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SUMMARY

This was a surveillance inspection of this OTC pharmaceutical manufacturer conducted per Detroit District work plan under FACTS assignment # 570809. The inspection was conducted per compliance program 7356.002 "DRUG MANUFACTURING INSPECTIONS". Inspection covered Quality System, Facility and Equipment System, and Production System.

Previous Inspection dated 7/8-17/02, noted 3 GMP deficiencies as follows: 1) change control documentation failed to identify justification for the change; 2) no SOP covering environmental monitoring frequency, location, and interpretation of results; 3) incomplete Facilities and Equipment Master Plan.

Current inspection revealed: One lot of Fiber Therapy which failed foreign matter routine testing was released without adequate justification; failure to follow SOP for cleaning dispensing equipment and room between lots of dissimilar material; failure to properly maintain and monitor temperature sensors located in the component and finished product warehouse; failure to maintain a equipment cleaning use log for bulk transfer (dispensing) equipment; failure to follow SOPs regarding deviation investigation and corrective actions; and one incident where environmental monitoring result exceeded action limit for mold count and no evaluation or investigation was performed.

Management promised written response within 30 days.

ADMINISTRATIVE DATA

Inspected firm:	L. Perrigo, Co
Location:	1761 Airport Park Ct Holland, MI 49423-9370
Phone:	(616) 392-2181
FAX:	
Mailing address:	1761 Airport Park Plaza Holland, MI 49423
Dates of inspection:	8/2/2005, 8/3/2005, 8/4/2005, 8/5/2005, 8/8/2005, 8/9/2005, 8/10/2005
Days in the facility:	7
Participants:	Patsy J Domingo, Investigator

HISTORY

This registered drug manufacturer has been in business since purchasing this facility from J.B. Laboratories in 1993. This OTC manufacturer produces psyllium based powdered fiber therapy products. NOTE: Due to the fact that psyllium can cause allergic reactions in some people, anyone visiting or working at this Perrigo facility should/must be psyllium sensitivity tested.

L. Perrigo Company corporate headquarters are located at 515 Eastern Ave., Allegan, MI 49010. In addition to this and the Allegan facilities Perrigo has a manufacturing facility, North Labs, located in Montague, MI; and in Greenville, SC. A newly acquired laboratory in India, Perrigo India, which performs acceptance testing of all psyllium lots prior to shipment to the United States. Perrigo's facility located in Mexico is utilized, among other things, to perform finish packaging activities for the powdered hot liquid products, Product numbers 555, 570, and 868, after the pouching process is complete.

Inspection history for this Perrigo location includes:

Inspection dated 7/8-17/02, noted 3 GMP deficiencies as follows: 1) change control documentation failed to identify justification for the change; 2) no SOP covering environmental monitoring frequency, location, and interpretation of results; 3) incomplete Facilities and Equipment Master Plan.

The inspection dated 5/9-7/2/01, noted 21 GMP deficiencies including: 1) failure to review Ethylene oxide (EtO) treatment of unmilled psyllium validation report in a timely manner (2 years later); 2) use of a bioburden reduction process despite knowledge that one of 3 validation batches exhibited failing results for three of the parameters tested; 3) available microbiological test data does not support the 2-log bioburden reduction documented in the "PERFORMANCE QUALIFICATION FOR THE PROCESSIGN OF PSYLLIUM" that was approved by management; 4) Protocol failures are not adequately justified or evaluated; 5)change (decreased to once annually) in the C of A residual limits verification test frequency for incoming raw materials is not justified by data; 6) annual raw material testing resulted in a failing ECH value yet acceptance based on C of A was allowed to continue; 7) basis for established residual limits could not be demonstrated; 8) established residual limits do not take into account method variability; 9) failure to follow SOP's; 10) annual product reviews not completed within established time frames; 11) data to support sampling plan could not be located; and 12) failure to develop an SOP for conducting validation of EtO treatment and retreatment processes.

