JACOBUS PHARMACEUTICAL COMPANY, INC.
37 CLEVELAND LANE
P.O. BOX 5290
PRINCETON, NEW JERSEY 08540

609-921-7447
Fax: 609-799-1176

March 9, 2011

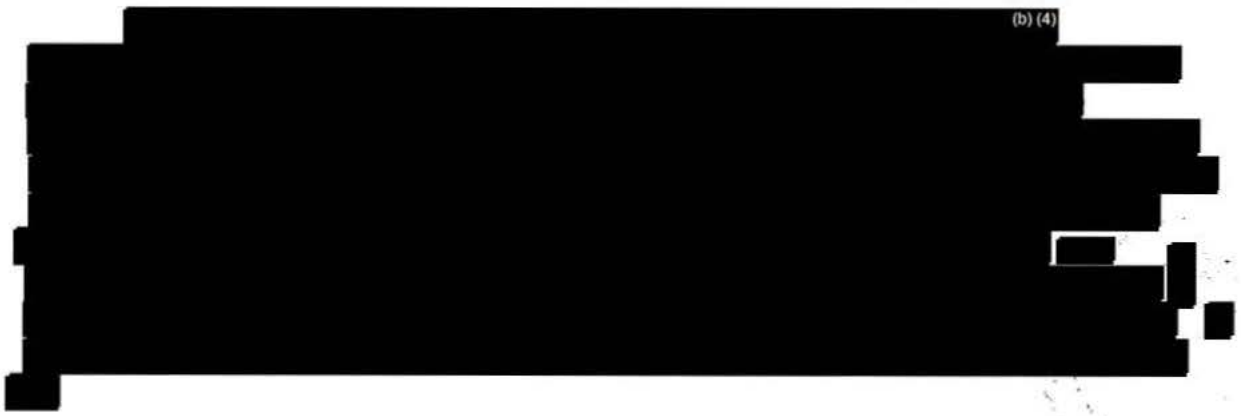
Nancy Rolli
U.S. Food and Drug Administration
New Jersey District Office
10 Waterview Boulevard
3rd Floor
Parsippany, New Jersey 07054

Dear Dr. Rolli,

We are writing in response to observations made by inspector Atul J. Agrawal, Consumer Safety Officer, during a routine inspection which started January 24, 2011. Mr. Agrawal issued a 483 on February 18, 2011 and it contained 10 specific observations. It was reissued due to a format revision and correction on February 24, 2011.

Mr. Agrawal's inspection was helpful on many levels. After the closeout we gave him a letter which summarized some of the items we discussed. It was written prior to the closeout and was not intended to be part of our response to the 483 at closeout. We have attached a copy to this letter. We hoped that it would provide Mr. Agrawal assurance that we took his and the Agency's observations seriously; we hope it will provide a similar re-assurance to you.

Our detailed response is organized according to the GMP system on the 2/24/2011 483. We appreciate the time that Mr. Agrawal spent at our facility. We look forward to a follow-up visit and hope that you will be pleased with the new controls and improvements.



Should you have any questions or comments regarding this response, please do not hesitate to contact us.

Sincerely yours,

David P. Jacobus, M.D.

Laura R. Jacobus

LRJ/lrj
cc: Mr. Atul J. Agrawal
Enclosure
Response to FDA 483
(b) (4) [redacted]

Response to FDA 483

FDA 483 comments are in bold; Jacobus responses follow.

Laboratory Control System
Observation 1

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

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

Observation 2

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

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

During the site inspection we reviewed our current assay, and the validation data for impurities' assay, [(b) (4)]-DAP-LC-4 (LC-4). This assay was developed as part of our revalidation (2001) of the Dapsone API manufacture as well as the qualification of an additional supplier for the technical grade starting material. During the qualification of the new supplier we discovered one previously unidentified impurity at a level which was higher than that typically found in the old source. An analysis of seven lots was undertaken and the highest value for this new impurity was [(b) (4)] Our specification requires that no unidentified peak exceed [(b) (4)] This impurity was fully characterized and was incorporated into the [(b) (4)] assay LC-4. It is worth noting that the technical grade starting material is of high purity so that with respect to the removal of impurities our current process produces material that easily meets our specification.

In 1999 we conducted [(b) (4)] [(b) (4)] stability studies using [(b) (4)] on our Dapsone API. We used [(b) (4)] as the control. As expected there was approximately a [(b) (4)] in comparison to the [(b) (4)] control [(b) (4)] No new peaks were found. [(b) (4)] We intend to repeat these studies on the API and will extend to the finished dosage form using [(b) (4)] as the control.

