TABLE OF CONTENTS

SUMMARY

A surveillance inspection of this manufacturer of active pharmaceutical ingredients and prescription pharmaceuticals was conducted pursuant to NWJ-DO FY'12 Drug Workplan under FACTS Assignment ID 1341733, Operation ID 5757919. CPGM 7356.002F, Active Pharmaceutical Ingredients and CPGM 7356.002, Drug Process Inspections, afforded inspectional guidance.

The previous inspection conducted in 2/2011 was a comprehensive cGMP inspection providing coverage to the Quality, Production, Laboratory Control, Materials, Facilities and Equipment, and Packaging and Labeling Systems. The previous inspection revealed the following deficiencies: the lack of a stability indicating test method for Dapsone tablets, the failure to perform impurity testing of Dapsone drug substance on stability, the failure to perform investigations into temperature excursions and the failure to perform investigations according to procedures, the failure to review all complaints and investigations during annual product reviews, the lack of controls over the data acquisition system, the failure to maintain the sampling suite in a state of repair, the failure to calibrate instruments, an inadequate process validation following a scale-up, the failure to take representative water samples, and the failure to identify containers in a manner to prevent mix-ups. The previous inspection was classified VAI.

The current inspection was a comprehensive cGMP inspection providing coverage to the Quality, Facilities and Equipment, Production, and Laboratory Control Systems. The inspection revealed the following deficiencies: the failure to adequately perform failure investigations, inadequate cleaning of manufacturing equipment, the failure to perform temperature mapping studies for a cold-storage warehouse, the failure to maintain facilities in a state of repair, and the failure to maintain manufacturing equipment in a state of repair, the lack of manufacturing instructions and control procedures for a (b) (4) step, the failure to label containers, the failure to validate a stability indicating test method, and the failure to validate a supplier's certificate of analysis. An FDA-483, Inspectional Observations, was issued at the close of the inspection to Dr. David P. Jacobus, President who promised a written response to the District within 15 days. Prior to the issuance of the FDA-483, Inspection Observations, I informed the firm's management that the firm's response may impact FDA's determination of the need for follow-up action, if FDA receives an adequate response to the FDA-483 within 15 business days of the end date of the inspection.

The firm made no refusals. Sample DOC 502452 was collected to document the interstate shipment of Dapsone 25 mg Tablets USP.

ADMINISTRATIVE DATA

Inspected firm:	Jacobus Pharmaceutical Company Inc.
Location:	Industrial Research Laboratory Building Schalks Crossing Road Plainsboro, NJ 08536
Phone:	609-799-8221
FAX:	(609)799-1176
Mailing address:	37 Cleveland Lane P.O. Box 5290 Princeton, NJ 08540-3049
Dates of inspection:	3/28/2012, 3/29/2012, 3/30/2012, 4/2/2012, 4/3/2012, 4/4/2012, 4/11/2012, 4/16/2012
Days in the facility:	8
Participants:	Addam S. Reynolds, Investigator

On 3/28/2012, Supervisory Investigator Kelli Dobilas and I, Investigator Addam S. Reynolds, presented our credentials and issued a FDA-482, Notice of Inspection, to Laura R. Jacobus, Vice President. Ms. Jacobus indicated that she was authorized to accept the Notice in the absence of Dr. David P. Jacobus, President, the most responsible person. I explained to Ms. Jacobus that Supervisory Investigator Dobilas is not directly participating in the inspection and is present solely for auditing purposes.

During the inspection, Laura R. Jacobus was the primary contact at the firm. She answered questions, provided documents, and made employees available when needed. Other Jacobus Pharmaceutical Company, Inc. employees that participated in the inspection include:

Richard Pursell, Plant Manager
Guy Schiehser, Director of Chemistry
Pete Raghubans, Quality Assurance Executive
Robert Warman Sr., Director of Engineering
Neil Lewis, Director of Chemical (API) Manufacturing
Raju Shah, Director of Quality Control

The before mentioned employees report to Dr. David P. Jacobus. A copy of the firm's organizational chart is included as **Exhibit #1**.

A close-out meeting was held with the firm on 4/16/2012. The attendees of the meeting were:

David P. Jacobus, President
Laura R. Jacobus, Vice-President
Richard Pursell, Plant Manager
Guy Schiehser, Director of Chemistry
Pete Raghubans, Quality Assurance Executive
Robert Warman Sr., Director of Engineering
Neil Lewis, Director of Chemical (API) Manufacturing
Raju Shah, Director of Quality Control

Prior to the issuance of the FDA-483, Inspection Observations, I informed the firm's management that the firm's response may impact FDA's determination of the need for follow-up action, if FDA receives an adequate response to the FDA-483 within 15 business days of the end date of the inspection. An FDA-483, Inspectional Observations was issued at the close of the inspection to Dr. David P. Jacobus, President. Dr. Jacobus promised corrective actions in writing to the District.

Provided as **Exhibit #94** is an original CD-ROM of photographs taken during the inspection. A copy of the original CD-ROM and a working copy of the original CD-ROM is provided as **Exhibit #95** and **#96**, respectively.

I, Investigator Reynolds, was present all inspectional days. Supervisor Investigator Dobilas was present on 3/28/2012 for the purpose of an on-site audit. I wrote this EIR in its entirety.

HISTORY

Jacobus Pharmaceutical Company, Inc. (hereinafter referred to as Jacobus) was incorporated in 1977 in the State of New Jersey and continues to operate as a privately-owned business. Jacobus is located at Industrial Research Laboratory Building, Schalks Crossing Road, Plainsboro, NJ 08536; there are no related facilities. This facility has approximately (b) (4) employees. The firm operates (b) (4) (b) (4) . This facility is registered as a manufacturer of active pharmaceutical ingredients and prescription pharmaceuticals, registration is current.

Ms. Jacobus stated the annual sales for products manufactured at the site total approximately (b) (4) (b) (4) Contract manufacturing sites include:

Firm	Location	Function
(b) (4)		- Drying of PAS API - Enteric coating of PASER granules
		- Blister packaging of Dapsone 25 mg and 100 mg tablets - PASER Granules Packaging
		- Distribution Center

The firm continues to operate as a manufacturer of active pharmaceutical ingredients and prescription pharmaceuticals. The firm's major customers are drug distributors. Examples of the firm's domestic customer's include:

(b) (4)

All FDA correspondence should be addressed to:
Dr. David P. Jacobus
Jacobus Pharmaceutical Company, Inc.
37 Cleveland Lane
P.O. Box 5290
Princeton, NJ 08540

INTERSTATE COMMERCE/JURISDICTION

The firm is a manufacturer of active pharmaceutical ingredients and prescription pharmaceuticals. Attached is the firm's current list of finished products being manufactured (**Exhibit #2**). The firm manufactures active pharmaceutical ingredients which are used during the commercial manufacture of finished products; the firm does not sell active pharmaceutical ingredients. Ms. Jacobus estimated that over (b) (4)% of the products manufactured at this site are shipped into interstate commerce. Ms. Jacobus indicated that approximately (b) (4)% of PASER granules are distributed domestically. Ms. Jacobus also indicated that approximately (b) (4)% and (b) (4)% of Dapsone 25 mg and 100 mg Tablets USP were distributed domestically, respectively.

The table below summarizes information regarding the firm's commercial drug products:

Product	Strength	Dosage Form	Indication
Dapsone USP Tablets	25mg, 100mg	Prompt-release tablets	Used to treat *Mycobacterium leprae* infections and Dermartitis hepetiformis
PASER Delayed-Release Granules	4 grams per packet	Enteric-coated, Granules (granules are mixed with an acidic beverage or food prior to the patient taking the medication)	Used in the treatment of tuberculosis

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

David P. Jacobus, President: Dr. Jacobus remains the firm's most responsible person. Dr. Jacobus is responsible for the over-sight of the firm's daily operations and has the power, responsibility and authority to detect, prevent and correct all cGMP violations. All Jacobus Pharmaceutical Company Inc. employees ultimately report to Dr. Jacobus. Dr. Jacobus did not participate during the current inspection; Dr. Jacobus was present at the close-out meeting.

Laura R. Jacobus, Vice-President: Ms. Jacobus remains as the firm's Vice-President. Ms. Jacobus is the most senior level person in charge of the firm's quality unit. Ms. Jacobus makes disposition decisions, is responsible for regulatory affairs, and has final approval authority over documents. In the absence of Dr. Jacobus, Ms. Jacobus serves as the most responsible person. Ms. Jacobus reports directly to Dr. Jacobus.

Richard Pursell, Plant Manager: Mr. Pursell is responsible for the oversight of the firm's dosage form manufacturing operations and serves as the firm's shipping coordinator. Mr. Pursell is in charge of dosage form production schedules. Mr. Pursell's other responsibilities include: assisting in validation activities, providing oversight of equipment cleaning, and coordinating product transfer and all shipping related activities. Mr. Pursell reports to Ms. Jacobus.

