that quality assurance and quality control review immediate actions related to deviations within [redacted] (b) (4) For example,

   - During the production of lot 1163, a pH drop to 1.35 occurred on [redacted] (b) (4) at the [redacted] (b) (4) step; the batch record states on page 15 prior to the [redacted] (b) (4) step that "[redacted] (b) (4)." The deviation was recorded on a deviation sheet and production employees determined that there was no anticipated impact on quality; the pH was adjusted by [redacted] (b) (4) and the manufacture of the batch continued. The firm's QA unit signed off on the deviation (no date entered), released the batch, and required the batch to be put on stability. When I asked Ms. Jacobus on what date she reviewed the deviation, she stated that she reviewed the deviation at the time of batch release on [redacted] (b) (4), not within [redacted] (b) (4) as required by the firm's procedure. Refer to **exhibit 48** for copies of relevant pages.
   - During the production of lot 1171, a pH drop to 3.44 occurred on [redacted] (b) (4) at the [redacted] (b) (4) step. The deviation was recorded on a deviation sheet and production was

continued. The QA unit did not review the deviation until (b) (4), the date that the batch was reviewed and released. Additionally, QA did not enter its decision to release the batch or to place the batch on stability (both fields left blank). Refer to **Exhibit 49** for copies of relevant pages.

- During the production of lot 1219, a (b) (4) malfunction occurred and required the unit to be sent out for calibration. While the unit was out for calibration, a different unit was installed and production was continued; however, the unit was not reading correctly. The incident was documented on a deviation sheet (**Exhibit 50**). The same issue occurred in 8 subsequent lots (1220-1227) and was documented on deviation sheets attached to those batch records (**Exhibit 51**). In each instance (for lots (b) (4)), the QA unit did no review the deviation or perform its review within (b):

Lot	Date of Deviation	QA Review of Deviation	Were "Batch Release" and "Stability Requirement" fields entered by QA?
1219	(b) (4)	(b) (4)	No
1220	(b) (4)	None	No
1221	(b) (4)	(b) (4)	No
1222	(b) (4)	None	No
1223	(b) (4)	None	No
1224	(b) (4)	(b) (4)	Yes
1225	(b) (4)	(b) (4)	Yes
1226	(b) (4)	(b) (4)	Yes
1227	(b) (4)	(b) (4)	Yes

- During the production of lot 1364, an (b) (4) malfunction occurred on 10/20/10 at the (b) (4) step. This led to an increase in the pH for the intermediate API; the firm's employees had stated that maintaining the pH is a critical process parameter during the production of the API. Production employees completed a deviation sheet after the (b) (4) malfunction; I reviewed the deviation sheet and found that employees speculated that the increase in pH may have an effect on the (b) (4) of the API. The (b) (4) is a quality attribute for the API; according to the firm's management, the (b) (4) is (b) (4) when the API is produced. Dr. Shiehser stated that this deviation was considered a critical deviation at the time of occurrence. A decision was made (i.e. immediate action taken) by production employees to finish the process by (b) (4) the (b) (4). I asked if the QA unit reviewed and approved the immediate action within (b) (4) of occurrence. Ms. Jacobus stated that she did not review or approve the immediate action within (b) (4) of occurrence and that she reviewed the deviation and immediate action on 12/13/10, as indicated by her sign-off. The batch was released based on specifications being met during QC testing. Refer to **Exhibit 52** for copies of relevant pages related to this deviation.

While reviewing the firm's 2009 annual product review for the production of the API Aminosalicylic Acid (**Exhibit 53**), I observed that the APR states that 24 deviations occurred; according to the list of deviations provided by Dr. Shiehser, there were 36 deviations in 2009

(**Exhibit 47**). The APR was reviewed by four individuals. Ms. Jacobus stated that this is an error that should have been caught. Additionally, the final assessment in the APR included the need to resolve issues related to equipment in a timely manner. There are no further details regarding specific corrective actions taken or follow-up.

I asked Ms. Jacobus for a procedure that defines the quality unit's roles and responsibilities. She provided me with a copy of SOP # QA-0012 titled "Responsibilities of the Department of Quality Control" (**Exhibit 54**). She stated that she established this procedure during the current inspection based on a previous request I had made. I reviewed the procedure and found that it addresses the roles and responsibilities for Mr. Shah and his unit but does not address the roles and responsibilities for the firm's QA unit. When I brought this up to Ms. Jacobus, she agreed. I asked if any other procedure has been established that defines her roles and responsibilities (i.e. QA); she stated that a formal SOP or procedure for QA does not exist.

Discussion with Management:

I asked Ms. Jacobus for the reason that the excursions in the CRT stability chamber, in-process cold room and shipment and handling of the PASER granule lots were not documented as deviations and investigated. Ms. Jacobus stated that this is an oversight based on a lack of procedures and lack of proactive involvement by her. She stated that she has been trying to hire someone to help her manage the facility. I stated that a resource issue is not adequate justification; employees were not aware of the excursions that I found. I stated that this indicates that even though systems and practices are set up, there is no review of these systems. For example, data loggers are used for monitoring purposes; however, no one is actually reviewing the data. Additionally, I stated that there should be established procedures for monitoring the firm's systems on an on-going basis.

Prior to the closeout meeting, Mr. Shah informed me that his group has taken responsibility for monitoring the stability and storage chambers throughout the facility and for reviewing the data from data loggers that are returned after shipment of PASER granule lots. He also stated that he will be reviewing all of the excursions that have occurred with Ms. Jacobus and determining whether there is any impact on product quality or need to extend stability studies.

I also discussed with Ms. Jacobus and the rest of the firm's management the need for the quality unit to be aware of deviations that occur. I stated that the quality unit needs to be involved in determining the criticality of deviations and appropriate actions.

At the closeout meeting, Ms. Jacobus stated that she accepts and agrees with the observation. Dr. Jacobus stated that he has given Ms. Jacobus oversight over the entire facility as the firm's quality assurance representative. He asked for clarification on whether investigations need to be completed within [redacted] (b) (4) I stated that, according to the SOP titled "Deviations," immediate actions following deviations must be reviewed by production management, quality assurance,

and quality control within [redacted] (b) (4). I stated that his firm needs to establish reasonable timeframes for conducting and completing investigations. Dr. Jacobus then stated that he understood and agreed with the observation.

