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April 30, 2012

Captain Joseph F. McGinnis
Food and Drug Administration
New Jersey District Office
10 Waterview Blvd
Parsippany, New Jersey 07054

FEI Number 2243092
Response to FDA 483 dated April 16, 2012

Dear Captain McGinnis,

Included in this letter is a formal response to the inspection conducted at our facility located in the Industrial Research Laboratory Building, Schalks Crossing Road, Plainsboro, New Jersey 08536. The inspection was conducted by Mr. Addam S. Reynolds on March 28, 29 and 30, 2012 and April 2, 3, 4, 11 and 16, 2012.

At the close-out of that inspection, we presented Mr. Reynolds with a summary document of the immediate corrective actions taken in response to his observations as well as a letter which summarized our proposed management of the facility, our company and the products. [1]

We conveyed to Mr. Reynolds and would like to do so formally to you that we take the observations very seriously and not only as specific issues that need to be addressed, but as examples which may extend to our company's operations and systems in principle. We do believe the relationship between the Food and Drug Administration and industry is collaboration. As a company, we always benefit from inspections especially from the fact that each CSO and auditor brings a different set of insights and expertise.

We are fully aware that we produce sole-source and medically necessary products and we are committed to the well-being of those patients who rely on our integrity.

This site inspection stimulated our thinking in regard to the actions that we need to take to implement the appropriate revisions to upgrade FDA cGMP compliance. Prior to this inspection, we made the commitment to upgrade the manufacturing building. Some upgrades currently remain unfinished but are in progress at this time. We have therefore made the decision to explore collaboration with the [redacted (b) (4)] to transfer approximately [redacted (b) (4)] of our production to their facility in [redacted (b) (4)]. The [redacted (b) (4)] has been our partner for many years and is our approved contract manufacturer that coats the PASER granules which are marketed for multi-drug resistant TB. On Thursday April 19, 2012 [redacted (b) (4)], Director of

Quality Assurance at the [redacted] (b) (4) came to our facility and we provided him with copies of all of our finished dosage form records. [2]

The [redacted] (b) (4) has just completed an FDA inspection and no observations were noted. [3]

We reviewed the equipment and timeframes with the senior staff at the [redacted] (b) (4) to ensure a smooth transition should we move forward with a technology transfer program. They are prepared to work with us. We discussed our plan with CSO Reynolds and he indicated that he appreciated our commitment to develop both a short term solution which will allow us to upgrade our plant for improved cGMP compliance as well as our willingness to ensure an uninterrupted supply of these essential medications. It is our intention to consider a [redacted] (b) (4) for both strengths of the Dapsone Tablets, 25 mg and 100 mg and for the PASER granules. We will retain all quality control batch release testing and stability at our facility.

We have also made another broad-based management decision and that is to hire independent consultant [redacted] (b) (4), to help us evaluate the entire operation. His commitment includes additional staff training, review of plant operations and compliance upgrading and to perform comprehensive quality-related audits to determine where additional staff is needed. We are confident that he can help us not only to ensure that all FDA observations are addressed – by SOP and systems review, audits for cGMP compliance and personnel training – but that the actions that will be taken are both comprehensive and enduring. We have attached his credentials to this response.[4]

It is our full intention, with the assistance of [redacted] (b) (4), to have the facility evaluated by outside contractors experienced in designing and upgrading pharmaceutical facilities. This will ensure that all manufacturing and laboratory areas are compliant for the intended purposes and, that going forward we will decisively address the concerns that have been raised by FDA for both short term and long term upgrades.

Immediately following this letter are specific responses to the observations raised by CSO Addam Reynolds during his inspection. We appreciate and respect his comments and observations and are committed to integrate those points in our procedures and systems so as to upgrade our overall compliance. One additional immediate action that has been taken was to hold a personnel training meeting with all company employees. This re-emphasized the importance of cGMP requirements in our operation and we reviewed the inspection results and discussed the 483 observations. Subsequent to completion of this letter, all company employees were assembled again and the response letter read to them. [5]

We will keep you informed regarding our immediate plans as well as our on-going quality improvements including the validation of the stability-indicating method for the Dapsone Tablet finished product. A corrective action schedule is being submitted with this letter and a monthly status report will be sent to your office so as to indicate the progress made in addressing the observations. This monthly report will continue to be sent until all observations have been corrected. [6]

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 [redacted] of 4-Aminosalicylic Acid USP, an Active Pharmaceutical Ingredient (API), failed specification for moisture content (spec: [redacted]; 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.