We have maintained the on-going requirement that any source for starting material, technical grade Dapsone, is [(b) (4)] that [(b) (4)]; this requirement [(b) (4)]. The supplier of our technical grade material uses only [(b) (4)] in their [(b) (4)]; there is

(b) (4) (b) (4) or in our (b) (4). We continue to test for the (b) (4)

The (b) (4) LC-4 is always run on incoming technical grade material as well as the (b) (4) production batch of purified material (b) (4). Following the suggestion of Mr. Agrawal during the inspection, we modified our stability protocol to include LC-4 for the release of our Dapsone USP (API).

The related substances test (b) (4) for Dapsone tablets, as per the European Pharmacopoeia, has also been incorporated into our stability protocol.

We have begun a re-validation of the (b) (4)C-DAP-LC-4 to determine if it is appropriate for use on tablets. If it is not suitable we will develop an additional stability-indicating method for the dosage form. The re-validation includes forced degradation studies on the technical grade material, Dapsone USP (API), Dapsone 100 mg tablets and Dapsone 25 mg tablets.

We will continue to run LC-4 on all (b) (4) during the purification of the Dapsone API as part of our (b) re-validation. This analysis will be incorporated into our (b) (4) product reviews. The finished dosage forms (25 mg and 100 mg) made with the (b) (4) Dapsone API lot (b) (4) (re-validation batch) will also be placed on stability.

Quality System
Observation 3

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

We have implemented an administrative system to ensure that all quality-related issues are immediately brought to the attention of the Director of Quality Assurance. A company-wide meeting was held to discuss this mandate. Each current employee has signed a quality-related statement to reinforce this requirement. All quality-related issues regardless of the nature (e.g. temperature excursion on a chamber, shipment, equipment or production problem or deviation) will be thoroughly investigated in a timely manner. Further, as owners we are prepared to dismiss an employee who does not follow this mandate.

We anticipate problems and deviations but we also expect that the employees of Jacobus Pharmaceutical will comply with our requirement. We fully recognize that not investigating a problem immediately and assessing the impact up front not only compromises our ability to understand the problem thoroughly but hinders immediate remedy.

We have revised our SOPs accordingly and conducted company-wide training.

Specifically,

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

    a. **For the CRT chamber used for long-term stability samples for APIs and finished drug products (e.g. Dapsone, [redacted]):**

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

The over-arching issue is that the Engineering Department did not thoroughly review or "chase down" excursions in a timely manner. We have now implemented a two-tier response; Engineering will immediately notify both Quality Control and Quality Assurance. Any excursion will be thoroughly evaluated in a timely manner. We have revised our SOP to reflect this requirement. In addition to this we have modified the procedure that includes a [redacted] recording by a member of the Department of Quality Control to take [redacted] readings of all stability chambers and the cold room. Any excursions will be addressed immediately. All stability boxes and product storage areas are equipped or are being equipped with [redacted] alerts which will [redacted] a member of the Engineering Department who can take immediate action.

Mr. Agrawal also pointed out during his visit that the space we have been using for a CRT is unusual and under-utilized from a volume standpoint. During his visit we reviewed the original mapping study with him and installed an additional temperature and humidity monitor which indicated the study was still accurate. The excursions were related to mechanical failures in the building. We have begun a mapping study to qualify a chamber which will be used rather than this room. We think that it was a good suggestion and have begun implementation. Because the room is a limited access, fire-proof room we will use it for document storage and archival.

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

Dates	# of Excursions	Humidity	Temperature	Total Length of Time
3/18-4/9/10	4	N/A	High	>14 hours
7/8-8/9/10	16	N/A	High	>2 days

You have no SOP that defines the monitoring and maintenance of your stability chambers and cold room. The stability chamber is not monitored on a frequent basis and has not been reviewed for adequacy since the sole qualification of the chamber in 1999.

We have modified our SOP for stability which includes the (b) (4) recording of all chambers including the cold room. Temperature excursions, high or low, will be brought to the attention of both Quality Control and Quality Assurance for a full assessment regarding potential impact on the product. We fully appreciate that if a temperature is low it may require the extension of a stability study and if a temperature is high then it must be evaluated to determine the immediate impact on the product as well as any potential compromises to an on-going study.