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 ~~3 complaints received and~~ 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.

Supporting Evidence and Relevance:

a. I reviewed the annual product review (APR) for the finished product PASER granules (**Exhibit 55**). The APR did not include a review of the following 9 manufacturing investigations conducted for the product during the calendar year 2009: MF032009, MF032609, MF040309, MF040709, MF071309, MF091009, MF091109, MF091409, and MF092209; during the write-up of this EIR, I found one additional investigation for the product for 2009 (MF093009). Three of these investigations (MF032009, MF032609, and MF040309) were investigations conducted for moisture content failures related to 6 lots during the production of the product (after the [redacted] (b) (4) step). In each case, the in-process lots were [redacted] (b) (4) for an additional [redacted] (b) (4) (b) (4) the lots were re-tested after the additional [redacted] (b) (4) (b) (4) time and passed moisture content specifications. When reviewing the investigations, I asked to review data that supported the additional [redacted] (b) (4) time. Mr. Pursell provided data from 2010 that showed that additional [redacted] (b) (4) had no effect on the quality of the product.

I observed that in each case, the cause of the deviation/failure was determined to be a combination of mechanical and operator issues and training was given as part of the corrective actions. However, the three investigations were not assessed at the time of the APR to determine if further corrective actions are warranted (e.g. additional training, assess equipment maintenance practices, the need to implement any product improvement projects). Additionally, the other 7 investigations conducted for the product were not reviewed to determine if any broader problems exist.

I reviewed the APR for Dapsone tablets for 2009 and found the same issue, specifically, the firm does not include complaints and investigations as part of its annual product review.

b. The firm's SOP # G-0025-01 titled "Product Quality Review" addresses annual reviews for APIs (**Exhibit 56**). I asked if there is any other SOP or procedure for annual reviews; I was informed that SOP G-0025-01 is the only SOP that addresses annual reviews.

Discussion with Management:

During the inspection and at the closeout meeting, I stated to the firm's management that a procedure for conducting reviews, at least annually, of finished drug products needs to be established and that this procedure needs to include a requirement to review complaints and investigations. I stated that the annual reviews provide an opportunity to review processes and systems on a more global level in order to assess the need for any corrective and/or preventative actions. Ms. Jacobus stated that she agreed with the observation and would establish and implement procedures to conduct annual product reviews more effectively. She stated she would provide further details in her firm's response to the FDA 483.

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 [redacted] (b) (4) and [redacted] (b) (4) instruments with no audit trail to document such an event. 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.

Supporting Evidence and Relevance:

The firm's Quality Control laboratories are using [redacted] (b) (4) systems for raw material, in-process, API, and finished product testing. Raw data are captured and stored on local workstations and backed up [redacted] (b) (4) onto CDs or DVDs. The firm has not established adequate controls to prevent unauthorized access, changes, and omission of raw data files and folders. On 1/25/11 and 2/10/11, I asked Mr. Shah to right-click on raw data files and folders located on the local drives of each workstation. When Mr. Shah did this, a pop-up window appeared in which the "Delete" function was active (not grayed out). I asked if this meant that the file/folder could be deleted. On 1/25/2011, Mr. Shah stated that he was not sure. However, on 2/10/2011, when I asked again, Mr.

Shah stated that the files/folders can indeed be deleted. He created a test run in my presence and then deleted the raw data file and folder on the local hard drive. Mr. Shah stated that there is no audit trail or trace in the software to document the event.

On 2/10/11, I observed the same issue with the [(b) (4)] instrument. Mr. Shah stated that this instrument is used in many different tests, including [(b) (4)] studies for commercial lots of PASER granules and identification tests for Dapsone. The electronic data files generated during experiments are treated as the primary raw data files. These electronic raw data files are stored on the local workstation and backed up onto CDs and DVDs periodically (no specific timetable). In a manner similar to the [(b) (4)] instruments, Mr. Shah right-clicked on raw data files located on the local drive. When Mr. Shah did this, a pop-up window appeared in which the "Delete" function was active (not grayed out). As with the [(b) (4)] instruments, I asked if this meant that the file could be deleted. Mr. Shah stated that the file could indeed be deleted. He ran a "blank" sample in my presence and then deleted the raw data file on the local hard drive. Mr. Shah stated that there is no audit trail or trace in the software to document the event.

I also observed that one general account and password is used to access the operating systems on the [(b) (4)] and [(b) (4)] workstations by the QC managers and analysts. During my walk-throughs, I observed that the workstations were always in a logged-in status, even when not in use; the main Windows screen (i.e. desktop) was always visible. The workstations are not locked out and do not have a lock mechanism configured (e.g. locks out after a certain amount of time); this allows for unauthorized access to data.

Additionally, I found no written SOPs or procedures for data security controls. I expressed a concern to Mr. Shah about backing up the data only [(b) (4)], stating that there is no protection for data generated in between these [(b) (4)].

Discussion with Management:

I discussed the observation with the firm's management on several occasions, including the closeout meeting. Ms. Jacobus stated that her firm's management accepts and agree with the observation. She stated that she is in the process of hiring a contractor to install a server and implement data security controls. This will probably include disabling access for the local hard drives for the analysts. She stated that she would provide further details in her written response to the FDA 483.

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.

Supporting Evidence and Relevance:

During a walk-through of the facility on 1/26/11, I observed that the firm's sampling area (room) for raw materials and components is not adequately maintained. The area is a room built on the firm's loading dock as an extension to the shipping and receiving and warehousing areas. The sampling area has 2 sets of doors; one set of doors leads to the warehousing area from where raw materials and components are brought in for sampling. A second set of doors leads to the outside of the facility to the firm's loading dock. The facility maps include a schematic of the sampling room (**Exhibit 4**).