We have placed PASER® Granule Lot #14269 on long-term stability and will monitor its performance throughout the expiry period. We will notify your office of any confirmed OOS result.[7]

Following our standard procedure, a [redacted]. *Quality Control followed the internal procedure for OOS which included a re-analysis, confirming the high (OOS) moisture results for one drum in the* [redacted] *Quality Assurance rejected* [redacted] *drums in this* [redacted] *drying run. API manufacturing conducted an investigation due to the low PAS lot yield due to the rejection of the* [redacted] *drying run (*[redacted] *drums); therefore we did not see a need to extend our investigation beyond the OOS for 1437-11-3308-9A/9B to the other* [redacted] *runs. The* [redacted] *other drying runs for this lot* [redacted] *drums) were tested and met specifications for moisture. We did not include an analysis of the potential impact on the other drying runs for PAS Lot* [redacted] *because we evaluate each run independently. Each drying run (*[redacted] *drums)is processed under a separate batch record, tested and evaluated independently and carries a unique run number. As in this case, we reject the full drying run* [redacted] *drums) if* [redacted] *drum is OOS.*

The issue under consideration was not the broad rejection by Quality Assurance of [redacted] *drums of material* [redacted] *with passing results and* [redacted] *OOS) but rather that the Quality Control OOS analysis confirming the high moisture did not include a root cause analysis or further examination of the* [redacted] *drum. The SOP for OOS investigations has been revised to accommodate any such occurrence in the future. All future investigations will include an extended root cause and impact analysis by Quality Assurance, including when applicable, an investigation by all third-party contractors.* [8]

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 [redacted] test (i.e. particle size of the granules) determined variability in [redacted] Lot [redacted] as the root cause. Lot # 14032 and #14045 of uncoated PASER granules were

aborted at the [redacted] due to atypically large granules. Lot #14029 of uncoated PASER granules containing [redacted] Lot [redacted] was permitted to finish processing. The investigation failed to include an impact of assessment for evaluating if other batches of uncoated PASER granules utilizing [redacted] Lot [redacted] were impacted.

Representative lots of PASER Granules and Dapsone tablets 25 mg and 100 mg manufactured with [redacted] Lot [redacted] are on long-term stability. We will continue to monitor their performance throughout the expiry period.

During the site inspection we spent a considerable amount of time reviewing this investigation. PASER granules are a unique delayed-release dosage form which is evaluated continuously throughout the manufacturing process. When Lot #14028 failed the in-process [redacted], it was immediately rejected and quarantined for destruction. The next two PASER granule lots manufactured using [redacted] Lot [redacted] were rejected at the [redacted] step and not subject to further processing.

Our investigation determined that [redacted] Lot [redacted] was the root cause of the failure. We held extensive meetings with the manufacturer, [redacted], which concluded that their product typically includes "noise". [redacted] lot [redacted] met the USP/NF and Jacobus specification and performed as expected prior to PASER granule Lot #14028. Following an extensive analysis neither [redacted] nor our research department was able to assign a definitive cause for performance variability of [redacted] Lot [redacted] Our investigation concluded that the in-process [redacted] test was the only sensitive measure to detect such slight intra-lot variability. We are pleased that the controls built into the granule production are discriminating to indicate that a batch is either acceptable or unacceptable for further processing. The remainder of the [redacted] lot was destroyed.[9] Our future investigations will include a Quality Assurance analysis to ensure that all product batches manufactured with a material, which meets specifications but results in one of the product batches that does not perform as expected, does not have a negative impact on other product batches. Such Quality analysis will include a retrospective review and the expansion of long-term stability studies.[9] / [8]

FACILITIES AND EQUIPMENT SYSTEM
OBSERVATION 2

Procedures for cleaning equipment used during the manufacture 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 manufacture of 4-Aminosalicylic 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 the [redacted] JPC # [redacted] used in the manufacture of 4-Aminosalicylic Acid USP. The manufacturing record for Lot # 1481 of 4-Aminosalicylic 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.