Guy Schiehser, Director of Chemistry: Dr. Schiehser is responsible for the oversight of the firm's research and development activities. Dr. Schiehser indicated that he is currently responsible for the oversight of the firm's active pharmaceutical ingredient (API) manufacturing operations. Dr. Schiehser indicated that his responsibilities related to API manufacturing (b) (4) (b) (4) Dr. Schiehser reports to Ms. Jacobus.

Pete Raghubans, Quality Assurance Executive: Mr. Raghubans is responsible for performing the firm's quality unit oversight activities, review of documentation, and has the authority to make disposition decisions. Mr. Raghubans has joined the firm since the previous inspection. Mr. Raghubans reports to Ms. Jacobus.

Robert Warman Sr., Director of Engineering: Mr. Warman is responsible for the oversight of the firm's engineering department. The Engineering department is responsible for all maintenance related activities. Mr. Warman reports to Ms. Jacobus.

Neil Lewis, Director of Chemical (API) Manufacturing: Dr. Lewis has joined the firm since the previous inspection. Dr. Lewis is responsible for the oversight of the firm's API manufacturing operations along with Dr. Schiehser. The firm is currently in the process of (b) (4) (b) (4) Dr. Lewis reports to Ms. Jacobus.

Raju Shah, Director of Quality Control: Mr. Shah is responsible for the oversight of the firm's quality control laboratory. Since the previous inspection Mr. Shah has taken over the responsibility of monitoring the firm's purified water system. All laboratory personnel report to Mr. Shah. Mr. Shah has the authority to make disposition decisions based on release specifications. Mr. Shah reports to Ms. Jacobus.

FIRM'S TRAINING PROGRAM

The firm's training program consists of (b) (4) cGMP training, self-study, training on job-related procedures, and on-the-job training. During the inspection, I reviewed laboratory and manufacturing personnel training records. I did not note any specific deficiencies with the firm's training program.

MANUFACTURING/DESIGN OPERATIONS

Attached as **Exhibit #3** is the schematic of the facility. Since the previous inspection the firm has completed its construction of a warehouse. Currently, the firm is (b) (4) (b) (4) the new warehouse; product is not being stored in this location.

A. QUALITY SYSTEM

The Quality System was given full coverage during the current inspection. I reviewed quality complaints, change controls, rejected materials, relevant SOPs, and training records. I reviewed annual product reviews (APRs) for the firm's commercial products. I reviewed the firm's manufacturing investigations and laboratory investigations. Of the items reviewed, one deficiency was noted regarding the failure to perform a failure investigation and the failure to properly extend

failure investigation to other batches that may be affected. Please refer to Observation #1 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

B. FACILITIES AND EQUIPMENT SYSTEM

I reviewed the firm's equipment usage logs, cleaning documentation, equipment maintenance, and facility maintenance records. I noted the following deficiencies: batch records fail to include a visual assessment for vessel cleanliness prior to use, I observed "clean" manufacturing vessels with residue, I observed product storage facilities not maintained in a state of repair, I observed the firm's manufacturing areas not maintained in a state of repair, and I observed a piece of manufacturing equipment not maintained in a state of repair. Please refer to Observations #2, 3, and 4 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

C. PRODUCTION SYSTEM

The Production System was given full coverage during the course of the inspection. The firm uses dedicated and some non-dedicated equipment in the manufacture of commercial product. During the inspection I reviewed: training records, manufacturing investigations, master production records, batch records, equipment usage logs, and cleaning logs. In addition, I reviewed procedures related to employee gowning and cleaning procedures. I noted the following deficiencies: the master manufacturing record for Dapsone USP failed to include specific instructions for performing a (b) (4) step, the firm's gowning procedure listed two separate gowning requirements for Dapsone (b) (4) there is no established procedure for the reuse of gloves used during Dapsone (b) (4), and there is not an established yield specification or a requirement to investigate Dapsone USP lots that exhibit an atypical yield. In addition, I observed an in-process container of PASER granules that was not labeled to identify its contents. Please refer to Observation #5 and 6 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

D. LABORATORY CONTROL SYSTEM

During the walkthrough of the laboratory I noted that equipment in use was within its calibration, and equipment outside of calibration was identified as non-operational. I noted that reagents, standards, and samples preparations were labeled appropriately. I reviewed the electronic controls instituted over the firm's data acquisition system. I reviewed the firm's stability program. I reviewed the firm's release testing of raw materials, in-process materials, and finished products. I noted the following deficiences: the failure to validate a stability indicating test method for Dapsone 25 mg and 100 mg Tablets USP and the failure to perform full testing of Nitrogen, NF without

validating a supplier's Certificate of Analysis. Please refer to Observation #7 and 8 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

MANUFACTURING CODES

The firm continues to assign manufacturing codes as follows:

Type of Material	Description	Example
Raw materials	(b) (4)	1234J
Active Pharmaceutical Ingredients		1234
Finished Products		12345

RECALL PROCEDURES

Since the previous inspection the firm has not initiated a recall. Recalls are governed by SOP, G-0015-011, Recall Policy. During my review of documents, I noted that the firm appears to keep adequate distribution records to facilitate a recall.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

QUALITY SYSTEM

OBSERVATION 1

There is a failure to thoroughly investigate batches that do not meet specification.

A. There was a failure to request a manufacturing investigation from a contract manufacturer after one drum of Lot # (b) (4) of 4-Aminosalicyclic Acid USP, an Active Pharmaceutical Ingredient (API), failed specification for moisture content (spec: (b) (4) ; result: 1.094% KF). There is no investigation to determine: root-cause, if other segments of the lot were impacted, and whether corrective actions were identified to prevent reoccurrence. The remainder of the lot continued processing and was incorporated into Lot #14269 of PASER granules.

Supporting Evidence and Relevance/Discussion with Management:

Investigation 12142011-CM **(Exhibit #4)** was initiated after the percent theoretical yield of Lot (b) (4) of 4-Aminosalicylic Acid was outside of the standard range (result: 82.3% target: (b) (4)). The manufacturing record for Lo (b) (4) is provided as **Exhibit #5**. The investigation notes the low yield is attributable to one drum out of (b) (4) which failed for moisture content (spec: (b) (4) result: 1.094% KF) and that affected drum (b) (4) and it's pair (b) (4) were rejected. The lot is dried at the (b) (4) in multiple sub lots. The firm rejected drum (b) (4) as it was part of the same drying cycle as drum (b) (4) The investigation concludes that all remaining drums were unaffected and were permitted to continue processing. The Certificate of Analysis and release of the material is provided as **Exhibit #6**. The remainder of Lot (b) (4) (Material #3682J) was incorporated into Lot #14269 of PASER granules **(Exhibit #7)**.

I requested the associated Laboratory Investigation into OOS results and the manufacturing investigation from the (b) (4) the contract manufacturer that dried the material. Mr. Raju Shah informed me that an OOS investigation was not documented. I requested the investigation performed by the contract manufacturer. Mr. Pursell stated that an investigation was not requested from the contract manufacturer. I requested the procedures related to performing Laboratory Investigations and Manufacturing Investigations. Mr. Shah and Mr. Pursell provided SOP, QC-0047-02, Laboratory Investigations, and SOP, G-0023-01, Deviations **(Exhibit #8 and #9**, respectively). I noted that the Laboratory Investigation procedure fails to include provisions for performing a manufacturing investigation, regardless of site of manufacturer, after confirming OOS results. I noted that the Deviation procedure fails to include a provision to request a manufacturing investigation from a contract manufacturer following a deviation or a failure of a lot to meet the final yield specification.

During the inspection, I explained that after the firm generated OOS results an OOS investigation should have been initiated. I also explained that the firm should have requested the (b) (4) to perform a manufacturing investigation into the failure. I stated that the firm needed to perform an investigation to identify root-cause, perform an impact assessment to evaluate if other portions of the lot were affected, and identify corrective actions to prevent reoccurrence. Ms. Jacobus stated that the other portions of the lot were generated during a different drying cycle and containers were tested and met specification. I explained to Ms. Jacobus that an investigation needed to be conducted to determine if an equipment malfunction or other deviation occurred at the (b) (4) that could have potentially impacted the entire lot. I also stated that the root cause of the failure could have been determined to be related to the pre-dried material. I stated in the absence of an investigation the firm failed to provide a documented justification and evaluation why the other portions of the lot were not affected. Mr. Shah provided revisions to SOP, QC-0047, Laboratory Investigations, and SOP, G-0023, Deviations, to include provisions to initiate a manufacturing investigation at a contract manufacturer following a batch failure **(Exhibit #10 and #11)**.

During the exit-meeting, I explained that a failure of a batch to meet specification needs to include a laboratory investigation into OOS results and upon confirming OOS results a manufacturing investigation should be initiated regardless of the originating site. I stated that the firm's investigation into out-of-range yield failed to determine root-cause, failed to identify corrective actions, and failed to demonstrate why other portions of the lot were not affected. The firm's officials acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response to the District.