I observed powder-like residues (e.g. dust and white powder) on the floors and walls of this area as well as leaking water from the outside of the facility. **Exhibit 57** includes photographs that I took to demonstrate the condition of this area. I also observed gaps in the two doors that lead to the loading dock. I expressed concerns for the condition of this area and the potential for contaminating raw materials and components. I asked Mr. Pursell and Mr. Warman, Sr. whose responsibility is to maintain the area in a clean and sanitary condition. Mr. Pursell stated that the maintenance of the entire facility is the responsibility of the Engineering department. Mr. Warman, Sr. stated that the room is designed to have laminar air flow and is HEPA-filtered. The HEPA filter is located inside a latched door on the ceiling with an opening on one end (**Exhibit 57, page 7**). I asked if the HEPA filter is changed according to a defined schedule. Mr. Warman, Sr. stated that the filter is changed regularly. I asked for the records for the changing of the HEPA filter and maintenance of this area. Mr. Warman, Sr. stated that there probably are no records for the replacement of the HEPA filter and for the sampling area's overall maintenance. I also observed that there is no use log for the sampling room; Mr. Pursell stated that use of the sampling area could only be determined by pulling raw material and component sampling records.

On 2/9/11, I went back to the sampling area and observed a pallet sitting in the area that appeared to have been brought in directly from the outside. The vinyl laminar hood adjacent to the doors leading to the loading dock were pushed in to the furthest end of the pallet away from these doors (**Exhibit 58**). According to information previously provided by Mr. Pursell and Mr. Warman, Sr., these doors are not opened and raw materials and components are received and placed in the firm's quarantine area (in the shipping and receiving area) and then brought into the sampling area for sampling from

the warehouse and not from the outside. I asked Mr. Pursell why the pallets were brought in directly from the loading dock. He stated that someone probably brought the pallet in to the sampling area due to space constraints in the quarantine area. I stated that this practice may be one of the causes of the facility's condition. He agreed with my statement.

I observed similar conditions in several other areas of the facility. For example, I observed powder-like residues on the walls of manufacturing areas (rooms) (b) (4). Mr. Pursell informed me that these areas were dedicated rooms for the production of PASER granules. I still expressed concerns for the cleanliness and maintenance of these rooms.

Discussion with Management:

I spoke with Dr. Jacobus and Ms. Jacobus about the condition of the sampling area as well as other areas on 2/9/11. I stated that the facility is not maintained in a clean and sanitary condition. I asked for the SOP or written program that defines the maintenance of the facility. I was provided with a copy of SOP # G-0011-01 titled "Building Maintenance" (**Exhibit 59**). This SOP fails to define sanitary requirements for the facility as well as responsibilities for the facility's maintenance.

Prior to the closeout meeting, Ms. Jacobus provided me with a copy of SOP # QA-0005-01 titled "Building and Facilities" that addresses the requirements and responsibilities for the maintenance of the facility (**Exhibit 60**).

At the closeout meeting, Ms. Jacobus stated that her firm's management accepts and agrees with the observation. She stated that she would provide further details in her written response to the FDA 483.

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 (b) (4) (serial # (b) (4)) used during the production of the finished drug product PASER granules to monitor the (b) (4), a critical parameter of the (b) (4). The (b) (4) was due for calibration on June 30, 2010. Based on your firm's records, the (b) (4) has been used on a (b) (4) basis in the manufacturing process of more than (b) (4) batches of PASER granules since June 30, 2010. In addition, I observed another (b) (4) that is connected to your (b) (4) with no tag or sticker to indicate its calibration status.

Supporting Evidence and Relevance:

During a walk-through of the firm's manufacturing areas on 1/26/11, I randomly selected and checked the calibration status of equipment. I observed that the [redacted] (serial # [redacted]) used to monitor the [redacted] for the [redacted] was due for calibration on 6/30/10. I pointed this out to Mr. Pursell, who accompanied me on the walk-through; Mr. Pursell agreed with my observation that the unit's calibration was overdue. I asked Mr. Pursell if any other equipment is used to check the [redacted]. He stated that the controller on the front of the [redacted] is set to [redacted] when a product is set for [redacted] but this [redacted] is the main equipment used to monitor the [redacted]. I asked whose responsibility it is to ensure the calibration and proper performance of all equipment. Mr. Pursell stated that it is the responsibility of the Engineering department, who check equipment for calibration by going around the facility and checking the calibration status of equipment; he further stated that production employees should be looking at the calibration stickers during production as a check. I checked the master production record for the manufacture of PASER granules. I observed that on page 1 of the record, the [redacted] is identified as the operator check point for the [redacted]; step 10 on page 3 of the record states that the [redacted] should be turned on; step 14 on page 4 states to verify the [redacted] using the [redacted] (**Exhibit 61**). I found no step or space that documents that employees are checking the calibration status of equipment. According to the firm's use log for the [redacted], more than 200 in-process batches of PASER granules have been [redacted] using the [redacted] since June 30, 2010 (**Exhibit 62**).

I also observed on 1/26/11 that a [redacted] used to monitor the [redacted] for one of the [redacted] in Manufacturing Area [redacted] (identified as Unit 2) did not have a calibration sticker. Mr. Pursell stated that the [redacted] is the main method of telling whether the [redacted] of the [redacted] is [redacted] in order for [redacted] material to be [redacted] into the [redacted]; the calibration sticker is important as a check for production employees to ensure that the unit is in calibration.

I found that the firm does not have an established written procedure or program that defines the firm's overall program for preventative maintenance and calibration of equipment. Checks for calibration and preventative maintenance for equipment are performed manually by the firm's engineering department going around and checking equipment or production employees observing the calibration and preventative maintenance status of equipment based on stickers. There is no documented proof that employees are checking equipment for calibration and preventative maintenance needs.

Discussion with Management:

At the closeout meeting, I stated that the firm needs to establish a program to monitor calibration and preventative maintenance for equipment. Mr. Warman, Sr. stated that it was easier for his department to monitor equipment when the firm started production 20 years ago because there was

less equipment; he stated that it has become more difficult to monitor the calibration and preventative maintenance of equipment now. Ms. Jacobus stated that she is in the process of implementing a program to monitor equipment calibration and preventative maintenance; she stated that her firm may use a computer program or software to track all of the firm's equipment. She stated that her firm's management accepts and agrees with the observation and that she would provide further details in her firm's written response to the FDA 483.

PRODUCTION SYSTEM

OBSERVATION 8

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

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 (b) (4)) 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.