The batch record and all product batch records will be modified prior to the next run to include multiple steps with oversight to ensure that all equipment has been properly cleaned prior to use and that this cleaning check is documented. Manufacturing staff have been retrained in the cGMP requirement to label all process equipment with clean and use status.

During the site inspection, this dedicated vessel was undergoing maintenance, which included the installation of (b) (4) *to automate and facilitate cleaning. Production staff has been retrained on SOP G-0018.*[29] *We have also implemented a Quality Assurance inspection to verify that all equipment is clean and production suitable prior to use for batch processing.*[10]

B. On 4/3/2012, I observed what appeared to be a brown residue in (b) (4) JPC (b) (4) used in the manufacture of 4-Aminosalicylic Acid USP. The manufacturing record for Lot #1481 of 4-Aminosalicylic Acid USP indicated that the vessel was rinsed (clean) 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.

We have retrained the operators regarding the cleaning and use of equipment. [29] *As stated, all batch records will be modified to include an operator and Quality Assurance sign off that the equipment is suitable for use. In order to facilitate evaluation of this particular dedicated vessel, we will relocate it in order to facilitate cleaning, maintenance and inspection. This relocation will be undertaken prior to its next use. The sight glass manhole cover will be replaced. A re-qualification protocol to evaluate the move will be undertaken and approved by Quality Assurance before it is placed back in service. We anticipate that this change will take approximately 4 to 6 weeks.*[11]

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. The warehouse is used to store uncoated PASER granules and 4-Aminosalicylic Acid USP.

This space has been continuously monitored during the (b) (4) *it has been in use. There have been eight excursions for a total of four hours (conditions =* (b) (4) *). The highest and longest excursion during this monitoring period was* (b) (4) *for one hour, 17.9°C. We fully accept that temperature monitoring is a component of storage qualification and that mapping must be*

completed prior to building commission. During the FDA site inspection we developed and executed a [redacted] *mapping protocol to support temperature control at different locations when the warehouse was full. The results confirmed the temperature uniformity of the warehouse. Copies of the mapping protocol and data,* [redacted] *historical data and a product temperature matrix study were reviewed with CSO Reynolds and are attached.* [12] *The cool room was emptied and closed on April 13, 2012 prior to close-out and verified by CSO Reynolds. All product stored in this space was transferred to our third-party logistics provider,* [redacted], [redacted], *where it is stored in a cGMP warehouse (*[redacted]*).* [13] *We have constructed a large cGMP warehouse which is scheduled to be mapped and qualified. It has been a very lengthy process to secure the Certificate of Occupancy for this building and it will not be used for the storage of any production related material until the qualification is complete and approved by Quality Assurance. This new warehouse will have a temperature mapping study and is constructed in such a way that it will facilitate cleaning and provide sufficient space for orderly storage of materials to prevent mix-ups. The delay in receiving the COO is attributable to local zoning requirements. CSO Reynolds visited the building and was pleased with the final punch list and its construction.*[14]

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 Aminosalicyclate Sodium BP.

The ambient side of the warehouse was also relocated and closed. This side contained sealed and logged drums of technical grade sodium PAS and technical grade Dapsone and the last [redacted] *lots of purified lots of Proguanil HCl. On April 16, 2012 prior to closeout the technical grade Dapsone was transferred to the Quarantine Cage in the main building for sampling. The potency, impurity and wet chemistry tests for this material have been performed and the results are well within the specification. Results for residual solvents are expected within the week. The results are within the trend of the historical data of the technical grade product. The Sodium PAS has been moved to our locked cage for approved material. The Proguanil HCl - which we no longer manufacture - has been moved to the locked area for rejected material and manifested for destruction (with the exception of* [redacted] *reserve samples for research).*

It is our intention to upgrade and qualify this warehouse according to cGMP requirements. Until such time, the space will not be used for storage or warehousing of any starting materials, intermediates or finished products.