JURISDICTION

The following is a list, see also **Exhibit F-12**, of drug products manufactured at this facility together with the Exhibit # for an example label:

POWDERS
Product #301, 100% Natural Fiber Original Texture Regular Flavor, **Exhibit F-1**
Product #303, Fiber Original Texture Orange Flavor, **Exhibit F-2**
Product #347, Fiber Smooth Texture Orange Flavor, **Exhibit F-3**
Product #366, Sugar Free Fiber Laxative Smooth Texture Orange Flavor, **Exhibit F-4**
Product #399, Sugar Free Fiber Therapy Orange Flavor, **Exhibit F-5**
Product #543, Fiber Therapy Orange Flavor, **Exhibit F-7**
Product #6J2, Fiber Powder Sugar Free, **Exhibit F-8**
Product #555, Regular Strength Night Time Flu, Cold & Cough, **Exhibit F-9**
Product #570, Maximum Strength Non-drowsy flu, serve cold & congestion, **Exhibit F-10**
Product #868, Max. Strength Night Time Flu, Serve Cold & Congestion Lemon Flavor, **Exhibit F-11**

CAPSULES

Product #512, Fiber Capsules, **Exhibit F-6**

Pre-Mixes
(b) (4) used to produce product 366AN
used to produce product 347BG
used to produce product 303

These products are contract manufactured under various customer labels including:
(b) (4) (**Exhibit F-1**);
(b) (4) (**Exhibit F-2/3**);
(b) (4) (**Exhibit F-4**);
(b) (4) (**Exhibit F-5**);
(b) (4) (**Exhibit F-6,9**);
(b) (4) (**Exhibit F-8**);
(b) (4) (**Exhibit F-10**).

Product is also labeled and distributed under Perrigo's own GOOD SENSE brand by Perrigo Company, Allegan, MI (**Exhibits F-7,11**).

INTERSTATE COMMERCE

Psyllium based drug products are all produced using raw psyllium which is imported from (b) (4) (b) (4) % of all drug products produced at this facility are sold in interstate commerce (see partial customer list above).

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Credentials were shown and FDA-482, Notice of Inspection, was issued to Nicholas Ford, QA/QC Chemist in the absence of local management who were offsite when I arrived. The following individuals were present throughout the inspection and provided requested information and documents during this inspection:

Christine Hassing, Airport Center Plant Manager

Leslie A. Paul, Quality Manager Airport Center/North Labs (beginning 8/1/05)
Kareena D. Parris, QA/QC Manager-Airport Center (ending 7/31/05) – new office Allegan, MI
Renee M. Robbins, Associate Director Quality Assurance – office at Allegan, MI

Scott Sterenberg, Internal/Contract Quality Audits

In addition, the following persons provided information or participated in the daily wrap up or inspection close-out meeting:
Sandy Hatten, Director Quality Assurance – office at Allegan, MI
David Schrage, Director of Manufacturing Services
Neil Muldoon, Manager of Maintenance & Facility Engineering
John Brown, Manager Continuous Improvement Tablets
Lisa McNeil, Associate Director of Validation (via phone)
(b) (6) Technical Support Specialist

By her own admission, Christine Hassing, Airport Center Plant Manager is the most responsible individual at this facility on a day to day basis. Ms. Hassing reports to Paul Weninger, Director of Operations who in turn reports to Greg Kurdys, Sr. Vice President Operations. Mr. Kurdys reports directly to John Hendrickson, Executive VP & General Manager Perrigo Consumer Healthcare who reports directly to David Gibbons. David Gibbons, Chairman, President & Chief Executive Officer is the most responsible individual at the corporate level. Organization Charts are attached as **Exhibits G-7/13**.

Quality organization is set up as follows: both Leslie Paul, QPC/NL Quality Manager and Kareena Parris, Finished Goods Manager report to Jerry Pando, Director QC Michigan; Renee Robbins Assoc. Director QA Operations reports to Sandy Hatten, Director QA Michigan. Both Mr. Pando and Ms. Hatten report to Eric Kolodziej, VP Quality & Compliance who reports to John Hendrickson who reports to David Gibbons as documented above.

FMD-145
Address any correspondence to Christine Hassing, Airport Center Plant Manager, 1761 Airport Court, Holland, MI 48423.

Address all other correspondence to:
David Gibbons, Chairman, President & Chief Executive Officer
L. Perriigo Company
502 Eastern Avenue
Allegan, MI 49010

MANUFACTURING/DESIGN OPERATIONS

Manufacturing operations remain as reported in the 7/8-11,15,17/02 inspection report. Pouching of Flu Cough & Cold powdered products (produced in Allegan and shipped to Holland in bulk), however, are currently on hold due to the need to reformulate these products to remove active ingredient pseudoephedrine.

This facility is equipped with a dispensing suite, [redacted] blenders (b) (4) [redacted], a Milling room, encapsulation room, and a capsule banding room. Packaging lines include: Line [redacted] - straight through fill and label, and also contains the capsule filler; Line [redacted] bright stock labeling, Line [redacted] bright stock filling; and Line [redacted] pouching line which is currently inactive due to reformulation of powdered products (555, 570, and 868) containing pseudoephedrine.