Supporting Evidence and Relevance:

The firm increased the batch size of the API Aminosalicylic Acid (PAS) by (b) (4) in 2010. Dr. Shiehser informed me on 2/10/11 that a validation was performed at the time of batch scale-up. I received a copy of the protocol and report for this validation (**Exhibits 63 and 64**). I reviewed the protocol and report and found that the validation was performed inadequately. Deficiencies I noted include the following:

a. The protocol does not identify any critical process parameter(s) that need to be monitored and controlled. For example, I was repeatedly told that maintaining the pH (b) (4) for Aminosalicylic Acid. There is no discussion of pH requirements in the protocol. When I reviewed batch records, I also noted that (b) (4) e requirements and (b) (4) are specified for certain steps. These are not specified in the validation protocol or report.

b. The protocol does not define any acceptance criteria. For example, no in-process or final specifications are defined in the protocol. The protocol states that (b) (4) lots at the increased batch size (b) (4) will be reviewed along with (b) (4) previous lots at the (b) (4) batch size; the protocol also states that "Specific attention will be placed on (b) (4) and (b) (4) levels." However, specific criteria and parameters related to

[redacted] and [redacted] levels are not defined nor are any criteria identified or defined that will be used to demonstrate that the process is reproducible at the [redacted] increased batch size. The firm's management informed me that [redacted] for the API; I stated that the protocol does not define specifications for [redacted] that need to be met; the report states that [redacted] specifications were met; however, the actual specifications are not defined.

c. The protocol states that the [redacted] increase in scale "necessitates changes in the size of the [redacted] and the time required for each step." However, none of the changes in the size of the [redacted] is described nor are any changes in the times for each step. The protocol does not include any detail of the manufacturing conditions that will be employed for the [redacted] increase in batch size, and describe how these conditions compare to the conditions used at the previous scale. In fact, the scaled-up process itself is not outlined in the validation protocol or report.

d. The validation protocol did not identify any sampling plans during the validations. When I asked what samplings were performed during the validation, I was informed that no additional sampling was performed compared to the normal process. For example,

   i. Due to the increase in batch size, certain steps required longer times. I asked if these longer times could have an effect on the impurity levels. Dr. Shiehser informed me that the increased times could have an effect on [redacted] levels, which can increase with longer process times; he believed that the time increases in this instance are not significant enough to cause [redacted] levels to rise significantly. I asked if the robustness of the process was studied to address these concerns and if [redacted] levels were monitored throughout the process as one kind of evaluation for robustness. He stated that this was not performed.

   ii. The firm began sending [redacted] PAS samples to [redacted] for [redacted]; Mr. Pursell informed me that the [redacted] PAS can be [redacted] at [redacted] or this location and that this provision is present because the [redacted] at [redacted] has a larger capacity than the [redacted] at this location. During this validation, no additional sampling was performed to assess any potential differences in product quality for [redacted] PAS that is [redacted] at [redacted] vs. [redacted] PAS that is [redacted] at Jacobus' facility. Additional sampling would also have been warranted to ensure that the quality of the product is maintained during transport since the product has a storage requirement of [redacted].

   The firm's SOP # QA-0004-01 titled "Process Validation Practices" states that the level of sampling must be statistically based (part 5.8) and calls for greater in-process and release testing during validation (**Exhibit 65**).

e. None of the validation batches were placed on stability. The changes in volumes and times and any potential effects on product quality (e.g [redacted] levels) over the shelf-life of the API and finished product were not assessed. The validation protocol did not call for any batches to be placed on stability. Ms. Jacobus stated that this was an oversight and that batches should have been placed on stability.

Discussion with Management:

At the closeout meeting, I discussed the deficiencies in this validation. I stated that the firm's approach to process validation is not well organized and not based on a well-defined procedure. Ms. Jacobus stated that she agrees that the validation was performed inadequately, and her firm accepts the observation. She stated that details regarding corrective actions will be provided in her firm's response to the FDA 483.

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 (b) (4) is inconsistent with actual practice. I observed employees acquiring (b) (4) for use at valve (b) (4) by using a plastic hose that is approximately (b) (4) 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 (b) (4) during the production of PASER granules.

Supporting Evidence and Relevance:

The firm utilizes a (b) (4) to acquire (b) (4) for use during the production of PASER granules (b) (4)). (b) (4) is acquired at valve (b) (4) which is located above the sink in Manufacturing Area (b) (4) the room in which (b) (4) is performed). Employees acquire (b) (4) using a plastic hose approximately (b) (4) feet long; (b) (4) is acquired into (b) (4) for use in (b) (4). When not in use, the hose is hung in several loops over the sink; this increases the possibility of bio-film buildup. I reviewed the firm's SOP # W-0002-004 titled "Procedures for Sampling, Testing, and Clearance of (b) (4) (JPC Code 1026) for the Jacobus Plant (b) (4)" **(Exhibit 66)** with (b) (6) on 1/28/11, who stated that he samples valve (b) (4) daily in the morning. (b) (6) stated that he samples by (b) (4) He pointed to step 5.5.1.1 of SOP # W-0002-004 that states to flush the valve by (b) (4). The SOP does not require sampling to be conducted with the plastic hose attached (for valves where (b) (4) is acquired using a plastic hose). I stated that employees acquire (b) (4) using a plastic hose connected to valve (b) (4) and asked why sampling is not conducted similarly. (b) (6) stated that he agreed that sampling should be with the hose connected and added that he has been instructed to disconnect the hose for every valve that has a hose connected and then sample directly from the valve. When I asked who provided these instructions, (b) (6) did not want to comment further.