B. There is a failure to properly evaluate other batches of a drug product that may be adversely impacted following the failure of a batch to meet specification. An investigation into the failure of Lot #14028 of uncoated PASER granules for dried, sifted in-process (b) (4) test (i.e. particle size of the granules) determined variability in (b) (4) Lot (b) (4) as the root cause. Lot #14032 and #14045 of uncoated PASER granules were aborted at the extrusion step due to atypically large granules. Lot #14029 of uncoated PASER granules containing (b) (4) Lot (b) (4) was permitted to finish processing. The investigation failed to include an impact of assessment for evaluating if other batches of uncoated PASER granules utilizing (b) (4) Lot (b) (4) were impacted.

Supporting Evidence and Relevance/Discussion with Management:

Investigation MF122111 (**Exhibit #12**) was initiated after uncoated PASER granules Lot #14028 failed the dried, sifted in-process (b) (4) test (i.e. particle size of the granules) with reported results of 26.9% **(Exhibit #14, page 7)** retained on the (b) (4) screen (spec: (b) (4) %). The in-process specification sheet is provided as **Exhibit #13**. The investigation notes that Lot #14028 (**Exhibit #14**) of dried, uncoated PASER granules was compromised of wet mass Lot #14024 (**Exhibit #15**) and a portion of Lot #14025 (**Exhibit #16**). The investigation notes that the remainder of wet mass Lot #14025 was incorporated into Lot #14029 (**Exhibit #17**) dried, uncoated PASER granules which passed specification. Lot #14029 was allowed to continue to process without further evaluation. I noted that Lot #14029 was ultimately incorporated into finished product Lot #14070 of PASER granules, which was ultimately released to the market (**Exhibit #18**). The investigation notes that the following lots of granules were aborted during extrusion due to atypical granules: 14032 and 14045. The investigation concludes that the root-cause of the failure of Lot #14028 was related to unknown variability in (b) (4) Lot (b) (4) The remaining portion of (b) (4) Lot (b) (4) was rejected, as it was determined to be the root-cause of batch failure.

I requested the raw material inventory card for (b) (4) Lo (b) (4) (**Exhibit #19**). I noted that the following PASER wet mass lots were manufactured using this material: 14021, 14024, 14025, 14032, 14033, 14036, 14037, 14038, 14045, 14046, 14047, and 14048. I noted that the following lots of PASER wet mass were manufactured using this material but were not mentioned in

Investigation MF1221111: 14036, 14037, and 14038. I asked Mr. Shah if the firm placed released finished product PASER lots containing (b) (4) Lot (b) (4) on stability, to evaluate if the product would meet specification throughout shelf life. Mr. Shah stated no batches were placed on stability. I asked Mr. Shah if additional sampling was performed to provide additional support that all other batches of uncoated PASER granules using (b) (4) Lot (b) (4) were not affected; Mr. Shah stated no.

I stated to Mr. Shah that the firm's investigation fails to extend to all batches of uncoated PASER granules that contain (b) (4) Lot (b) (4) I stated that the firm did not adequately evaluate uncoated PASER granules Lot #14029, which contained a portion of Lot #14025 of PASER wet mass. I stated that the remainder of Lot #14025 of PASER was incorporated into Lot #14028 of uncoated PASER granules, which failed to meet specification and was rejected. I stated that the firm's investigation fails to include a documented evaluation and justification, supported by data, that all other lots of PASER granules containing (b) (4) Lot (b) (4) were not adversely impacted. I stated that the firm elected not to place a lot of finished product on stability to evaluate whether or not potentially affected lots of PASER granules would meet specification throughout shelf life. Ms. Jacobus stated that all released lots of PASER granules met specification. I stated that the justification to release batches based on meeting a specification, by performing limited sampling, is not adequate. I stated that further evaluation is necessary to ensure that other batches manufactured with a common raw material, determined to be the root-cause in a batch failure, are not adversely impacted. Mr. Shah provided me with a stability protocol to place one lot of finished PASER granules on stability that contains (b) (4) Lot (b) (4) (**Exhibit #20**). Provided as **Exhibit #21** is the batch issuance log for traceability to all finished dosage lots.

The table below summarizes batches manufactured with (b) (4) Lot (b) (4)

(b) (4) Lot #	Uncoated Lot #	Dried Lot #	Status	Comment
(b) (4)	14021	14021, 14042	Passed	Not further evaluated
	14024 **Exh.15**	14028 **Exh.14**	Failed to meet specification	Lot #14028 Rejected
	14025* Exh.16			
(b) (4)	**14025* Exh.16**	14029 **Exh.17**	Passed	Not further evaluated
	14026			
(b) (4)	14032	N/A	Aborted at extrusion, rejected	Lot #14032 Rejected
	14033	14035	Passed	Not further evaluated
	14036	14039	Passed	Not mentioned in investigation; Not further evaluated
	14037			
	14038	14040		
	14045	N/A	Abort at extrusion, rejected	Lot #14045 Rejected

(b) (4) Lot #	Uncoated Lot #	Dried Lot #	Status	Comment
	14046	14049	Passed	Not further evaluated
	14047			
	14048	14050		

During the exit-meeting, I stated that Investigation MF1221111 failed to properly extend to other batches of a drug product that may be adversely impacted following the failure of a batch to meet specification. I stated that the firm did not provide a documented evaluation of all batches of uncoated PASER granules manufactured using (b) (4) Lot (b) (4) I stated that Lot #14029 contained a portion of Lot #14025. I stated that Lot #14028 failed to meet specification and contained the remainder of Lot #14025. I stated that the firm provided no justification to support that all other batches manufactured with a common raw material, determined to be the root-cause in batch failure, were not adversely impacted. I stated that part of the firm's investigation should have included a stability commitment to demonstrate that finished PASER granules containing (b) (4) Lot (b) (4) would meet specification throughout shelf-life. The firm's officials acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response to the District.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 2

Procedures for cleaning equipment used during the manufacturer of active pharmaceutical ingredients are not followed.

Specifically, there is not a requirement for the visual assessment of cleanliness of all equipment used in the manufacturer of 4-Aminosalicyclic Acid USP. Procedure, G-0018-01, Equipment Cleaning in General, dated 1/7/2004 requires all equipment to be visually inspected for cleanliness prior to use and requires the inspection to be documented in the batch record. The following was observed:

A. On 4/3/2012, I observed excessive white residue in (b) (4) JPC (b) (4) used in the manufacturer of 4-Aminosalicyclic Acid USP. The manufacturing record for Lot #1481 of 4-Aminosalicyclic Acid USP indicated that the vessel was rinsed (cleaned) with purified water on 3/29/2012. A visual assessment of cleanliness prior to use is not documented in the batch record.

B. On 4/3/2012, I observed what appeared to be a brown residue in (b) (4) JPC (b) (4) used in the manufacturer of 4-Aminosalicyclic Acid USP. The manufacturing record for Lot #1481 of 4-Aminosalicyclic Acid USP indicated that the vessel was rinsed (cleaned) with purified water on 3/29/2012. I noted that an adequate visual assessment of cleanliness of

the vessel is not possible for this piece of equipment as the viewing window appeared to be scratched making the inside of the vessel difficult to clearly observe. A visual assessment of cleanliness prior to use is not documented in the batch record.

Supporting Evidence and Relevance/Discussion with Management

During a walkthrough of the facility on 4/3/2012, I observed excessive white residue in (b) (4) JPC # (b) (4) used in the manufacturer of 4-Aminosalicyclic Acid USP. I took pictures of the inside of the vessel; the photos are provided as **Exhibit #22-24**. In addition, I observed what appeared to be a brown residue in (b) (4) JPC # (b) (4) used in the manufacturer of 4-Aminosalicyclic Acid USP. I noted that an adequate visual assessment of cleanliness of the vessel is not possible for this piece of equipment as the viewing window appeared to be scratched, making the inside of the vessel difficult to clearly observe. I asked Mr. Pursell if the vessel could be opened; Mr. Pursell stated that the firm does not open the vessel and it would violate their policy, as the vessel would open in an uncontrolled environment. Mr. Pursell indicated that the vessel is only opened during maintenance. I noted that both vessels are dedicated for this product.

I asked Mr. Pursell what the statuses of the vessels were. Mr. Pursell provided me with the manufacturing record for Lot #1481 (**Exhibit #25**). Mr. Pursell indicated that both vessels were cleaned. Mr. Pursell stated that Step 28 of the record documents that the (b) (4) was rinsed (cleaned) with purified water; Mr. Pursell informed me that this is the only documentation of cleaning for that particular vessel. Mr. Pursell stated that Section M of the record indicated that the (b) (4) was cleaned.