Laboratory activities include raw material ID's (Near IR) and LOD (oven), and swell volume testing of psyllium products. [redacted] HPLC's are used for Flu Cold Cough materials for North Labs (Montague). Micro samples (water, environmental) are sent to the Perrigo laboratory in Allegan, MI.

Products 399, Sugar Free Fiber and 543, Fiber Therapy are being discontinued once current stock is used up.

Psyllium Milling

The milling of raw psyllium occurs on a dedicated mill after bioburden reduction, by ethylene oxide treatment, at (b) (4) [redacted] a contract treatment facility. The milled psyllium, to be used for formulation 366 production only, is sent to (b) (4) [redacted] (b) (4) [redacted] for granulation. Psyllium milling is performed on dedicated equipment. Cleaning validation associated with the (b) (4) [redacted] bulk transfer system utilized as part of the Psyllium milling process was reviewed during this inspection. No deficiencies were noted.

MANUFACTURING CODES

Attached as **Exhibit G-1** is a document entitled "User Exit Functionality for Internal Batch Number Assignment" which describes the three categories for batch numbers. Essentially for the packaged batch number the 1st position (number) represents the last digit of the current year; the 2nd position (letter) represents the month (A-M, skipping I); the 3rd position (letter) indicates the plant with the letter R representing this Holland, MI facility; and the 4th - 7th positions (numbers) "rolling 4-digit number that is unique to the Year, Month and Site level".

QUALITY SYSTEM

During this inspection complaints (see EIR section below), deviations, OOS, Annual Product Reviews, environmental monitoring results and environmental trending were reviewed. In addition, cleaning validation for the (b) (4) (bulk transfer system) used in the manufacture of Psyllium intermediate materials was also reviewed; and process validation report for NVP Capsules.

Deviations reviewed include: (b) (4) (b) (4) (b) (4) See FDA-483 observation #1 regarding deviation (b) (4) and FDA-483 observation #6 regarding deviations (b) (4) (b) (4)

With regard to environmental monitoring see FDA-483 observation #6.

COMPLAINTS

Complaints reviewed during this inspection include the following:

1. #**30776**, dated 8/27/02 for product NVP-REG reporting container was full of bugs. As no lot number was provided, complaint flowchart required no investigation;
2. #**31592**, for lot #1KR0175/1J1272 found meal moth in product – grain is treated with methobromate
3. #**34772** dated 4/15/03, lot #1KR0046/1G2036 insects found. Batch record was reviewed, no other complaints for this lot.
4. #**36031** dated 6/16/03 lot 3CR0058 complaint of illness rash, nausea and drowsiness. Mouth burned for several hours. No other complaints, reserve sample was not evaluated
5. #**36327**, lot 3CR0079/3A1536 complaint of little wormy creatures. Did not send sample back. Response letter stated "Indian Meal Moth" have not been a problem at this facility.
6. #**47241** dated 4/25/05 another complaint from same consumer as above for the same problem.

Although I neglected to issue an observation regarding complaint handling for products produced at this location the following observations were noted:

1. no investigation is required or conducted when the lot number is not reported: example Complaint #30776 dated 8/27/02
2. failure to conduct a meaningful investigation: a) when insects were the noted problem for product 301 NVP Regular: 1) in that only a batch record review was documented for complaint #34772 dated 4/13/03; 2) customer did not send sample

back was documented for complaint #36327 dated 6/27/03. The response letter stated "Indiana meal Moth" have not been a problem at this facility; b) complaint of caused mouth to burn the documentation indicated no other complaints for the lot, and no sample returned by consumer (Complaint #36031 dated 6/16/03). Reserve samples were not evaluated for any of these complaints.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

Drug products failing to meet established quality control criteria are not rejected.

Fiber Therapy (543AC) batch 3M1393 was determined to fail the Foreign Matter routine testing performed on 12/23/03 and 1/19/04 as green particles later determined to be epoxy coating from green colored equipment carts used to transfer manufacturing parts between production and cleaning rooms were found in samples sent to the Quality Control Laboratory. The original particle documented as "Significant amount found" was lost. Resample of the lot found a second particle smaller in size but confirming the original failing result. Deviation (b) (4) justification for release of this lot and associated packaged lots included the statement "(b) (4) (b) (4) (b) (4) "

Reference: 21 CFR 211.165(f)

Supporting Evidence and Relevance:

Deviation # (b) (4) dated 1/19/04 (**Exhibit A-1/11**), was initiated after the laboratory found a foreign particle of significant size (1.5 mm x 0.75 mm) during routine foreign matter test (attached as **Exhibits A-12/14**) of Fiber Therapy batch 3M1393. A second sample, 1 sample from each of 4 super sacks (see request attached as **Exhibit A-27**), was obtained and submitted to the lab and a smaller particle (0.6 mm x 0.6 mm) was found. Both particles were green in color and following investigation determined to be green epoxy coating from the transfer carts (flaked off) used in the manufacturing areas. The analytical records for 3M1393 (**Exhibits A-15/28**) contains the original "Results of Investigation" which documents "Failure Confirmed" listing the resample result. This document was signed by Laboratory Management on 1/19/04 (**Exhibit A-23**). The Certificate of Analysis

for batch 3M1393 also dated 1/19/04 (**Exhibit A-15**) documents the disposition as "Rejected".

Review of the deviation write-up finds lot 3M1393 was the second lot processed since the equipment, (b) (4) had been cleaned and reassembled. Lot 3M1392 was also listed as affected by this foreign particle test failure (see **Exhibit A-1**). **Exhibit A-5** discusses the fact that the wash carts in use had green plastic coating on the shelves and that this coating can be scraped off while moving parts around on the shelves. The "Conclusion and Justification for Disposition" section of the deviation write-up (**Exhibit A-7**) states (b) (4) (b) (4) (b) (4) This document further states "(b) (4) (b) (4) (b) (4) ,

I requested and was supplied a copy of the MSDS referred to in Quality's justification for release of this lot, and is attached as **Exhibit A-29/35**. I questioned how they knew this MSDS was applicable to the epoxy coating on their carts. In response I was provided the Powder Coatings Product Data Sheet attached as **Exhibit A-36**.

Discussion with Management:

In discussing this investigation with John Brown, Technical Operations manager I pointed out that the investigation did not address the condition of the transfer cart(s) – condition of the remaining coating whether there were large sections of missing. I also pointed out that the statement "(b) (4) " was inaccurate since a second particle was found and documented.

OBSERVATION 2

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

SOP (b) (4) "Dispensing Cleaning Procedure" was not followed in that the "DISPENSING WASH CHECKLIST" was not performed between dispensing or transferring dissimilar materials as follows:

5/13/05 between premix (b) (4) lot 5D1214 and raw material (b) (4) (citric acid) lot #5014641
5/26/05 between raw material (b) (4) (Sucrose) lot 5023427and premix (b) (4) lot 5E0365

7/07/05 between premix (b) (4) lot 5F0886 and raw material (b) (4) (citric acid) lot 5016289
7/08/05 between raw material (b) (4) lot 5020286 and premix (b) (4) lot 5F0887
7/20/05 between premix (b) (4) lot 5G0357 and raw material (b) (4) lot 5020287

Reference: 21 CFR 211.67(b)

Supporting Evidence and Relevance:

The Dispensing Suite, actually one big room, is where raw materials are weighed out for the batch. Within this room is the (b) (4) Bulk Transfer Equipment for dispensing large supersacks and an area for weighing and dispensing from smaller containers as well.

SOP (b) (4) "Dispensing Cleaning Procedure" (**Exhibits B-1/17**) has attached to it two cleaning checklists. The first is the "DISPENSING WASH CHECKLIST" (**Exhibits B-10/15**) (b) (4) The second is the "DISPENSING CLEAN CHECKLIST" (**Exhibits B-16**) which is to be (b) (4) (b) (4) ". SOP (b) (4) "Cleaning procedure for (b) (4) and (b) (4)", page 15 of 26 (**Exhibit B-18**) contains a "MULTIPLE PRODUCT CAMPAIGN" chart which indicates whether a (b) (4) (b) (4) This document also states "(b) (4) ".

Product # (b) (4) listed in all 5 examples for this observation is a premix which is used to produce product #366AN. Product #366AN is a Sugar Free powder laxative. Review of the cleaning chart (**Exhibit B-18**), finds no reference for (b) (4). According to Perrigo management (b) (4) represents a reformulation of premix (b) (4) which is listed on the cleaning chart.