I also observed that valve (b)(4) is not sampled according to a defined schedule. SOP # W-0002-004 states in part 5.2.3 that all valves are to be sampled and tested (b)(4); however, I was informed by employees (i.e. Mr. Pursell, Dr. Shiehser, and (b)(6)) that sampling for valve (b)(4) is conducted on (b)(4) due to the frequency of use for valve (b)(4) to acquire (b)(4) for PASER granule production (sampling and testing is not conducted on (b)(4). I reviewed spreadsheets provided by Dr. Shiehser that has (b)(4) sampling and testing results for valve (b)(4) (**Exhibit 67**). The spreadsheets have 3 columns; the first column is the list of Julian dates on which valve (b)(4) was sampled, and columns 2 and 3 are heterotrophic plate count results (duplicate samples). Dr. Shiehser stated that the Julian dates in column 1 are supposed to correspond to sampling on (b)(4). After checking a Julian calendar for 2008-2010, I briefly checked the list of dates in the spreadsheet and found gaps in the Julian dates listed. For example, I noticed that valve (b)(4) was not sampled on the following dates in September, November, and December 2010:

Julian Date	Calendar Date	Day of Week
(b)(4)		

Discussion with Management:

On 1/28/11, 2/3/11, and at the closeout meeting, I discussed that (b)(4) sampling procedures need to be consistent with actual practices for acquiring (b)(4). I stated that by sampling directly from the valve and not with the hose attached, the results may reflect better microbial quality of (b)(4) than the (b)(4) used in production batches. This is of greater concern given the observation that the plastic hose is stored (hung) in loops when not in use. I stated that a similar deficiency was cited on the FDA 483 issued at the conclusion of the previous inspection. That specific issue was addressed; however, the sampling procedure as a whole was still not assessed for adequacy.

At the closeout meeting, Ms. Jacobus stated that she accepts and agrees with the observation and promised to revise the firm's procedures for sampling and testing the (b)(4).

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.

Supporting Evidence and Relevance:

During inspectional walk-throughs on 1/24/11 and 1/26/11, I observed that different in-process lots of PASER granules were stored in different locations in the firm's manufacturing areas (e.g. Manufacturing Area (b)(4) hallway outside Manufacturing Areas (b)(4)). **Exhibit 68** is a photograph taken on 1/26/11 of (b) large blue drums containing different in-process lots of PASER granules. I asked Mr. Pursell why the drums were sitting in the hallway; he stated that the drums were sampled for in-process QC testing after (b)(4) and were sitting in the hallway while production employees are awaiting QC test results; the (b) drums were identified with small white stickers as "PASER (b)(4) Mass" for lot numbers 13418, 13419, 13420; there were (b)(4) drums per lot number. There were (b) additional smaller white drums on a steel rack identified with lot number 13414; Mr. Pursell stated that production was awaiting QC testing results for these drums prior to (b)(4) using the (b)(4) I asked for the status of these lots; Mr. Pursell stated that the lots are in a "hold" status as QC testing is being conducted. After I asked how many lots are typically produced at a time, Mr. Pursell stated that up to (b)(4) lots of PASER granules are produced at a time; therefore, having (b)(4) drums of different in-process lots is common; many times, these different in-process lots end up at the same stage of manufacture as QC testing is being conducted. I stated that these drums containing different in-process lots at the same stage of manufacture did not have any identification of status. I also asked what controls are present to differentiate the drums; he stated that production employees are to read the white sticker to determine what drums to pull. I stated that these different lots should be identified with status tags (e.g. "quarantine" or "hold") and that additional controls need to be in place to prevent mix-ups of lots. Mr. Pursell stated that he understood.

I checked the master batch record for PASER Granules and 1 executed batch record; I found no controls to prevent mixups (i.e., for identifying in-process lots with status, e.g., "on hold," "under test," "approved").

I stated that without adequate controls, there is a potential for the following scenario: 4 lots of PASER granules are processed and are at the same stage of manufacture (after (b)(4) awaiting QC test results; all 4 lots pass QC testing and are ready for the next step; a production employee pulls drum 1A from lot 1 and drum 2b from lot 2 for further manufacture; there is a deviation or

failure further in the manufacture (e.g. after [redacted] (b) (4)); an investigation may be conducted inadequately because drums from different lots were inadvertently mixed, that is, 2 lots may actually be affected by the deviation or failure rather than 1 lot due to the mix-up.

Discussion with Management:

On 1/28/11, when I first discussed the deficiency with Ms. Jacobus, she stated that she agreed that lots from different drums could be mixed up and that she planned to institute a serialized method to tag and trace drums. At the closeout meeting, I reiterated my concerns, and Ms. Jacobus stated that she accepted and agreed with the observation. We jointly discussed the scenario I mentioned in the previous section about employees pulling drums from different lots. Ms. Jacobus stated that her firm is in the process of instituting controls to prevent mix-ups of in-process lots and that she would provide further details in her written response to the FDA 483.

See VOLUNTARY CORRECTIONS section of this report for additional comments.

REFUSALS

There were no refusals during the current inspection.

GENERAL DISCUSSION WITH MANAGEMENT

The following individuals were present during the closeout meeting on 2/18/11:

- Dr. David P. Jacobus – President
- Laura R. Jacobus – Vice-President of Quality Assurance
- Richard W. Pursell – Plant Manager and Pharmaceutical Manufacturing and Shipping Coordinator
- Raju Shah – Director, Quality Control
- Guy A. Shiehser – Director of Chemistry
- Robert J. Warman, Sr. – Director of Engineering

The FDA 483 was issued to Dr. Jacobus after the discussion with management.

I discussed the following points at the closeout meeting. I reminded the firm's management that I had already discussed these points in greater detail earlier in the inspection:

1. I informed the firm's management that I believed their handling of Dapsone complaints (**Exhibits 69-71**) between November and December 2010 for crushed tablets was inadequate as follows:

   a. A complaint (2010-P3) for crushed tablets was received from a pharmacist on 11/12/10 for lot 12804: Jacobus asked its contract packager, (b) (4), to investigate. The results of the investigation are not included. Part of Jacobus' conclusion was that there could only be a small amount of damaged product on the market.

   b. A 2nd complaint (2010-P5) for crushed tablets was received from a pharmacist on 11/18/10 for lot 12804; Jacobus again asked (b) (4) to investigate. The results of the investigation are not included. Jacobus again speculated that there could only be a small amount of damaged product on the market.

   c. A 3rd complaint (2010-P8) for crushed tablets was received from a pharmacist on 12/16/10 for lot 12762; after this complaint, Jacobus escalated the concern to (b) (4), who ultimately made a correction by making an equipment modification (die plates replaced with (b) (4) (b) (4) plates).