I requested the procedure that requires a visual assessment of cleaning of the vessel prior to use. Mr. Pursell provided me with SOP, G-0018-01, Equipment Cleaning in General, dated 1/7/2004 (**Exhibit #26**). I noted that Section 3.8 of the procedure requires a visual inspection of cleanliness prior to use and requires the inspection be annotated in the record. During my review of Lot #1481, I noted that the record does not have a step or a requirement for the visual inspection of cleanliness prior to use. I requested Mr. Pursell to provide me documentation that equipment used for all other products are visually assessed for cleanliness prior to usage. Mr. Pursell demonstrated that all other product manufacturing records have a requirement for visually assessing cleanliness prior to usage. The equipment usage log for the (b) (4) and the (b) (4) are provided as **Exhibit #27 and #28**, respectively. The table below summarizes the documents collected and observations made:

Lot #	Tank	Photos	Observation	Documentation	Cleaning Procedure	Usage Log
1481	(b) (4) JPC (b) (4)	**Exh.22-24**	Excessive white residue	Step 28 for rinse step; no visual assessment required **(Exh.25, p.29)**	SOP, G-0018-01, Section 3.8 **(Exh.26 , p.2)**	**Exh.27**
	(b) (4) JPC (b) (4)	N/A	Brown residue; viewing glass severely scratched rendering the inside of the vessel difficult to observe	Section M documents cleaning; no visual assessment required **(Exh.25, p.38)**		**Exh.28**

During the inspection, I stated that when I looked inside (b) (4) JPC (b) (4) noted excessive white residue in the vessel and that the vessel did not appear to be clean. In addition, when I looked inside the (b) (4) I observed what appeared to be a brown residue, and I noted that the viewing glass, constructed of plastic, was severely scratched to prevent adequate observation inside the vessel. I stated that the batch record for Lot #1481 indicated that the vessels were clean. I noted that Section M in the record, Equipment Clean-Up, lists all other equipment used during manufacturing except for the (b) (4) Mr. Pursell agreed and stated that the firm needs to update the record for clarity but commented that Step 28 is the step related to cleaning the vessel. Mr. Pursell also stated that the firm has recently installed a (b) (4) in the vessel in order to ensure adequate cleaning of the (b) (4) Mr. Pursell indicated that the firm will perform a cleaning re-validation study prior to executing any additional batches. Mr. Pursell also indicated that the firm will need to address the viewing glass for the (b) (4) Ms. Jacobus stated that the firm is evaluating an option to (b) (4) that would allow observation inside the vessel.

During the exit-meeting, I stated that vessels need to be visually assessed for cleanliness prior to use and during the inspection I observed a vessel that was not clean although the documentation stated the vessel was rinsed with purified water (cleaned). I stated that there is no documentation of visually assessing equipment used in the manufacture of 4-Aminosalicyclic Acid USP. I stated that their general cleaning procedure requires a visual assessment of cleanliness and requires documentation of the assessment in the batch record. The firm's officials acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response in writing to the District.

OBSERVATION 3

Facilities used in the manufacture and storage of components, active pharmaceutical ingredients, and in-process materials are inadequate.

A. There is no temperature mapping study for the cold-storage room in the auxiliary facility, located on the premises but separate from the main facility. The walls are lined with an insulating material that does not appear to facilitate cleaning. There is inadequate space to facilitate cleaning and inspection of containers and to prevent mix-ups. This warehouse is used to store uncoated PASER granules and 4-Aminosalicyclic Acid USP.

Supporting Evidence and Relevance/Discussion with Management:

During a walkthrough of the facility, I noted that the cold-storage room in the auxiliary facility, located on the premises but separate from the main facility, appeared to be constructed of material that does not appear to facilitate cleaning. The material appeared to be (b) (4) covering. In addition, I noted that there did not appear to be adequate space in the room to facilitate cleaning and inspection of containers and to prevent mix-ups. I noted that Section 1.1 and Section 3.1.1 of the firm's SOP, QA-0005-01, Building and Facilities, requires facilities used in the holding of a drug product to be of suitable size and construction to facilitate cleaning and requires adequate space to prevent mix-ups (**Exhibit #29, Page 1 and 2**, respectively). I took photos of the room; photos are provided as **Exhibit #30-34**. Mr. Pursell stated that the facility is used to store uncoated PASER granules and 4-Aminosalicyclic Acid USP. I noted that the following products have cold-chain temperature requirements (**Exhibit #35**).

I requested the qualification of the facility and a temperature mapping study. Mr. Pursell stated that there was not a temperature mapping study performed or a qualification of the facility. Mr. Pursell provided me a temperature mapping study that was performed over the course of two days during the current inspection **(Exhibit #36)**. Mr. Pursell stated that the building is monitored for temperature and humidity, and that the probe is located at the worst-case condition (near the door). The document Mr. Pursell provided stated that there have been minimal excursions in the facility, all of which based on a matrix study were determined to have no impact to quality. I stated that an initial temperature mapping study needs to be performed prior to storing product in the facility and a long term performance qualification should extend over a period of time and include an evaluation of seasonal variation. Mr. Pursell stated he understood my concern.

During the exit-meeting, I stated that buildings used to store active pharmaceuticals and drug products need to be constructed of materials that facilitate cleaning, and need to provide adequate space for the cleaning and inspection of containers and to prevent mix-ups. I stated that I observed a

facility that was constructed out of material that appears to be difficult to clean and appears porous. I stated that there appears to be inadequate space in the facility (**Exhibit #30-34**). In addition, I stated that an initial temperature mapping study needs to be performed prior to storing product in the facility and a long term performance qualification should extend over a period of time and include an evaluation of seasonal variation. Mr. Pursell provided a document which stated this facility would not be used any longer (**Exhibit #37**). Mr. Pursell escorted me to the facility and I verified that product was no longer being stored in this facility. Dr. Jacobus committed to sending a written response in writing to the District.

B. The ambient storage room in the auxiliary facility, located on the premises but separate from the main facility, is not maintained in a state of repair. There is a small hole (approximately 1 inch) in the posterior door; there is also a space between the floor and the bottom of the main door. I observed foliage in the warehouse. This warehouse is used to store technical grade Dapsone and Aminosalicylate Sodium BP.

—

Supporting Evidence and Relevance/Discussion with Management:

During a walkthrough of the ambient storage room in the auxiliary facility, located on the premises but separate from the main facility, I noted that the storage room did not appear to be adequately maintained. I observed the following deficiencies: a small hole in the posterior door, a space between the floor and the bottom of the main door, and foliage in the warehouse. I took photos of the conditions of the warehouse (**Exhibit #38-43**). I noted that the facility itself is located on a nature preserve.

Mr. Pursell stated that this facility is used to store technical grade Dapsone and Aminosalicylate Sodium BP, both starting materials in the manufacturing of the active pharmaceutical ingredients Dapsone USP and 4-Aminosalicyclic Acid USP, respectively. I noted that Section 3.1.8.1.2 of SOP, QA-0005-01, Building and Facilities, requires any building used in the holding of a drug product to be free of trash and organic waste (**Exhibit #29, Page 2**). I noted that Section 3.1.9.1 of SOP, QA-0005-01 requires any building used in holding a drug product shall be maintained in good repair (**Exhibit #29, Page 2**).

During the inspection and at the exit-meeting, I discussed with the firm's officials that I observed a hole in the posterior door of the facility, I observed a space between the floor and the bottom of the main door, and I observed foliage in the warehouse. I added that the firm was storing raw materials next to unused equipment and that the facility did not appear to be clean. Mr. Pursell provided a document which stated this facility would not be used any longer (**Exhibit #37**). Mr. Pursell escorted me to the facility and I verified that product was no longer being stored in this facility. Dr. Jacobus committed to sending a written response in writing to the District.

C. Manufacturing Room #(b)(4) is currently under construction. I observed an exposed wall, an HVAC line with duct tape, cardboard covering a vent in the room, and vents with a dust-like appearance. This room is used to store in-process, uncoated PASER granules.

Supporting Evidence and Relevance/Discussion with Management:

During a walkthrough of the facility, I noted that the firm was storing in-process PASER granules Lot #14566, 14567, and 14568 in Manufacturing Room #(b)(4) Manufacturing Room #(b)(4) is currently under construction. I observed the following deficiencies in this room:

Observation	Photo Exhibit
An exposed wall	**Exh.44-47**
An HVAC line with duct tape	**Exh.48**
Cardboard covering a vent in the room	**Exh.49**
Vents with a dust-like appearance	**Exh.50**
In-process PASER being stored	**Exh.51**

I noted that Section 3.1.9.1 of SOP, QA-0005-01, Building and Facilities, requires buildings used in the holding of a drug shall be maintained in good repair (**Exhibit #29, Page 2**).

During the inspection and at the exit meeting, I explained to the firm's officials that I observed in-process PASER granules being stored in a room that is currently under construction. I stated that I observed an exposed wall, an HVAC line with duct tape, cardboard covering a vent in the room and vents with a dust-like appearance. I stated that the firm should not store products in a room that is under construction and not maintained in a state of repair. Ms. Jacobus agreed and stated that during the walkthrough an employee mistakenly placed the product into that room. She stated that prior to my arrival the product was stored in the hallway, which is monitored for temperature and humidity. Ms. Jacobus indicated that her employee should not have moved the containers into Manufacturing Room #(b)(4) Dr. Jacobus committed to sending a written response in writing to the District.