In the first example listed for this observation, dated 5/13/05, premix (b) (4) lot #5D1214 had been dispensed and the next material dispensed was raw material (b) (4) Citric Acid lot 5014641 as documented on the "Equipment Log for Manufacturing Area: Disp" (see **Exhibit B-31**). As documented on the DISPENSING CLEAN CHECKLIST (**Exhibit B-20**) attached to the Equipment/Suite Start-Up Inspection document (**Exhibit B-19**), and the equipment log, only a CLEAN was preformed. According to the cleaning chart (**Exhibit B-18**) (b) (4)

In the second example, dated 5/26/05, raw material (b) (4) lot 5023427 which is sucrose had been dispensed and the next material dispensed was the premix (b) (4) (sugar free), lot 5E0365, as documented on Equipment Log **Exhibit B-32**. As documented on Start-up Inspection and associated Dispensing Clean Checklist, **Exhibits B-21/22**, only a clean was

performed. Review of the cleaning chart (**Exhibit B-18**) finds raw materials are not listed and therefore a wash must be performed.

In the third example, dated 7/7/05, premix (b) (4) lot 5F0887 was dispensed followed by citric acid lot 5020286 (**Exhibit B-29**). The Equipment/Suite Start-up Inspection and associated Dispensing Clean Checklist (**Exhibits B-23/24**) verify only a Clean was performed when as previously discussed the cleaning chart does not list raw materials and therefore a wash was to be performed. The Manufacturing Equipment Log, however, originally documented that a clean was performed was crossed out to incorrectly reflect a wash was performed (**Exhibit B-29**). It is not clear when this edit was made as it was not footnoted, as other cross outs have been, with date and initials.

In the forth example, dated 7/8/05, Citric Acid lot 5020286 was dispensed, followed by a Clean rather than a wash, and then dispensed premix (b) (4) lot 5F0887 as documented on the dispensing room log (**Exhibit B-29**) and the Equipment/Suite Start-Up Inspection and associated Dispensing Clean Checklist (**Exhibits B-25/26**).

And in the fifth example, dated 7/20/05, premix (b) (4) was dispensed, followed by a Clean rather than a Wash, and then Citric Acid lot 5020287 as documented on the Equipment/Suite Start-Up Inspection and associated Dispensing Clean Checklist (**Exhibits B-27/28**) and dispensing room log attached as **Exhibit B-30**.

Discussion with Management:

Management promised a written response.

OBSERVATION 3

Procedures describing the warehousing of drug products are not followed.

SOP (b) (4) "Monitoring and Recording Temperature Readings at APC" calls for (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). Review of the alarms generated 12/03 - present revealed several instances where temperature sensors were in alarm (b) (4) or registering as (b) (4) (the default for malfunction) for extended time periods as follows:

Location	Alarm Began	Alarm Ended	Temperature registering as	# Days	Exhibits
Rack (b) (4) South	12/10/03	12/12/03	(b) (4) F	2+	C-6/7
Pole (b) (4) High	02/03/04	02/18/04	F	15	C-8/13
Pole (b) (4) Low	05/10/04	05/18/04	F	8	C-14/17
"	07/20/04	08/09/04	F	20	C-18/23
"	08/09/04	09/02/04	F	17	C-23/33
Pole (b) (4) High	10/03/04	10/08/04	F	5	C-34
"	10/10/04	10/23/04	F	13	C-34/36
"	10/24/04	10/28/04	F	4	C-36/37
"	11/04/04	12/16/04	F	42	C-37/38
"	12/16/04	03/19/05	F	93	C-38/40
Pole (b) (4) High	04/06/05	06/03/05	F	58	C-41/48

There is no data available documenting evaluation/investigation of the above sensor malfunctions, no documentation of maintenance performed, and no evidence of the existence of an excursion binder. Mean Kinetic Temperature, when calculated, includes these (b) (4) temperature readings.

Reference: 21 CFR 211.142

Supporting Evidence and Relevance:

Due to the extremely hot weather Michigan has been experiencing this Summer, I requested information on monitoring warehouse temperatures for this facility. Neil Muldoon, Manager of Maintenance & Facilities Engineering was brought in from Perrigo's Allegan location to discuss their system with me. Mr. Muldoon accompanied me on a walking tour of all of their temperature sensor locations throughout the warehouse. Mr. Muldoon provided me with a copy of a map of the warehouse with the locations of the various temperature sensors marked (see **Exhibit C-1**). I also requested SOP (b) (4) "Monitoring and Recording Temperature Readings at APC" (**Exhibit C-2/5**) for review. According to this SOP Engineering is (b) (4) (b) (4) (**Exhibit C-2**). In addition this SOP states (b) (4) (b) (4) (b) (4)

The SOP describes Daily Reports that are (b) (4) (b) (4)". These reports are to be (b) (4) (b) (4) The

temperature excursion warnings, according to SOP (b) (4), are (b) (4) (b) (4) (**Exhibit C-3**).