   I informed the firm's management that I found their handling of these complaints to be inadequate in several ways. First, there is no indication that Jacobus checked its retains after the complaints were received to see if the same defects were present in the blister packaging. Second, the investigation should have been elevated after the 2nd complaint was received for the **same** lot. Third, the investigation was not expanded to all lots potentially affected. The breadth of this problem is unknown. Fourth, there is no follow-up regarding the adequacy of corrective actions. Ms. Jacobus stated that she agreed that her firm should have conducted a more thorough investigation after the 2nd complaint. She stated that her firm is following up with (b) (4) regarding the adequacy of corrective actions.

2. I observed the following deficiencies related to the manufacture of Dapsone 25 mg and 100 mg tablets:

   a. Daily activities are not recorded for (b) (4). Specifically, the (b) (4) step for Dapsone 25 mg and 100 mg tablets lasts approximately (b) (4), respectively, and is completed over (b) (4) days. Employees start-up and shut-down the (b) (4), but these activities are not recorded in the batch record. The daily (b) (4) setting for the (b) (4) is not recorded in the batch record; only the (b) (4) settings at the beginning and end of (b) (4) are recorded. The daily start and end time for (b) (4) is also not recorded. **Exhibits 72-73** are pages from the master batch records for Dapsone 25 and 100 mg tablets.

b. The [redacted] operates by [redacted]. I observed that the batch record instructs employees to ensure that the hopper does not run out of [redacted] (**page 6 of Exhibits 72 and 73**). However, specific instructions regarding levels at which [redacted] needs to be added are not given. Mr. Pursell informed me that only certain employees are responsible for [redacted] based on this requirement. At the closeout meeting, I stated that the batch record still needs to have more specific instructions and requirements to maintain the hopper level.

c. The firm needs to establish a defined specification for tablet thickness for Dapsone 25 mg and 100 mg tablets. For Dapsone 25 mg tablets, the thickness specification is defined as [redacted] (**Exhibit 72, page 5**); for Dapsone 100 mg tablets, the thickness specification is defined as [redacted] (**Exhibit 73, page 5**). I stated that these specifications need to be defined with upper and lower limits. I informed the firm's management that the reason I mentioned this deficiency as a verbal observation is because I found during my review of batch records that the thickness values obtained have been tight around the values specified in the batch record.

3. Following an investigation into a moisture content failure for PASER granules in July 2010, a corrective action was implemented to set a stop on the [redacted] adjustment for the [redacted] (**Exhibit 74**) at the [redacted] position (setting of "[redacted]"); employees were trained to set the [redacted] adjustment at this position. Even though there have been no moisture content failures after this corrective action, the step [redacted] in the batch record needs to be updated with clear instructions (**Exhibit 75**) and requirements for recording the [redacted] setting.

4. During an inspectional walk-through on 1/24/11, I observed that employees were not entering information on batch records contemporaneously during the manufacture of lot # 13409 of PASER granules; the tank and motor numbers were not entered in steps [redacted] and an end time was not entered for step [redacted] When I brought up the deficiency, the employee filled in the missing spaces (including entering a time that had already passed).

5. I found the following deficiencies in the firm's SOP # QC-0047-01 titled "Laboratory Investigations" (**Exhibit 76**):

   a. The SOP states that in Phase II, additional testing or retesting is performed; the SOP does not state the purpose of Phase II testing.

   b. Section 4.13 titled "Re-measures" does not specify how many re-measures are allowed.

6. I discussed the following points related to SOPs:

   a. On 1/24/11, I observed that the [redacted] used to [redacted] Dapsone and [redacted] was not cleaned; according to the use log, the [redacted] was last used on 1/17/11 (**Exhibit 77**); the firm's SOP # G-0018-01 titled "Equipment Cleaning in General" states that dosage form equipment is to be cleaned within [redacted] of use (**Exhibit 78**). On 1/26/11, I observed that the [redacted] [redacted] (dedicated for the product [redacted]) in the API manufacturing

area had not been cleaned since its last use on 5/3/10 (**Exhibit 79**); I was informed that the overall policy is for all equipment to be cleaned within [redacted] of use.

b. I observed on the Master SOP list that many SOPs have been in place for many years (e.g. SOPs dated 1998, 1999); I stated that SOPs need to be reviewed on a periodic basis to ensure that they are relevant and reflect current practices. The Master SOP list also needs to be updated with all existing and current SOPs (**Exhibit 80**).

7. I found deficiencies with the firm's re-validation for Dapsone tablets conducted from 2003-2006, as follows:

   a. The protocol was written in 2003, but the reports were written in 2006 (**Exhibits 81-83**); there is no justification for the gap in time between the protocol and report

   b. The manufacturing conditions are not outlined (e.g. equipment and raw materials used, a description of the process, operating parameters, batch sizes)

   c. Sampling during [redacted] was performed every [redacted]; during actual production, sampling is performed every [redacted] by production employees.

   d. Page 15 of the validation report for Dapsone 100 mg tablets contains cross-outs and corrections to data with no initials and date.

   e. The values for tablet weight, thickness, hardness, friability, and disintegration are the same for lots 10603 and 10607 for the following samples: "[redacted]," and "At start of tablets." I asked if the values for these samples were really the same or if these are transcription errors. Ms. Jacobus stated that she would follow up on this discrepancy. I expressed serious concerns regarding data integrity.

8. The firm's SOP titled "Deviations" (**Exhibit 46**) needs to include time frames for conducting investigations and provisions for extending investigations to other batches potentially affected.

9. The firm's SOP # G-0001-06 titled "Stability Testing Program" (**Exhibit 84**) does not specify a time frame for starting studies for stability lots; it also needs to establish timeframes for completing analyses.

ADDITIONAL INFORMATION

Access to the firm's manufacturing location in Plainsboro, NJ is gained via an access road located on the northbound side of Schalks Crossing Road between Scudders Mill Road and Research Way; the access road begins immediately before an overpass. There is a white sign at the beginning of the access road that states in black letters "Industrial Research Laboratory"; the access road leads into the Plainsboro Preserve and ends at the firm.

SAMPLES COLLECTED

I collected no samples during the current inspection.

VOLUNTARY CORRECTIONS

PREVIOUS INSPECTION:

I reviewed the firm's corrective actions to the July 2008 FDA 483 issued at the closeout of the previous inspection.