D. The walls in the drying suite, used in the manufacturer of uncoated PASER granules, is not in a suitable state of repair. I observed several, small gouges (approximately 1 inch long) in the wall located within the suite.

Supporting Evidence and Relevance/Discussion with Management:

During a walkthrough of the facility, I noted that the drying suite, used in the manufacturer of uncoated PASER granules did not appear to be adequately maintained. I noted that the one wall appeared to have several, small gouges (approximately 1 inch long). I took photos of the wall; the photos are provided as **Exhibit #52**. I noted that due to the condition of the wall, the wall appeared to be difficult to clean. I asked Mr. Pursell why there were gouges in the wall and why it wasn't addressed. Mr. Pursell stated that at times equipment knocks into the wall, causing the gouges I observed. Mr. Pursell stated that he was aware of the issue and planned to apply an epoxy liner to the wall to prevent reoccurrence. I noted that Section 3.1.9.1 requires all buildings used in the manufacture of a drug product be maintained in good repair (**Exhibit #29, Page 2**). Provided as **Exhibit #91**, is the batch record for PASER Granules Lot #14441, demonstrating the recent use of the (b) (4) dryer located within this suite.

During the exit-meeting, I discussed with the firm's officials that the wall in the drying suite did not appear to be in a good state of repair. The firm's officials agreed and stated that the wall has been repaired. Mr. Pursell provided me a document requesting the wall in the drying suite to be fixed during the scheduled shut-down on 3/30/12 (**Exhibit #53**). Mr. Pursell escorted me to the drying suite and I verified that the firm has placed an epoxy liner on the wall. I informed Ms. Jacobus that when I looked at the firm's corrective action I noted that the liner was screwed into the wall and the end of the screws are still exposed. I stated that the wall does not appear to facilitate cleaning. Ms. Jacobus agreed and stated that she observed the same thing. Ms. Jacobus commented that the firm's engineering department is evaluating how to remediate the wall. Dr. Jacobus committed to sending a written response in writing to the District.

E. The manufacturing area for Dapsone USP is not maintained in a state of repair. The ceiling in the area used in Dapsone (b) (4) has a hole (approximately 2 inches) in the plastic covering. The entrance to the suite is lined with a plastic sheet. In addition, I observed unidentified black residue on the floor adjacent to manufacturing vessels.

Supporting Evidence and Relevance/Discussion with Management:

During the walkthrough of the facility, I noted that the manufacturing area for Dapsone USP does not appear to be maintained in a state of repair. I observed the following:

Observation	Photo Exhibit
A 2 inch hole in the ceiling in the area used in Dapsone (b) (4)	**Exh.54-55**
The entrance to the suite is lined with a plastic sheet	**Exh.56-57**
I observed unidentified black residue on the floor adjacent to manufacturing vessel	**Exh.58-59**

I noted at the time of my observations, 4/4/2012 the firm was in the process of manufacturing Dapsone USP Lot #1476.

Mr. Pursell stated that the hole in the ceiling was related to the removal of a support structure for the (b) (4) vessel in the room. Mr. Pursell stated that when the support structure was removed, the plastic ceiling was neither repaired or replaced. Mr. Pursell stated that he agreed that the ceiling needed to be addressed.

After my observation related to the unidentified black residue on the manufacturing floor, the firm performed an investigation (**Exhibit #60**). The firm's investigation revealed that the black residue was not mold and that the bio-burden was relatively low. The firm sent the material out to a contract laboratory for identification. Based on preliminary results the firm concluded the residue was (b) (4) used during the manufacture of Dapsone USP. Ms. Jacobus stated that the likely explanation is that an operator split (b) (4) used in the manufacture of Dapsone USP, and never cleaned the spill. I noted that Section 3.1.8.1 of SOP, QA-0005-01 required any building used during manufacturing be maintained in a clean and sanitary condition (**Exhibit #29, Page 2**).

During the exit-meeting, I stated that the Dapsone manufacturing area is not adequately maintained. I stated that I observed a hole in the plastic ceiling used during Dapsone (b) (4) (b) (4) a manual operation. I stated that I observed the entrance to the suite is covered with a plastic lining, which does not appear to facilitate cleaning. I stated that I observed black residue on the floor adjacent to a manufacturing vessel while the firm was manufacturing a batch. I stated that only after I brought this to the firm's attention did the firm determine that the residue was not mold. I stated that the firm needs to make an evaluation of the maintenance and cleanliness of a manufacturing suite prior to commercially manufacturing batches of product. The firm's officials acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response in writing to the District.

OBSERVATION 4

Equipment used in the manufacture of drug products are not maintained in a state of repair.

Specifically, (b) (4) used during milling of Dapsone USP in not maintained in a state of repair. I observed chipped paint on this piece of equipment. This piece of equipment was used during milling of Dapsone USP Lot #1470, Part I and II on 3/20/2012.

Supporting Evidence and Relevance/Discussion with Management:

During the walkthrough of the facility, I observed chipped paint on (b) (4). I took photos of the condition of the (b) (4) photos are provided as **Exhibit #61-62**. I requested the usage log for this piece of equipment (**Exhibit #63**). I noted that the last time this piece of equipment was used was on 3/20/2012 during the milling of Dapsone USP Lot #1470, Part I and II. I noted that the vessel was clean and appeared to be ready for future use. I stated to Mr. Pursell that the (b) (4) did not appear to be adequately maintained. I stated that the surface of the piece of equipment appears to be difficult to clean, as the finish is not properly maintained. I stated that while the risk of product contamination is remote, it doesn't negate a requirement to properly maintain pieces of equipment used in the manufacture of active pharmaceutical ingredients. Mr. Pursell agreed and stated that the (b) (4) needed to be sent out for powder coating.

During the exit-meeting, I stated that equipment needs to be maintained in a state of repair. I stated that I observed chipped paint on (b) (4) used during Dapsone milling. I stated that the records indicate the piece of equipment is ready for use. Ms. Jacobus stated that the (b) (4) is being sent out for powder coating. Dr. Jacobus committed to sending a written response in writing to the District.

PRODUCTION SYSTEM

OBSERVATION 5

There is a lack of specific manufacturing instructions and control procedures.

A. The manufacturing process for the Active Pharmaceutical Ingredient (API) Dapsone USP includes a (b) (4) Dapsone (b) (4) step, for the removal of (b) (4) which requires operators to (b) (4) mix the material to assure adequate (b) (4) Step 53 in the master manufacturing record instructs operators to (b) (4) (b) (4) The following deficiencies were noted:

1. Dapsone USP is not routinely evaluated for residual (b) (4) to verify that the (b) (4) step reduces (b) (4) to an acceptable level.

2. The master manufacturing record fails to include adequate instructions for performing this (b) (4) operation to ensure consistency. Step 53 in the master manufacturing record instructs operators to (b) (4) (b) (4) however, instructions do not

detail how this (b) (4) operation is performed by operators or when the (b) (4) is determined to be adequately (b) (4)

3. Procedure G-0004.003, Personal Hygiene and Proper Dress, dated 3/3/2011, requires (b) (4) (b) (4) gowning requirements for this step. It is not clear what are the correct gowning requirements for this step.

4. There is not an established procedure requiring operators to sanitize their gloved hands before (b) (4) mixing Dapsone (b) (4) In addition, gloves are reused and there is no procedure to detail: the cleaning of gloves, the requirements for when gloves can be reused or how used gloves are stored prior to additional use.

Supporting Evidence and Relevance/Discussion with Management:

During my review of the manufacturing process for Dapsone USP, I noted that the manufacturing process includes a (b) (4) Dapsone (b) (4) step, for the removal of (b) (4) which requires operators to (b) (4) mix the material to assure adequate (b) (4) Mr. Pursell stated that this process is detailed in Step 53 in the master manufacturing record (**Exhibit #64, Page 32-33**). I noted that Step 53 instructs operators to (b) (4) (b) (4) and to (b) (4) (b) (4) I noted that this product is manufactured in Part I and Part II; the (b) (4) step for Part II is Step 69 **(Exhibit #64, Page 39)**.