Prior to close out, CSO Reynolds was informed that the materials stored in the entire warehouse were transferred and that it was effectively closed until such time that it will be upgraded. CSO Reynolds verified that the entire building was emptied and decommissioned.

C. Manufacturing Room [redacted] 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.

During the inspection, the shift supervisor moved the in-process material to this room in a presumed effort to ready the area for the inspector. The room was under construction and personnel are not authorized to store in-process materials in any non-designated space. We have retrained the shift-supervisor about not only adherence to the cGMP but also the importance of not deviating from any routine procedure regardless of a regulatory inspection. [29]

The room has been locked. No manufacturing personnel have access to this room. General contractors and pharmaceutical engineers will evaluate this room as part of the physical plant assessment for upgrade.

D. The walls in the drying suite, used in the manufacture 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.

This dedicated room was scheduled for upgrade prior to the inspection which was undertaken during the visit. The walls have been covered with appropriate sheeting to facilitate cleaning and maintenance. Quality Assurance will approve the state of the room prior to use. CSO Reynolds saw the room following close-out of his observations. This room will be evaluated by the pharmaceutical / facility contractors during the building renovation assessment.

Further, as above in observation "3C", during the company-wide personnel training and discussion, all employees were instructed in the importance of cleanliness and the need to adhere to standard procedures. Specifically, it was discussed that appropriate corrective actions must be taken that are within the cGMP guidelines and that the use of duct tape, cardboard and "stop gap" repairs are simply not appropriate in a pharmaceutical plant. The use of unacceptable methods and lack of communication for corrective actions was stressed. [29]

E. The manufacturing area for Dapsone USP is not maintained in a state of repair. The ceiling in the area used in Dapsone [redacted (b) (4) (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.

Following the observation of CSO Reynolds, we analyzed the black residue during the inspection and confirmed that it was [redacted (b) (4)] *from the process. We have retrained the operator in cGMP and the importance of cleanliness. The hole in this positive pressure space was immediately repaired. Again, we have modified our internal procedure to require Quality Assurance sign-off clearance prior to the use of any manufacturing space. Both Quality Assurance and operator verification for cleanliness will be incorporated into all batch manufacturing records. For the current batch underway, this requirement will be incorporated via a supplemental document.* [20]

The Engineering department has been retrained to ensure that a senior member of the department shall inspect the work as completed following any repair and or modification to ensure that a proper impact assessment has been undertaken and that, if needed, all appropriate

change control documents and protocols have been conducted and reviewed by Quality Assurance. [29]

This area will be evaluated by the outside contractors / pharmaceutical engineers and upgraded to facilitate compliance with cGMP.

OBSERVATION 4
Equipment used in the manufacture of drug products are not maintained in a state of repair.

Specifically, [redacted] (b) (4) used during milling of Dapsone USP is 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.

This piece of equipment was scheduled to be sent for powder coating with an FDA approved material as was additional equipment. The equipment was sent out on April 9, 2012. All employees have been retrained regarding their personal responsibility to assess equipment prior to use. All batch records and critical steps will include operator sign-off for verification that a piece of equipment is suitable for use in batch processing. Quality Assurance shall inspect all equipment and areas prior to batch processing and approval or non-approval for proceeding shall be noted in the batch record. [15]

The Engineering department has been retrained in implementing maintenance procedures to specifically evaluate not only the mechanical state of a piece of equipment but its suitability for pharmaceutical processing and use. Further, as above in observation "3C" and "3D", during the company-wide personnel training and discussion, all employees were instructed in the importance of cleanliness and the need and proper procedures for corrective actions. Conditions that lead to paint chipping and cracks were listed also as being unacceptable. The use of acceptable methods and proper communication for corrective actions was stressed. [29]

All equipment used in the batch processing, both API and finished product (dosage form), will be inspected [redacted] (b) (4) and evaluated under a separate Quality Assurance program.

PRODUCTION SYSTEM
OBSERVATION 5
There is a lack of specific manufacturing instructions and control procedures.