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

Date	# of Lots	# of Excursion Events	Total Time	Extreme Temp Recorded
6/12 – 7/7/09	8	7	> 25 days (I event = 23 days)	82.9 °F
2/19-3/8/10	8	5	>20 hours	74.8 °F
6/4 – 7/21/10	8	8	1 day	73.7 °F

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

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

We have implemented a system whereby the Engineering Department will immediately notify the Department of Quality Control and Quality Assurance if there are any temperature excursions in a critical environment. We have reviewed the handling issues with all partner facilities to ensure better management of our products during processing. We will continue to review the data loggers and will review all deviations. Mr. Agrawal also pointed out that our SOP did not include provisions with specific parameters for product handling, i.e. when a truck is loaded and unloaded. We have revised that SOP and agree that such parameters will not only make the management easier but will ensure that "an excursion" is really an excursion so that additional testing can be completed to assess product impact when necessary. We will use appropriate calculations to assess product impact (MKT). The use of (b) (4) logs will also allow us to correlate and distinguish product handling (human) from equipment malfunction. Attached is an annotated printout from the data logger covering the period 7/8/2010-8/9/2010. The use of a log book will allow us to definitely correlate the excursions throughout the work

week with movement of product in and out of the cold room. We are unable to provide a definitive reason for the event of 7/12/2010; the most plausible explanation is that the room door was not closed completely on Friday. We are in the process of adding a (b) (4) al alarm. We have discussed the (b) (4) . We do believe that the use of a log book will facilitate better control of excursions and enable us to put them in perspective. We will continue to review any incidents and evaluate the impact. Attachment 1.

2. **Deviations during the production of 4-Aminosalicylic Acid (AKA PAS) are not reviewed by your firm's quality unit at the time of occurrence. According to your firm's SOP #G0023-01 titled "Deviations"; your quality assurance department is responsible for reviewing and approving all proposed actions and corrective actions following deviations within (b) (4) of the event. Examples of deviations not reviewed by your QA unit within (b) (4) include:**

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

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

**** Production indicated that this may affect the (b) (4). The (b) (4) was (b) (4) (b) (4) and the production of the batch was continued.**

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

Our original Drug Master File defines the roles and responsibilities of both the Department of Quality Control and Quality Assurance as does our Organizational chart. The responsibilities of both departments were formalized in statements rather than SOPs. We have now replaced the statements with formal SOPs. The organizational chart will continue to be used for an overview for company assignments and responsibilities.

Mr. Agrawal's review and assessment of the (b) (4) malfunction was correct in that it was not resolved in a timely manner. However, the batch record does include an alternative (b) (4) (part of the approved equipment list) (b) (4) This (b) (4) was substituted which ensured that the product would in no way be compromised. The malfunctioning (b) (4) however, took an extraordinarily long time to repair which left us vulnerable without a qualified replacement part. The (b) (4) issue" is a perfect example as

to how, as a company, we need a better system to ensure coordination among departments. We have taken steps to ensure that deviations are immediately brought to the attention of Quality Assurance. Quality Assurance will in turn coordinate with both Quality Control and production to assess impact and coordinate an appropriate response.

Observation 4
Written procedures are not established for evaluations done at least annually and including provisions for a review of complaints and investigations conducted for each drug product.

Specifically, a) your quality unit failed to review all complaints and investigations related to finished drug products when conducting annual reviews. For example, the 2009 annual review of PASER Granules did not include a review of the 9 manufacturing investigations conducted for the product. Three of these investigations were for the same issue (moisture content failures during manufacturing).

b) You do not have an established procedure for evaluating finished drug products on at least an annual basis that would include a review of complaints and investigations. Your SOP titled "Product Quality Review" addresses annual reviews for APIs but not finished drug products.

We have revised our SOP to include finished dosage forms. All finished dosage forms are reviewed annually but the annual review was, in fact, separate from our annual summary of complaints and investigations. Under the revised SOP, Quality Control, Manufacturing and Quality Assurance will be combined into a single report. We agree that such a consolidated report will serve us better and will ensure compliance with the regulations.

Facilities and Equipment System
Observation 5

Appropriate controls are not established over computerized systems.

Specifically, computerized systems in your Quality Control Laboratory do not have sufficient controls to prevent unauthorized access to, changes to, or omission of data. Electronic data can be deleted from computerized systems connected to your (b) (4) and (b) (4) instruments with no audit trail to document such an event.