I asked Mr. Schiehser to explain this step in detail to me. Mr. Schiehser informed me that operators (b) (4) (b) (4) the operators (b) (4) Mr. Schiehser stated that the (b) (4) (b) (4) I asked Mr. Schiehser if there was a procedure or any other document that detailed the process. Mr. Schiehser stated Step 53 is the only place this step is described. I noted that Step 53 does not include specific instructions for performing this (b) (4) step and fails to include an end-point determination for when the (b) (4) (b) (4)

I asked Mr. Schiehser to explain why this particular step is necessary; Mr. Schiehser stated that this step is used to ensure the removal of residual (b) (4) from the Dapsone (b) (4) I asked Mr. Schiehser if Dapsone USP is evaluated for residual (b) (4) as part routine release testing. Mr. Schiehser informed me that the firm has evaluated certain batches to demonstrate effectiveness of the (b) (4) step to remove residual (b) (4) however, not every batch is tested. The specification sheet for Dapsone USP is provided as **Exhibit #65**. Mr. Schiehser provided me with the protocol for verifying the effectiveness of Dapsone (b) (4) **(Exhibit #66)**. I stated that the process for Dapsone USP includes a (b) (4) (b) (4) step and as with all (b) (4) operations it is dependent on the operators. I stated that every batch of Dapsone USP should be evaluated for

residual (b) (4) Mr. Schiehser stated he understood the concern. During the inspection, Mr. Shah provided me a revised specification to include evaluating residual (b) (4) as part of Dapsone USP batch release criteria (**Exhibit #67**).

I asked Mr. Pursell is there was a procedure that outlines the gowning requirements for Dapsone (b) (4) Mr. Pursell provided me with Procedure G-0004.003, Personal Hygiene and Proper Dress, dated 3/3/2011 (**Exhibit #68**). During my review of the procedure, I noted that Level 3 gowning on Page 4 of the procedure and Level 4 gowning of Page 5 both indicated that level of gowning for precipitating Dapsone. Level 3 gowning includes: a hair cover, Tyvek suit (includes hoods and booties), goggles, and gloves. Level 4 gowning includes: hair cover, disposable lab coat, goggles, botties, gloves, and dust mask. I brought this to the firm's attention; Mr. Pursell stated that there must have been a typo and clarified that Level 3 gowning is required for this step. I stated that the procedure needs to be modified to make it clear what the gowning requirements for this step are.

I asked Mr. Pursell what type of gloves are used during this step. Mr. Rich showed me the gloves that are used for this step. They are chemical resistant (b) (4) gloves that extend about six inches up a person's forearm. Mr. Pursell stated that operators are to first put on a pair of (b) (4) gloves, and then put on the (b) (4) gloves. Mr. Pursell stated that operators are required to sanitized their hands prior to performing the operations. Mr. Pursell indicated that gloves can be reused during Part I and Part II of the process. During my review of Dapsone USP Lot #1408, I noted that Part I occurred on 6/27/2011 and Part II occurred on 7/11/2011 (**Exhibit #69, Page 37 and 43, respectively**). I asked Mr. Pursell if this information was captured in a procedure; Mr. Pursell indicated no. I stated that there needs to be a procedure to require operators to sanitize their hands prior to performing this step. In addition, I stated that a procedure was needed to define cleaning the gloves, define requirements for when gloves can be reused, and storage requirements prior to additional use. I suggested that the firm should evaluate the bio-burden of the gloves and the effectiveness of the sanitizing agent to ensure that the gloves were not introducing a contaminant into the product. Mr. Pursell stated he understood the concern.

The table below provides examples of Dapsone USP manufactured and the Dapsone Tablet batches manufactured using the associated Dapsone USP lot:

Dapsone USP Lot #	**Exhibit #**	**Residual (b) (4) Evaluated**	**Raw Material Inventory Card/Release**
1408	**Exh.69**	No	**Exh.71**
1419	**Exh.70**	No	**Exh.72**

I requested an example of a batch record and release documentation for a finished product manufactured using Dapsone USP Lot #1408. Provided as **Exhibit #73** is the batch record and release for Lot #14017 of Dapsone 25 mg Tablets USP.

During the exit-meeting, I stated that there are not specific instructions for performing th (b) (4) Dapsone (b) (4) and that the firm is not routinely testing Dapsone USP at release for residual (b) (4) In addition, I stated that the firm's personnel gowning procedure requires (b) (4) different gowning requirements for Dapsone (b) (4) I stated there are no established procedures to require operators to sanitize their gloves prior to performing the operation and there are no procedures describing the cleaning, storage, and conditions for reuse of gloves used in this operation. The firm's officials acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response in writing to the District.

B. There is a failure to establish a final yield specification for Dapsone USP. A percent theoretical yield is calculated at the end of the manufacture of Dapsone USP; however, there is no specification for the final yield or provisions to require an investigation if the yield is atypical.

Supporting Evidence and Relevance/Discussion with Management:

During my review of the master manufacturing record for Dapsone USP, I noted that there is not an established yield specification. I noted that the firm is performing a percent theoretical yield calculation, but a specification or provision to require an investigation into batches exhibiting an atypical yield is not in the batch record. During my review of Lot (b) (4) I noted that the yield was 75.8% **(Exhibit #69).** I noted the yield for Lot (b) (4) was lower than the rest of the records I reviewed. I asked Mr. Schiehser if 75.8% was a typical yield for this product. Mr. Schiehser stated that while the firm was preparing their annual report they noted that the yield for this batch was (b) (4) than expected. Mr. Schiehser provided Investigation 04052012-CM, dated 4/5/2012 (**Exhibit #74**). I stated to Mr. Schiehser that this investigation should have been performed prior to releasing the batch, and he agreed. I stated that the firm needs to establish a yield specification to identify atypical batches prior to release. I stated that the firm needs to include a provision to require an investigation into batches exhibiting an atypical yield to determine if there is any impact to the quality attributes of the product.

During the exit-meeting, I stated that the firm needs to establish a final yield specification for Dapsone USP and include a provision to require an investigation into batches exhibiting an atypical yield. Ms. Jacobus stated she acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response in writing to the District.

OBSERVATION 6

Containers used during the production of drug products are not identified at all times.

Specifically, during a walkthrough of the facility on 3/28/2012, I observed an orange container of in-process PASER without a label identifying the material. Lot #14563 (blend, in-process of being extruded) and #14569 (blend) of in-process PASER were being processed in Manufacturing Room (b) (4) during this time.

Supporting Evidence and Relevance/Discussion with Management:

During a walkthrough of the facility on 3/28/2012, I observed an orange container of in-process PASER without a label identifying the material in Manufacturing Room # (b) (4) The container was in a blend stage and an operator was in the process of extruding the material. I also observed another batch of product that just finished blending, also in an orange container. I asked Mr. Pursell which batches were in the room; Mr. Pursell indicated that Lot #14563 and #14569 were in Manufacturing Room # (b) (4) The table below details the batches being processed in Manufacturing Room # (b) (during the walkthrough of the facility.

Lot#	Product	Stage	Container Color	Exhibit
14563	PASER	Blend, in-process of being extruded	Orange	**Exh.75**
14569	PASER	Blend	Orange	**Exh.76**

During the inspection, I stated that during a walkthrough of the facility I observed an unlabeled container in a manufacturing suite where there were multiple batches of the same product in the room. I stated that containers need to be labeled at all times in order to prevent a mix-up from happening. Ms. Jacobus stated that as a result of the firm's previous inspection, the firm purchased different color containers in order to prevent a mix-up from happening. Ms. Jacobus explained that an orange container would correspond to the (b) (4) batch of PASER manufactured on a particular day. I stated to Ms. Jacobus that during the walkthrough I observed two different batches, both in orange containers, one of which did not have an identifying label. Mr. Pursell explained that both batches were in orange containers because Lot #14563 was the (b) (4) batch blended on the previous day, and Lot #14569 was the (b) (4) batch blended on 3/28/12. Ms. Jacobus stated she understood the concern.

During the exit-meeting, I discussed with Ms. Jacobus that containers need to be identified at all times in order to prevent a mix-up from occurring. Ms. Jacobus stated she acknowledged the concern and agreed. Dr. Jacobus committed to sending a written response in writing to the District.

LABORATORY CONTROL SYSTEM

OBSERVATION 7

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

Specifically, the stability program for Dapsone 25 mg and 100 mg tablets does not include a stability-indicating method to monitor potential impurities. Test method, (b) (4) Determination of Related Compounds in Dapsone Tablets: 25 mg and 100 mg, has been developed to evaluate impurities; the method is in draft and has not been validated for its intended use.

This is a repeat observation from the FDA-483 issued on 2/24/11.

Supporting Evidence and Relevance/Discussion with Management:

The previous FDA-483, dated 2/24/11, cited the firm for the lack of a stability-indicating method to monitor impurities on stability for Dapsone 25 mg and 100 mg tablets. During my review of corrective actions to the previous FDA-483, I asked Mr. Shah if a stability-indicating impurity method had been developed and validated to monitor Dapsone 25 mg and 100 mg tablets on stability. Mr. Shah presented the development data for method, (b) (4) Determination of Related Compounds in Dapsone Tablets: 25 mg and 100 mg. The draft test method is provided as **Exhibit #77**. Mr. Shah indicated that the method has not been validated for its intended use. I stated that the method needs to be validated for its intended use. In addition, I stated that upon successful completion of the method validation, the stability protocols needs to be amended to include a method that has been demonstrated to be suitable during a validation study. Mr. Shah stated that he understood the concern and expected the validation to be completed within the next month. Mr. Shah provided me with reported results for products tested using the draft method during the research evaluation phase (**Exhibit #78**).