I requested the Excursion Binder be provided for my review. I was told it did not exist. I requested alarm reports generated 12/03 – present for my review. These are attached as **Exhibits C-6/60**. With Mr. Muldoon I began review of these alarm reports. I immediately noted low readings of (b) (4) According to Mr. Muldoon this is the default reading when the sensor is not operating.

The following is a description of the alarm situations listed for this observation:

#1 **Exhibit C-6/7** Although it appears this sensor was fixed as of 12/12/03, after registering (b) (4) for 2 days, some question remains in that the rest of the page (**Exhibit C-7**) is blank and the next page provided me began starts on 2/3/04 with no entries from 12/12/03 through 2/3/04 recorded.

#2 **Exhibits C-8/13** (Page 1-6) Again it appears the alarm was cleared however there is a date gap from 2/12/04 – 3/12/04.

#3-#5 **Exhibits C-14/16** As can be seen from these pages (Page 1-4), this sensor (Pole (b) (4)) was going into and out of alarm, registering (b) (4) F from May 10th through May 18th. As can be seen on **Exhibit C-17** the last entry is 5/18/04 at 8:17:16 and the rest of this page is blank. The next alarm printout I was given, **Exhibit C-18/23**, the first date is 7/20/04 (2 months later) and this same sensor (Pole (b) (4)) is still going into and out of alarm registering below (b) (4) F as low as (b) (4) F in July. Then on 8/9/04 the sensor registered (b) (4) F (**Exhibit C-23**) and again on 8/11/04 (**Exhibit C-24**), 8/12-14/04 (**Exhibits C-25/26**), 8/23/04 (**Exhibit C-29**), 8/25/04 (**Exhibit C-30**), 8/29-9/2/04 (**Exhibit C-32/33**), and finally disappearing from the alert list at 10:10:41 on 9/2/04. In between these (b) (4) F readings this sensor location was still registering below (b) (4) ° cycling into and out of alarm every few minutes.

#6-#10 **Exhibit C-34/40** Sensor location Pole (b) (4) first registered a (b) (4) F alarm on 10/3/04 (**Exhibit C-34**). On 10/8/04 the alarm reset (cleared) for the time period 22:10:40 – 22:23:56 (13 minutes) went back into alarm and back out within a few minutes. Then on 10/10/04 went into alarm at 5:42:05 (**Exhibit C-34**) and remained in alarm for 13 days until 10/23/04 (**Exhibit C-36**). From 10/24-12/16/04 this sensor went into and out of alarm many times, each time registering (b) (4) F (**Exhibits C-36/38**). Then on 12/16/04 it went into alarm and remained there solid for 3 months until 3/19/05 (**Exhibits C-38/40**).

#11 On 4/6/05 sensor Pole (b) (4) went into alarm at (b) (4) F and continued in/out for the next 2 months until 6/3/05 (**Exhibits C-41/48**).

In response to my concern over their temperature monitoring program, (b) (6) Technical Support Specialist presented me with a "MEAN KINETIC TEMPERATURE" report for the period 8/1/04 – 7/31/05 (**Exhibit C-61**). This report documents the average temperature for each of 52 weeks. I requested the data that supported this report and

questioned whether or not the (b) (4) °F temperatures would be included in the calculations. In response to my request I was provided 4 reports (**Exhibits C-62/65**) which for each location reports the highest and lowest temperature reached for the previous day. These reports are dated 1/1/05, 3/19/05, 4/16/05, and 6/4/05. As can be seen on the 1/1/05 document (**Exhibit C-62**) the "West Warehouse, NE High Elevation Sensor" lists -(b) (4) °F for both the highest value and lowest value. The same is true for "West Warehouse, NW High Elevation Sensor (**Exhibit C-64**) where the lowest value is listed as -(b) (4) °F and the Highest Value was (b) (4) °F which corresponds to the into and out of alarm documented on **Exhibit C-43** for the date 4/16/05. I was told that the negative numbers, which represent a sensor that is not working at all, are included in these calculations.

I requested data documenting any maintenance performed on these sensors. I was told no such documentation exists. Only calibration reports were available. The most recent calibration reports bear dates of 3/28/05 and 4/1/05 (**Exhibits C-66/85**). Each report indicates the sensor was "Found in Tolerance". I did not determine, however, the correlation between sensor's ability to read the temperature as tested during calibration and it's connectivity to the monitoring system.

Discussion with Management:

In response to my observations regarding the unevaluated alarm issues, investigation revealed excursion reports had not been printing out since a software change. According to Rene Robbins, Associate Director Quality Assurance a correction was implemented. In addition, an excursion binder was begun.