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

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

During the inspection, we presented CSO Reynolds a verification protocol which was developed in March of 2011 to verify that the [redacted] was effective. Under protocol samples were taken at the time of the initial transfer and then following each [redacted] The conductivity of the initial sample (baseline) was 324.0 µS/cm and the first [redacted] reduced the conductivity to 110.9 µS/cm. Conductivity after the [redacted] was 5.54 µS/cm. The conductivity for the standard [redacted]. The conductivity [redacted] was 0.54 µS/cm. [16]

During the site inspection, to address the concerns of CSO Reynolds, we retrospectively analyzed lots of the Dapsone API manufactured in 2011 and 2012. The results confirmed that the [redacted] process remains effective in removing [redacted] from the [redacted] [17]

In addition, we revised the finished product specification to include a [redacted] test for Dapsone USP API. [18] *A copy of the revised specification was presented to CSO Reynolds.*

2. The master manufacturing record fails to include adequate instructions for performing this [redacted] operation to ensure consistency. Step 53 in the master manufacturing record instructs operators to [redacted]; however, instructions do not detail how this [redacted] operation is performed by operators or when the [redacted] is determined to be adequately [redacted].

We have developed a written procedure which describes the [redacted] procedure. [19] *The master batch record will be modified to include instructions for the [redacted] as well and which includes an additional oversight person for verification. For the Dapsone batch which is in process, we have developed a protocol to evaluate the presence of [redacted] throughout the entire run and increased the amount of [redacted] to [redacted] and will continue this practice in subsequent batches based on the subject batch results. Based on the test results generated to determine [redacted] levels after [redacted] we are confident that the [redacted] is effective.* [20]

During the site inspection, we informed CSO Reynolds that we had purchased a [redacted] and were developing the appropriate protocols to qualify this equipment and [redacted] process. CSO Reynolds was shown the [redacted] and communicated support for our plans to [redacted] of the [redacted]

3. Procedure G-004.003, Personal Hygiene and Proper Dress, dated 3/3/2011, requires [redacted] gowning requirements for this step. It is not clear what are the correct gowning requirements for this step.

We have revised this SOP and developed a separate written procedure for the gowning requirements for use during the Dapsone [redacted]. All operators have been retrained in proper gowning. Gowning will be verified by an additional supervisor who will note compliance in the master batch record. [21]/ [29]

4. There is a not an established procedure requiring operators to sanitize their gloved hands before [redacted] mixing Dapsone [redacted] In addition, gloves are reused and there is no

procedure to detail: the cleaning of the gloves, the requirements for when gloves can be reused or how used gloves are stored prior to additional use.

During the site inspection, to address CSO Reynolds concerns, we evaluated the gloves for bio-burden and the results supported our technique for sanitizing as being effective. The procedure has been formalized in the gowning SOP, the master batch record and a specific SOP. Historically, the (b) (4) *gloves used for this process have only been re-used during a single run (part) and re-sanitized accordingly. A single part is approximately* (b) (4) *Gloves are not exchanged among operators and the inner gloves are disposed of each time an operator removes the* (b) (4) *gloves. If* (b) (4) *over-gloves are removed during processing they remain in the contained* (b) (4) *area. Operators do not remove the inner gloves within the processing area.*[22]

We have developed specifications for the gloves and tape. Quality Control will examine and approve these materials prior to use. Purchased gloves are received in sealed bags and are stored in two bags ("double-bagged" and individually tied) prior to use, in a closed, dedicated cabinet. [23]

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.

The master batch record will be modified to include theoretical yield and actual yield. The theoretical yield will be established based on historical data. The Quality Assurance review and approval will include the requirement to investigate an atypical yield.

For the batch underway, the yield calculation will be incorporated under a planned deviation.[24]

OBSERVATION 6
Containers used during the production of drug products are not identified at all times.

Specifically, during a walk through 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.