I requested the stability protocol for Dapsone 25 mg and 100 mg tablets (**Exhibit #79**). I requested reported results for stability stations since the previous inspection (**Exhibit #80**). For Lot#13520, Dapsone 100 mg Tablets, I requested the six month stability station reported results, the notebook pages for assay and the associated assay method (**Exhibit #81, #82, and #83**, respectively). I noted

that currently the stability protocol includes an evaluation of impurities utilizing a (b) (4) method. I collected the notebook pages for impurities and the associated (b) (4) impurity method for the aforementioned stability station (**Exhibit #84 and #85**). Provided as **Exhibit #21** is the batch issuance log, documenting each batch of Dapsone Tablets executed.

During the inspection and at the exit-meeting, I stated to Ms. Jacobus that the firm needs to have a validated, stability-indicating test method for evaluating potential impurities in Dapsone 25 mg and 100 mg Tablets during stability. Dr. David P. Jacobus committed to sending a written response to the District.

OBSERVATION 8

Test results from component suppliers are accepted without testing each component according to the established specification without evaluating the reliability of the supplier's analyses.

Specifically, full testing for (b) (4) is not performed; an identity test is performed with all other testing accepted from the supplier's Certificate of Analysis (COA). There is no procedure for performing reduced testing to require an initial assessment of the reliability of the supplier's COA, and verification of the supplier's COA at appropriate intervals. (b) (4) (b) (4) is used during the commercial manufacture of Dapsone USP, 4-Aminosalicyclic Acid USP and uncoated PASER granules.

Supporting Evidence and Relevance/ Discussion with Management:

During my review of release documentation for (b) (4), I noted that the firm is not performing full testing. The firm performs identification and odor tests upon receipt and accepts assay, limit of oxygen, and carbon monoxide from the supplier's Certificate of Analysis. Mr. Shah stated the firm has not performed full testing for any lot of (b) (4) received. I requested a procedure related to performing reduced testing of raw materials; Mr. Shah indicated that there is no procedure. I stated that when the firm elects to perform reduced testing of a material an evaluation to determine the reliability of the supplier's Certificate of Analysis is necessary prior to accepting test results. I also explained that once a supplier's Certificate of Analysis has been evaluated for reliability, the firm needs to reevaluate the Certificate of Analysis at appropriate intervals. Mr. Shah stated that he understood the concern.

Mr. Pursell stated that (b) (4) is used during the manufacture of Dapsone USP, 4-Aminosalicyclic Acid USP, and PASER Uncoated Granules. The table below provides three examples of (b) (4) usage in each of the aforementioned products.

(b) (4) Lot # (b) (4)	Exhibit #	Product	Lot#	Exhibit #
	Exh.86	Dapsone USP, API	1385	**Exh.89**
	Exh.87	4-Aminosalicyclic Acid USP, API	1453	**Exh.90**
	Exh.88	PASER Uncoated Granules	14441	**Exh.91**

During the inspection, Mr. Shah provided me a newly generated procedure, OC-0079-01, Reduced Testing of Raw Materials, that will require full testing of (b) (4) of (b) (4) (b) (4) **(Exhibit #92)**. The new procedure also requires that a supplier is approved and meets the vendor requirements in SOP, G-0031-03, Vendor (Supplier) Certification **(Exhibit #93)**, which requires full testing of (b) (4) lots as criteria for approving a supplier. Mr. Shah also comments that the quality unit is in the process of finding a control laboratory to perform full testing for (b) (4)

During the exit-meeting, I discussed with the firm's officials that if the quality unit elects to perform reduced testing of a material the expectation is to evaluate the reliability of a supplier's Certificate of Analysis prior to accepting test results, and to reevaluate the supplier's Certificate of Analysis at appropriate intervals. Dr. Jacobus committed to sending a written response in writing to the District.

REFUSALS

I did not encounter any refusals during this inspection.

SAMPLES COLLECTED

Sample DOC 502452 was collected to document the interstate shipment of Dapsone 25 mg Tablets USP. An FDA-463a, Affidavit, was prepared for and presented to Laura R. Jacobus, Vice President prior to the issuance of the FDA-483, Inspectional Observations, on 4/16/2012. Ms. Jacobus read the Affidavit but refused to sign the document on the advice of her legal counsel.

GENERAL DISCUSSION WITH MANAGEMENT

On 4/16/2012, I held a close-out meeting with firm's officials. Present at the close-out meeting were:

David P. Jacobus, President
Laura R. Jacobus, Vice-President
Richard Pursell, Plant Manager
Guy Schiehser, Director of Chemistry

Pete Raghubans, Quality Assurance Executive
Robert Warman Sr., Director of Engineering
Neil Lewis, Director of Chemical (API) Manufacturing
Raju Shah, Director of Quality Control

I issued an FDA-483, Inspectional Observations, to Dr. David P. Jacobus, President. Before the issuance of the FDA-483, Inspectional Observations I read the compliance statement at the top of the FDA-483. I informed the firm's management that the firm's response may impact FDA's determination of the need for follow-up action, if FDA receives an adequate response to the FDA-483 within 15 business days of the end date of the inspection. Complete details regarding the FDA-483, Inspectional Observations can be found in the *Objectionable Conditions and Management's Response* section of this EIR

The following issues were discussed with the firm, but not documented on an FDA-483, Inspectional Observations:

Stagnant Water

During a walkthrough of the facility, I observed stagnant water near the PASER granule drying suite. I noted that the water was observed in the track of a large door, approximately one inch lower than the ground level, leading to the outside of the facility. The large door is not routinely opened; the door is used when installing new manufacturing equipment. I stated the Mr. Pursell that the stagnant water needed to be addressed; Mr. Pursell agreed. On 4/16/2012, I noted that the stagnant water was removed from the door track.

A space observed between the floor and the door in the new warehouse constructed

During a walkthrough of the new facility, I noted that there was a space between the door and the floor of the emergency exit. I noted that currently the firm is not storing product in this facility. I stated to Ms. Jacobus that during my walkthrough of the new facility that the space between the floor and the door needed to be addressed. I stated that the gap in the door was a possible route of entrance for pests. I noted that the firm is located on a nature preserve. Ms. Jacobus agreed and committed to addressing the space in the door.

ADDITIONAL INFORMATION

Access to the firm's manufacturing location in Plainsboro, NJ is gained via an access road located in the northbound side of Schalks Crossing Road between Scudders Mill Road and Research Way. When taking Scudders Mill Road, make a left onto Schalks Crossing Road. The access road begins

immediately before an overpass and is identified with a white sign that states "Industrial Research Laboratory".

EVIDENCE MATRIX

Obs.	Description	Pages in EIR	Exhibits	Reference to DOC #502452
1a	Failure to perform adequate investigations	9-11	4-11	
1b	Failure of investigations to extend to other lots	11-13	12-21	
2	Failure to clean equipment	13-15	22-28	
3a	Failure to perform a temperature mapping study; inadequate facility design	16-17	29-37	
3b	Facilities not properly maintained	17	29, 37-43	X
3c	Facilities not properly maintained	18	29, 44-51	
3d	Facilities not properly maintained	18-19	29, 52-53, 91	
3e	Facilities not properly maintained	19-20	29, 54-60	X
4	Equipment not properly maintained	20-21	61-63	X
5a	Lack of specific manufacturing instructions and control procedures	21-24	64-73	X
5b	Failure to establish a yield specification	24	69, 74	X
6	Failure to label containers	25-26	75-76	
7	Failure to validate a stability-indicating method	26-27	21, 77-85	X
8	Failure to validate a supplier's Certificate of Analysis	27-28	86-93	X

VOLUNTARY CORRECTIONS

I reviewed the firm's corrective actions to the firm's previous FDA-483, Inspectional Observations, dated 2/24/2011. A summary of the Observations listed on the previous FDA-483 and the firm's corrective actions are below.

Observation #1

This observation was related to the failure to establish a stability-indicating test method to monitor impurities in Dapsone 25 mg and 100 mg Tablets USP, throughout shelf-life.

The current inspection revealed that the firm has developed a stability-indicating test method and created a draft test method. To date the firm has not validated the draft test method for its intended use. Currently, impurities for Dapsone 25 mg and 100 mg Tablets USP are evaluated using a (b) (4) method on stability. Please refer to Observation #7 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

Observation #2

This observation was related to the failure to evaluate Dapsone USP drug substance for impurities during stability. The previous inspection noted that the firm had a validated test method for this purpose, but the method was not being used by the firm.

The current inspection revealed that the firm revised the stability protocols for Dapsone USP to include an evaluation of impurities using test method, (b) (4) No further deficiencies were noted.

Observation #3

This observation was related to the failure to perform investigations following temperature and humidity excursions and the failure to perform investigations according to the firm's procedures.