Observation #1:

For the manufacturing of [redacted] lots of the Active Pharmaceutical Ingredient, Proguanil Hydrochloride starting with Lot 2349J manufactured 8/29/07 to the present date:

The firm failed to assure that this drug meets the requirements of the FD&C Act as to safety, and meets the quality and purity characteristics which it purports or is represented to possess.

Specifically, the firm's on going investigation confirmed finding metallic particles (iron / rust) in the product and the firm has suspended production of this product since March 2008. The disposition of the following quarantined lots returned by the firm's customer is still pending: Lot 2349J, 2350J, 2397J, 2398J, 2399J, 2400J, 2401J, 2402J, 2403J, 2404J, 2444J, 2465J, 2466J, and 2467J.

The firm identified the sources of the metallic contamination in Proguanil HCl to be interior "wounds" along with rust and damage at the [redacted] the wounds were repaired and an [redacted] was designed and installed to preclude extraneous material from entering the [redacted]. Additionally, the firm constructed an [redacted] over the [redacted] under [redacted] to prevent external contaminants from entering the [redacted] installed [redacted] for all transferred fluids between major equipment (e.g. [redacted]), and instituted magnetic surveillance steps into the process. The firm had three manufacturing investigations since the previous inspection related to metallic particles found in PASER granule lots at [redacted]. Additional corrective actions were implemented, which included enclosing all equipment related to the manufacture of PASER granules (i.e [redacted]) inside [redacted] rooms. Since the implementation of these corrective actions, the firm has not had any metallic particles detected in any lots.

Observation #2:

For the manufacturing of the finished drug product, Aminosalicylic Acid Delayed-release Granules (e.g. Lot 11096 EXP. 04-2010)

Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality control unit.

Specifically, on or about 3/17/08, the manufacturing department installed a larger (b)(4) with different process settings. The firm's change control procedure (SOP G-0030-01) was not followed. The impact upon the validated manufacturing process and the finished drug product was not accessed and documented as required by this procedure. Additionally, a pen change to the master batch record, and all subsequent production records dating back to 3/17/08, was never formally approved by the quality control unit.

I verified that batch records for PASER Delayed-Release Granules were updated with the new (b)(4) Mr. Pursell stated that, as a result of this observation, management decided to implement equipment changes as planned deviations. Additionally, training was provided to employees to follow the firm's change control procedures for all types of changes (e.g. equipment, process); I reviewed and observed that this training was provided to all production employees. The impact of the change was addressed and documented.

Observation #3:

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

A.) Inconsistent departmental procedures have the potential to reflect better microbial (b)(4) quality then what is actually used during the (b)(4) of (b)(4) sensitive Aminosalicylic Acid Delayed-release Granules. Sampling procedures for monitoring the (b)(4) include (b)(4) Production batch records do not require the (b)(4) prior to manufacturing batches of product.

Though the firm corrected the specific issue cited in part A, I found that the firm's procedure for sampling the (b)(4) is still not consistent with actual practices for acquiring (b)(4) Refer to Observation 9 in the Objectionable Conditions and Management's Response section of this EIR.

B.) The firm has no procedure for periodic chemical sanitization of the (b)(4) to directly control biofilm build up in the (b)(4). Although the firm's microbial data on the (b)(4) is below their alert limit of (b)(4) the microbial trend on the system has been steadily increasing. The (b)(4) system design does incorporate (b)(4)

The firm now sanitizes their (b)(4) system using (b)(4). This sanitization is conducted at least (b)(4) when the system is regenerated, or more frequently if the system is "opened" or serviced for any reason.

CURRENT INSPECTION:

At the end of the closeout meeting, Dr. Jacobus and Ms. Jacobus stated they have ceased all manufacturing activities until all of the deficiencies identified during the inspection have been addressed and corrected. I stated that corrective actions should not be limited to items cited on the FDA 483 or discussed with the firm's management; I stated that the firm's management needs to assess their systems and practices as a whole for compliance to cGMPs. Dr. Jacobus and Ms. Jacobus agreed and stated that they have begun assessing their entire firm's facility and systems. I conducted a walk-through of the facility and verified that the firm ceased all manufacturing activities. Manufacturing Area (b)(4) has been vacated with all of the equipment having been moved to Manufacturing Area (b)(4). Ms. Jacobus stated that the larger size of Manufacturing Area (b)(4) will allow for improved flow and control of the process. The QC lab continues to perform testing for commercial lots on the market. Dr. Jacobus and Ms. Jacobus stated that they would provide a written response to NWJ-DO within 15 days regarding the firm's corrective actions.

EXHIBITS COLLECTED

1. A copy of information provided with each (b)(4) product (25 pages)
2. A copy of labeling associated with US marketed lots of PASER granules and Dapsone 25mg and 100mg tablets (6 pages)
3. A copy of the firm's organizational chart and list of employees (2 pages)
4. A copy of maps of the firm's facility in Plainsboro, NJ (3 pages)
5. A copy of a change control dated 11/10/09 (11 pages)
6. A copy of the SOP # G-0032-001 (3 pages)
7. A copy of SOP # G-0006-2 (8 pages)
8. A copy of a letter and attachments dated August 20, 2010 sent to the FDA regarding modified bar code labeling (3 pages)
9. A copy of SOP # G-0015-01 (3 pages)
10. A copy of stability data sheets for Dapsone 25 mg and 100 mg tablets (3 pages)
11. A copy of the product specifications document for Dapsone 25 mg tablets (3 pages)
12. A copy of the product specifications document for Dapsone 100 mg tablets (3 pages)
13. A copy of the stability protocol for Dapsone 25 mg and 100 mg tablets (1 page)
14. A copy of test method DF-DAP-LC-1 (4 pages)
15. A copy of a re-validation protocol and report for test method DF-DAP-LC-1 (37 pages)
16. A copy of an inventory of stability samples in the CRT chamber (3 pages)
17. A copy of test method RM-DAP-LC-4 (22 pages)
18. A copy of results for an evaluation of impurities dated 1/18/11 (1 page)
19. A copy of test method RM-DAP-LC-1 (6 pages)
20. A copy of test method RM-DAP-TLC-1 (3 pages)