The identifying label was prematurely placed in the batch record. The Shift Supervisor and the operators have been retrained regarding the proper labeling of production materials. [25] / [29] *We have revised our SOP to include additional instruction. Quality Assurance staff and the Director of Manufacturing will conduct an audit during production to ensure cGMP compliance during batch processing.*

LABORATORY CONTROL STYSTEM
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, [redacted] (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

As reviewed during the FDA audit, over the past year, efforts have focused on generating data in order to develop a stability indicating method for use in stability assessment of 25 mg and 100 mg Dapsone tablets. A draft HPLC method designated [redacted] (b) (4), *is the basis for a stability indicating method. This draft method and data were reviewed during the site inspection by CSO Reynolds. The developmental work included the stressing of finished dosage forms (25 mg and 100 mg) under FDA/ICH conditions. The chromatograms of finished products did not exhibit any unknown peaks throughout the expiry period and up to seven (7) years.*

The organic chemistry department reviewed with CSO Reynolds their on-going work of the past year which included API stress testing and the isolation and synthesis of API degradation products. We have run these degradants as standards using the current draft method for tablets and those peaks are not found in the tablets on dosage form stability. Testing for these degradation products may necessitate developing a second stability indicating method. This work will continue and we will provide regular updates in our monthly reports.

Enclosed with this response is the approved method: [redacted] (b) (4) *and the approved validation protocol.* [26]

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 [redacted] (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. [redacted] (b) (4) is used during the commercial manufacture of Dapsone USP, 4-Aminosalicylic Acid USP and uncoated PASER granules.

- *During the inspection we addressed this specific issue. We revised our internal SOP to ensure that full testing is completed annually to confirm and recertify a vendor's COA. This revision*

was presented to CSO Reynolds. During the site inspection we discussed our vendor qualification program and have conducted re-training on this issue.[27]

On April 12, 2012 prior to closeout we ordered a new lot of [redacted] *from the current supplier. The supplier sent one cylinder to* [redacted]*, for full confirmatory testing. The independent testing laboratory was audited by our Director of Quality Assurance. The confirmatory full testing supports the supplier's Certificate of Analysis.*[28]

We trust that you will find this response to be satisfactory in addressing your concerns. If you require additional information or require further clarification please do not hesitate to contact us. We request that you send us a copy of the Establishment Inspection Report.

Sincerely yours,

David P. Jacobus, M.D.

Laura R. Jacobus

Cc: Mr. Addam S. Reynolds
Food and Drug Administration
Consumer Safety Officer
120 North Center Drive
North Brunswick, New Jersey 08902

Summary of Attachments

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[1] Letter presented at closeout to CSO Addam S. Reynolds including list of corrections implemented
[2] Technology transfer to the [redacted]: Batch records for Dapsone 25 mg & 100 mg and PASER Granules
[3] [redacted] Notice of Inspection and No Findings
[4] [redacted] Credentials
[5] Company wide 483 review and training with [redacted]
[6] Corrective action schedule
[7] PASER Lot 14269 stability schedule, [redacted] pedigree
[8] SOP for OOS including root cause analysis
[9] [redacted] pedigree and destruction record
[10] Form to document Operator and Quality Assurance approval to proceed
[11] Relocation of PAS [redacted] vessel
[12] [redacted] temperature mapping study [redacted] month monitoring documentation, temperature matrix study
[13] Pedigree of material transferred from the decommissioned storage building
[14] IQ, OQ and PQ for new warehouse: [redacted]
[15] SOP: Quality Assurance's Review of cGMP Observations
[16] March 2011 protocol to the removal of [redacted] from the Dapsone [redacted]
[17] Retrospective analysis of [redacted] levels in all Dapsone USP API manufactured 2011 and 2012

[18] Revised Dapsone USP API product specification which includes a test for [redacted]
[19] SOP: [redacted] of the Dapsone [redacted] with [redacted] following Dapsone [redacted]
[20] Protocol for the sampling and evaluation of [redacted] of the Dapsone [redacted] (current batch)
[21] SOPs: Gowning requirements (general), solid dosage form, API manufacture
[22] Bio-Burden study for [redacted] gloves, SOP for sanitizing gloves, training record for manufacturing personnel.
[23] Quality Control Specification for [redacted] over gloves
[24] Planned deviation to incorporate yield calculation for Dapsone API
[25] SOP: Internal Label Generation and Use and training record
[26] Stability Indicating Assay for Dapsone USP 25 mg and 100 mg Tablets and Validation Protocol
[27] SOPs for the testing and management of raw materials and vendors
[28] Full testing of [redacted] certification of supplier and QA review
[29] Training records for revised procedures and SOPs and re-training on cGMP