The current inspection revealed, that the firm appears to be performing investigations into temperature and humidity excursions noted in stability chambers, warehouses, and during transport of materials. I reviewed investigations into temperature and humidity excursions; I noted no deficiencies. During my review of investigations, I noted that the firm failed to adequately investigate batch failures and failed to extend a failure investigation to other batches that may be adversely impacted. In addition, I noted that the firm's procedures for handling OOS results and deviations were deficient. Please refer to Observation #1 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

Observation #4

This observation was related to the failure to review all complaints and investigations during annual product reviews.

The current inspection revealed that the firm is still in the process of completing their annual product reviews. I reviewed the firm's completed annual product reviews completed since the previous inspection; I did not note any specific deficiencies.

Observation #5

This observation related to the lack of appropriate controls established over the firm's data acquisition system.

The current inspection revealed that the firm's current data acquisition system has audit trail capabilities, all users have a unique username and password, all data is backed-up to a secure server. I reviewed the security controls established over the firm's server; the firm demonstrated that data cannot be removed from the server.

Observation #6

This observation related to the failure to maintain the sampling suite in a state of repair. During the previous inspection, the investigator observed residue covering the floor and walls and observed water leaking in the suite.

The current inspection revealed that the sampling suite has been renovated. I did not note any deficiencies related to the sampling suite. I noted deficiencies related to the failure of the firm to maintain other areas and equipment in a state of repair. Please refer to Observation #3 and 4 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

Observation #7

This observation related to the failure to calibrate production equipment.

The current inspection did not reveal any deficiencies related to the failure to calibrate equipment.

Observation #8

This observation related to the failure to adequately perform a scale-up validation study for PAS API.

The current inspection revealed that the firm executed a scale-up study for PAS API batch size (b) (4) kg. I did not note any deficiencies during my review of this validation study.

Observation #9

This observation related to the failure to sample water in the same manner water is used during production.

The current inspection revealed that the firm has changed their written procedures for water sampling to be performed in the exact manner water is used during production.

Observation #10

This observation related to the failure to identify containers in terms of status and the lack of controls to prevent mix-ups.

The current inspection revealed that the firm purchased colored drums in order to visually identify different batches of PASER granules. During the inspection, I observed a container of PASER granules without a label identifying its contents. Please refer to Observation #6 under the *Objectionable Conditions and Management's Response* section of this EIR for further details.

EXHIBITS COLLECTED

Exhibit #	Description	# of Pages
1.	Organizational Chart	1
2.	Product List	1
3.	Facility Diagram	2
4.	Investigation 12142011-CM	1
5.	Manufacturing Record for Lot #1437	75
6.	COA and Release for Lot #1437, Material (b) (4)	3
7.	Traceability of Material # (b) (4) into PASER Lot #14269	7
8.	SOP, QC-0047-02, Laboratory Investigations	17
9.	SOP, G-0023-01, Deviations	5
10.	SOP, QC-0047-03, Laboratory Investigations	16
11.	SOP, G-0023-02, Deviations	7
12.	Investigation MF122111	3

Exhibit #	Description	# of Pages
13.	PASER Uncoated Granules Specification for Particle Size	1
14.	Manufacturing Record for Lot #14028	21
15.	Manufacturing Record for Lot #14024	31
16.	Manufacturing Record for Lot #14025	32
17.	Manufacturing Record for Lot #14029	20
18.	Traceability of Lot #14029 into PASER Lot #14070 and Release	7
19.	Raw Material Inventory Card for Material (b) (4)	2
20.	Protocol #03292012QC	13
21.	Dosage Form Batch Issuance log	28
22.	Photo of Dissolution Vessel, JPC #(b) (4)	1
23.	Photo of the opening of Dissolution Vessel, JPC # (b) (4)	1
24.	Photo of white reside observed in Dissolution Vessel, JPC #(b) (4)	1
25.	Manufacturing Record for Lot #1481	71
26.	SOP, G-0018-01, Equipment Cleaning in General	2
27.	(b) (4) Usage Log	8
28.	(b) (4) Usage Log	10
29.	SOP, QA-0005-01, Building and Facilities	3
30.	Photo, Large view of the cold-storage room	1
31.	Photo, Close-up of containers stored in cold-room	1
32.	Photo, The ceiling in the cold-room	1
33.	Photo, Close-up of ceiling in the cold-room	1
34.	Photo, Close-up of the foil, foam board material that lines the cold-room	1
35.	PASER and PAS Storage Requirements	2

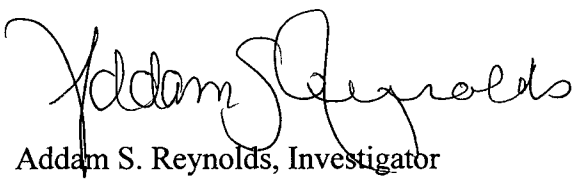
Exhibit #	Description	# of Pages
36.	Temperature Mapping Study, dated 4/2/12	8
37.	Memo, dated 4/16/2012	1
38.	Photo, Taken from the Front door to show proximity to the nature preserve	1
39.	Photo, The posterior door with hole in the door	1
40.	Photo, Foliage observed in the warehouse	1
41.	Photo, Large view of the inside of the warehouse	1
42.	Photo, Close-up of containers stored in the warehouse	1
43.	Photo, Close-up of containers stored in the warehouse	1
44.	Photo, Exposed wall	1
45.	Photo, Exposed wall	1
46.	Photo, Close-up of exposed wall	1
47.	Photo, Close-up of exposed wall	1
48.	Photo, HVAC line with duct tape	1
49.	Photo, Cardboard covering a vent	1
50.	Photo, Close-up of vents with dust-like appearance	1
51.	Photo, In-process PASER being stored	1
52.	Photo, Gouges in the wall in the drying suite	1
53.	Memo dated 3/26/12	1
54.	Photo, Large view of Dapsone slurry area	1
55.	Photo, Close-up of hole in plastic ceiling in Dapsone slurry area	1
56.	Photo, Large of entrance to Dapsone manufacturing area	1
57.	Photo, Close-up of plastic sheet that serves to separate the Dapsone manufacturing area from the interstitial space	1

Exhibit #	Description	# of Pages
58.	Photo, Settling Vessling in Dapsone manufacturing area	1
59.	Photo, Black residue observed adjacent to manufacturing (b) (4)	1
60.	Investigation into Black Residue in Dapsone Manufacturing Area	2
61.	Photo, Chipped Paint on (b) (4)	1
62.	Photo, Chipped Paint on	1
63.	(b) (4) Usage Log	3
64.	Dapsone USP Master Manufacturing Record	51
65.	Dapsone USP Raw Material Specification	4
66.	Report #03102011QC, Dapsone (b) (4) Verification	6
67.	Revised Dapsone USP Raw Material Specification	5
68.	Procedure G-0004.003, Personal Hygiene and Proper Dress	6
69.	Manufacturing Record for Lot #1408	51
70.	Manufacturing Record for Lot #1419	51
71.	Raw Material Inventory Card and Release for Lot #1408	5
72.	Raw Material Inventory Card and Release for Lot #1419	6
73.	Batch Record and Release for Lot #14017	46
74.	Investigation 04052012-CM	3
75.	Manufacturing Record for Lot #14563	33
76.	Manufacturing Record for Lot #14569	32
77.	(b) (4) Determination of Related Compounds in Dapsone Tablets: 25 mg and 100 mg	9
78.	Reports Results during Research Evaluation Study	13
79.	Stability protocol for Dapsone 25 mg and 100 mg tablets	3

Exhibit #	Description	# of Pages
80.	Reported Results for Dapsone Tablets Stability Stations After 2/2011	53
81.	Lot#13520, Dapsone 100 mg Tablets, COA	2
82.	Lot#13520, Dapsone 100 mg Tablets Assay Testing	3
83.	(b) (4) n Dapsone Tablets, USP	4
84.	Lot#13520, Dapsone 100 mg Tablets (b) (4) Impurity Testing	4
85.	(b) (4) Related substance test by (b) (4) (b) (4) for Dapsone Tablets as Per European Pharmacopeia	3
86.	Raw Material Data Summary for Material (b) (4)	2
87.	Raw Material Data Summary for Material	2
88.	Raw Material Data Summary for Material	2
89.	Manufacturing Record for Lot #1385	51
90.	Manufacturing Record for Lot #1453	65
91.	Manufacturing Record for Lot #14441	16
92.	SOP, QC-0079-01, Reduced Testing of Raw Materials	3
93.	SOP, G-0031-03, Vendor (Supplier) Certification	21
94.	Original CD of Photographs taken during the current EI	N/A
95.	Copy of Original CD of Photographs taken during the current EI	N/A
96.	Working Copy of Original CD of Photographs taken during the current EI	N/A
97.	Contact Sheet of Photographs taken during the current EI (3 copies)	2

ATTACHMENTS

FDA-463a, Affidavit, dated 4/16/2012, 3 pages
FDA-482, Notice of Inspection, dated 3/28/2012, 3 pages
FDA-483, Inspectional Observations, dated 4/16/2012, 5 pages
Sample DOC 502452, 149 pages



Addam S. Reynolds, Investigator