21. A copy of the specifications document for Dapsone technical grade (3 pages)
22. A copy of the specifications document for Dapsone purified (3 pages)
23. A copy of the stability protocol for Dapsone API (1 page)
24. A copy of stability data sheets for the Dapsone drug substance (5 pages)
25. Photographs of the CRT chamber (5 pages)
26. A copy of temperature and humidity data for the CRT chamber for 6/8/09-7/23/09 (3 pages)
27. A copy of temperature and humidity data for the CRT chamber for 826/09-10/1/09 (29 pages)
28. A copy of temperature and humidity data for the CRT chamber for 10/1/09-11/10/09 (14 pages)
29. A copy of temperature and humidity data for the CRT chamber for 12/7/09-1/11/10 (7 pages)
30. A copy of temperature and humidity data for the CRT chamber for 1/11/10-2/23/10 (4 pages)
31. A copy of temperature and humidity data for the CRT chamber for 2/23/10-3/13/10 (4 pages)
32. A copy of temperature and humidity data for the CRT chamber for 3/13/10-4/19/10 (5 pages)
33. A copy of temperature and humidity data for the CRT chamber for 4/19/10-5/21/10 (3 pages)
34. A copy of temperature and humidity data for the CRT chamber for 5/21/10-6/22/10 (4 pages)
35. A copy of temperature and humidity data for the CRT chamber for 6/22/10-7/21/10 (4 pages)
36. A copy of temperature and humidity data for the CRT chamber for 8/19/10-9/28/10 (7 pages)
37. A copy of temperature and humidity data for the CRT chamber for 12/28/10-1/26/11 (2 pages)
38. A copy of temperature and humidity data for the in-process cold room for 3/18/10-4/9/10 (4 pages)
39. A copy of temperature and humidity data for the in-process cold room for 7/8/10-8/9/10 (17 pages)
40. A copy of temperature and humidity data for the in-process cold room for 8/9/10-9/10/10 (7 pages)
41. A copy of temperature and humidity data for the shipment and handling of PASER granule lots for 6/12/09-7/22/09 (38 pages)
42. A copy of temperature and humidity data for the shipment and handling of PASER granule lots for 2/19/10-3/8/10 (5 pages)
43. A copy of temperature and humidity data for the shipment and handling of PASER granule lots for 6/4/10-7/21/10 (5 pages)
44. A copy of temperature and humidity data for the shipment and handling of PASER granule lots for 6/11/10-7/7/10 (5 pages)
45. A copy of temperature and humidity data for the shipment and handling of PASER granule lots for 6/19/10-7/6/10 (13 pages)
46. A copy of SOP # G-0023-01 (5 pages)
47. A copy of a list of deviations for PAS and Dapsone (2 pages)
48. A copy of pages from the batch record for PAS Lot # 1163 (4 pages)
49. A copy of pages from the batch record for PAS Lot # 1171 (4 pages)
50. A copy of pages from the batch record for PAS Lot # 1219 (4 pages)

51. A copy of the deviation sheets for PAS Lot #s 1220-1227 (8 pages)
52. A copy of pages from the batch record for PAS Lot # 1364 (7 pages)
53. A copy of the 2009 annual product review for Aminosalicylic Acid (9 pages)
54. A copy of SOP # QA-0012 (4 pages)
55. A copy of the 2009 annual product review for the finished product PASER granules (4 pages)
56. A copy of SOP # G-0025-01 (2 pages)
57. Photographs of the firm's sampling area (7 pages)
58. A photograph of the sampling area taken on 2/9/11 (1 page)
59. A copy of SOP # G-0011-01 (1 page)
60. A copy of SOP # QA-0005-01 (3 pages)
61. A copy of pages from the master batch record for Paser Uncoated Granules (3 pages)
62. A copy of pages from the equipment log book for the [redacted] (b) (4) (17 pages)
63. A copy of "Protocol 11102009" (1 page)
64. A copy of "Results of Protocol 11102009" (5 pages)
65. A copy of SOP # QA-0004-01 (11 pages)
66. A copy of SOP # W-0002-004 (14 pages)
67. A copy of spreadsheets with [redacted] (b) (4) sampling and testing results for valve [redacted] (b) (4) 12 pages)
68. A photograph taken on 1/26/11 of containers holding in-process lots of PASER granules (1 page)
69. A copy of complaint 2010-P3 (5 pages)
70. A copy of complaint 2010-P5 (3 pages)
71. A copy of complaint 2010-P8 (4 pages)
72. A copy of pages from the master batch record for Dapsone 25 mg Tablets (6 pages)
73. A copy of pages from the master batch record for Dapsone 100 mg Tablets (6 pages)
74. A copy of Investigation Number MF070210 (3 pages)
75. A copy of pages from the master batch record Paser Uncoated Granules (5 pages)
76. A copy of SOP # QC-0047-01 (21 pages)
77. A copy of pages from the equipment cleaning and use log for the non-dedicated [redacted] (b) (4) (5 pages)
78. A copy of SOP # G-0018-01 (2 pages)
79. A copy of pages from the equipment cleaning and use log for the [redacted] (b) (4) (b) (4) (2 pages)
80. A copy of the Master SOP list (7 pages)
81. A copy of Protocol No. PV081503 (5 pages)
82. A copy of Report No. QC091405 (23 pages)
83. A copy of Report No. QC071506 (22 pages)
84. A copy of SOP # G-0001-06 (7 pages)

85. The officially sealed original CD-R disk containing photographs taken during the inspection (1 packet)
86. Officially sealed CD-R disk that is a working copy of the original CD-R disk containing photographs taken during the inspection (1 packet)

EVIDENCE MATRIX

Current FDA 483 Observation Number	Page(s)	Exhibit Number(s)
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ATTACHMENTS

1. A copy of the FDA 482, Notice of Inspection, issued on 1/24/2011 (3 pages)
2. A copy of the FDA 483, Inspectional Observations, issued on 2/18/2011 (6 pages)
3. A copy of the FDA 482, Notice of Inspection, issued on 2/24/2011 (3 page)
4. A copy of the amended FDA 483, Inspectional Observations, issued on 2/24/2011 (6 pages)

Atul J. Agrawal, Consumer Safety Officer