OBSERVATION 4

Written records of major equipment cleaning, maintenance, and use are not included in individual equipment logs.

Bulk Transfer System (b) (4) used for citric acid and sucrose dispensing does not have an equipment cleaning, maintenance and use log. Examples of material dispensed using this equipment include Citric Acid Anhydrous lot 5014641 dispensed on 5/13/05 and Sucrose lot 5023427 dispensed on 5/23/05.

Reference: 21 CFR 211.182

Supporting Evidence and Relevance:

The (b) (4) Bulk Transfer System is utilized to dispense from supersacks of sucrose and citric acid. This equipment is physically located within the Dispensing Suite. Hand dispensing operations are also conducted in this same room. The Dispensing Suite has one log, which is actually a room log, where dispensing and cleaning activities are currently recorded. An equipment log documenting cleaning and use of this bulk transfer system does not exist. Observation #2 above lists 5 instances were a "CLEAN" was performed rather than the "WASH" specified by SOP. It is unclear from review of the room logs what cleaning occurred for the Bulk Transfer System. Attached as **Exhibits B-29/32** are the room logs associated with the examples listed in observation #2 above. The two examples cited in this observation, Citric Acid lot 5014641 on 5/13/05 and Sucrose lot 5023427 on 5/23/05 can be found on **Exhibits B- 31/32**.

Discussion with Management:

Management acknowledged the need for a separate log covering the (b) (4) Bulk Transfer System.

OBSERVATION 5

Written production and process control procedures are not followed in the execution of production and process control functions.

A. Deviation (b) (4) was initiated for an error in raw material transfer that was noted on 10/6/04. SOP (b) (4) "Unplanned Deviation Process" was not followed in that it (b) (4) (b) (4) The deviation was not initiated until 11/24/04 and the corrective action, creation of an SOP ((b) (4)) implementing specific transferring procedures was not accomplished until 12/2/04.

B. Deviation (b) (4) dated 4/11/05 was initiated following a cleaning validation failure

associated with SOP (b) (4) "Cleaning procedure for the (b) (4)b) (4)". The SOP has been in effect since 11/26/03. The failure deamed to be as a result of the operator's failure to perform the hand cleaning portion of the SOP (on or about 3/18/05) and the Supervisor's failure to inspect the equipment following cleaning. The corrective action includes recommendation that a cleaning checklist be added to this cleaning SOP. As of 8/4/05 a cleaning checklist has not been initiated.

C. Deviation (b) (4) dated 1/17/05 initiated after finding plastic in sublot (b) (4) of lot 4M0896 has a documented short term action plan to interview the operator and no long term action plan.

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

Observation 5.a.
Deviation (b) (4) dated 11/24/04 (**Exhibits D-1/8**), documents a dispensing error (wrong lot number of sugar) that occurred on 10/6/04. The error was noted the next day (10/7/04) and inventory adjustments were made by 10/13/04 (**Exhibit D-6**). The documented root cause for the error was (b) (4) (**Exhibit D-1**). Nothing in this document indicates why it took 6 weeks to initiate the deviation. SOP (b) (4) "Unplanned Deviation Process" (**Exhibits D-9/28**) describes Immediate (short term) Corrective Action as an action to prevent recurrence with targeted completion within 30 days (**Exhibit D-12**).

Observation 5.b.
Deviation (b) (4) dated 4/11/05 (**Exhibits D-29/49**), documents a cleaning failure associated with validation activities. The root cause was determined to be due to the (b) (4) (b) (4) (b) (4) The documented corrective action was to add a cleaning checklist to the SOP. As of this inspection, the checklist had not been implemented. When discussing this matter with Lisa McNeil, Associate Director of Validation she defended the failure to institute the check list corrective action stating the cleaning validation was not complete. I pointed out that this cleaning procedure/SOP (b) (4) (b) (4) (**Exhibit D-50/55**) had been in use since 11/26/03 and that it continues to be utilized whether validation activities are complete or not. Equipment Log pages attached as **Exhibits D-56/58** document several "(b) (4) (s) performed using SOP (b) (4)

Observation 5.c.

Deviation (b) (4) dated 1/17/05 (**Exhibits D-59/68**) was initiated after finding a portion of the plastic bag from the sampling scoop inside the sample sent to the Quality Assurance laboratory as the foreign matter test sample. The recommendation from this investigation placed the remedy on the 6 mesh screen before packaging (**Exhibit D-62**) and did not include any sort of precaution related to opening the plastic bag housing the sampling scoop over the product container. The short term action taken (see **Exhibit D-63**) was to interview the employee who pulled the sample. No long term action was identified.