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

We have contracted with an IT engineer and have designed a server which will prevent uncontrolled access to the raw data. The data will be written to a secure server built of (b) (4) . This system will also be backed up onto a minimum of (b) (4) which will be (b) (4) . Both the (b) (4) and (b) (4) systems will be re-configured to have a manager password, individual analyst's passwords and an administrator password.

Until the servers are in place we will continue to back up all of the raw data on [redacted] which are [redacted].

All future instruments will include password protection and one-way data back up.

Observation 6
Buildings used in the manufacturing, processing, or holding of drug products are not maintained in a clean and sanitary condition.

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

Mr. Agrawal's observations were correct. We have revised the design of the room to include the removal of two exterior doors to address the environmental and maintenance concern. The kick molding was damaged and had not been brought to the attention of the Engineering Department. The Engineering Department has implemented a new work order system to address such problems in an orderly fashion. The work orders indicate level as critical, immediate action required, maintenance or improvement. When Critical / Immediate work is required the equipment or area is quarantined until the work is completed by Engineering and signed-off by Quality Assurance. Critical / Immediate repairs will be reviewed to determine what impact the work had on the product. Attachment 2.

We have also implemented status boards outside of each critical room and/or equipment. This should eliminate any confusion as to the state of the room and whether it can be used.

Observation 7

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

Specifically, you failed to calibrate and ensure the proper performance of a [redacted] (Serial # [redacted]) used during the production of the finished drug product PASER granules to [redacted], a critical parameter of the [redacted]. The [redacted] was due for calibration on June 30, 2010. Based on your firm's records, the [redacted] has been used on a [redacted] basis in the manufacturing process of more than [redacted] batches of PASER granules since June 30, 2010. In addition, I observed another [redacted] that is connected to your [redacted] with no tag or sticker to indicate its calibration status.

We performed a verification calibration of the [redacted] meter with a [redacted] and it was accurate. Our major concern is that the administrative system we had for ensuring that instruments and equipment are calibrated failed. We are finalizing a database which will [redacted] alerts for calibration due dates. A hard copy will be printed out for the coming month for the Director of Engineering and the department director and overseen by Quality

Assurance. We have also modified the Paser Batch Record to include a Start-Up record which includes a list of all equipment and calibration due dates. We will modify all records in the same fashion.

Production System
Observation 8

The process validation for a [redacted] increase in the batch size [redacted]) of the active pharmaceutical ingredient PAS is inadequate.

For example:

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

We did review the scale up with Mr. Agrawal and we agree that the scale up, despite the robustness of the process, should have been examined and reviewed under a protocol. We have developed a protocol to evaluate the process changes due to the increased batch size. We have [redacted] PAS since [redacted] and will do so under a formal protocol. The [redacted] validation batches will be placed on stability. Finished dosage form (PASER Granules) manufactured with the API from the validation batches will also be placed on stability.

The protocol will include a retrospective analysis of the critical parameters, operational ranges and acceptance criteria in the context of the [redacted]. The critical parameters for the [redacted] batch will be fully examined.

Observation 9

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

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

The PASER Granule batch record includes a method for the sanitization of the hose prior to use. This was done with approximately [redacted]. The sampling of the valve (microbiology) was done at the point of use (not using the hose). Microbiology was routinely run and results were well within the limits as established under our SOP and the USP. We recognize that the sampling should have been done using the hose since it was the point of use. The sanitization of the hose was part of our initial validation work of the [redacted] and incorporated into the batch record. Over the last three weeks we have re-validated the sanitization of the hose using [redacted]. As part of our revision of the PASER Granule record we have divided the record into three records: [redacted]. The microbiology data collected under the protocols support what we had been doing in the batch record. We have developed a new SOP to reflect the sanitization of the hoses. Microbiology will continue to be run at the point of use, i.e. the hose.

Our original [redacted] validation data as well as the re-validation data indicate that it is [redacted]. We removed the hose sanitation steps from the [redacted] Production record because the hose is used throughout the day on multiple batches. The record, prior to revision, did include [redacted]

Observation 10

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

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

We have always labeled the drums in pairs with pre-printed labels which include the lot number, gross, tare and net weight. We agree that additional safe-guards are appropriate. To address this observation we have numbered the drums in pairs (1/1, 2/2 etc). In addition to the numbering we have added color bands. We think that these additional markings will add two additional levels of assurance to prevent mix-ups and will also make control easier for the operators. During the last month we expanded the use of another (qualified) room in the manufacturing area. This will undoubtedly be much easier on the personnel and will facilitate organization and control during production. Attachment 3