Discussion with Management:

A written response will be issued.

OBSERVATION 6

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

SOP (b) (4) "Environmental Monitoring at the Airport Center Facility" in that the May 2004 monthly "Environmental Monitoring - Air" result exceeded the action limit for mold count, result recorded as "TNTCC", and no evaluation was performed and an OOS investigation was not initiated.

Reference: 21 CFR 211.113(a)

Supporting Evidence and Relevance:
According to SOP (b) (4) (**Exhibit E-1/10**) (b) (4) (b) (4) (b) (4) (b) (4) (**Exhibits E-2/3**). Review of the (b) (4) environmental monitoring report for May 2004 and the attached (b) (4) Trend report (**Exhibits E-20/22**) found results over the action limits for mold count recorded for the month of May-04. The raw reporting data, attached as

Exhibits E-11/19, finds on the Air Sampling page (**Exhibit E-14**) results recorded as "TNTCC" (believed to mean too numerous to count colonies) in the Mold & Yeast column for the sampling location "Line (b) (4) – Center of Room". No data exists to show Quality made an evaluation of these results and a review of the OOS listing from 6/02 – present (**Exhibit G-2/6**) shows an OOS investigation was not conducted.

Discussion with Management:

A written response would be issued.

GENERAL DISCUSSION WITH MANAGEMENT

At the conclusion of this inspection, form FDA-483, Inspectional Observations, was issued to Eric W. Kolodziej, Vice President Quality. In addition to Mr. Kolodziej, the following individuals were present for this close-out meeting:
David Schrage, Director of Manufacturing Services
Kareena D. Parris, Quality Control Manager
Christine Hassing, Airport Center Plant Manager
Renee M. Robbins, Associate Director Quality Assurance
Sandy Hatten, Director Quality Assurance
Leslie A. Paul, Quality Manager Airport Center/North Labs

A written response was promised within 4 weeks.

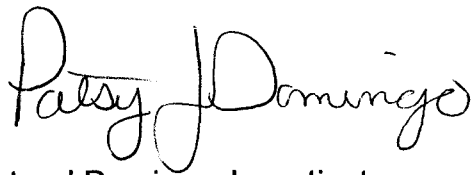
VOLUNTARY CORRECTIONS

SOP (b) (4) "Environmental Monitoring at Airport Center Facility" (**Exhibit E-1/10**), written in response to observation #2 from the 7/8-17/02 inspection was verified to be in effect. One example of cleaning validation approved 12/11/02 was reviewed which verifies the commitment that all cleaning validations were completed by May 2003.

EXHIBITS COLLECTED

A-1/11	Deviation (b) (4) dated 1/19/04
A-12/14	Procedure (b) (4) "Foreign Matter in Raw Materials"
A-15/28	Analytical record Batch 3M1393

A-2935	MSDS Epoxy
A-36	Product Data Sheet for Expoxy
B-1/17	SOP (b) (4) "Dispensing Cleaning Procedure"
B-18	Page 15 from SOP (b) (4) covering Multiple Product Campaign Clean Checklist
B-19/27	Cleaning records
B-29/32	Equipment Logs – Dispensing Room
C-1	Warehouse map of temperature & humidity sensor locations
C-2/5	SOP (b) (4) "Monitoring and Recording Temperature Readings at APC"
C-6/60	OOS temperature Alarm reports 12/10/03-8/2/05
C-61	Mean Kinetic Temperature calculation for the period 8/1/04-7/31/05
C-62/65	Daily Printer Test documents
C-66/85	2005 Temperature Indicator calibration reports
D-1/8	Deviation (b) (4) dated 11/24/04
D-9/28	SOP (b) (4) "Unplanned Deviation Process" dated 6/24/04
D-29/49	Deviation (b) (4) dated 4/11/05
D-50/55	SOP (b) (4) "Cleaning procedure for the (b) (4)
D-56/58	Equipment Logs – (b) (4)
D-59/68	Deviation (b) (4) dated 1/17/05
E-1/10	SOP (b) (4) "Environmental Monitoring at Airport Center Facility"
E-11/19	May 2004 Environmental Monitoring results
E-20/22	May 04 Environmental Monitoring Trend Report
F-1/11	Product Labels
F-12	Airport Center Product List
G-1	Batch Number Assignment explanation document
G-2/6	Printout of OOS 6/2/02 to Present
G-7/13	Organization Charts



Patsy J Domingo, Investigator