

Establishment Inspection Report

McNeil Healthcare, LLC
Las Piedras, PR 00771

FEI: 2650141
EI Start: 07/22/2008
EI End: 08/06/2008

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SUMMARY

The inspection of this manufacturer of human OTC drug products was conducted in accordance to SJN-DO FY-2008 work plan and FACTS assignment # 892290. It covered the Quality, Laboratory, Facilities & Equipment, and Production Systems. Coverage was given under CP 7356.002, Drug Manufacturing Inspections and CP 7356.021, Drug Quality Reporting System (DQRS)/NDA Field Alert Reporting.

Previous inspection of 03/2006 covered the Quality and Laboratory Control Systems and did not disclose adverse findings. It was classified NAI.

Current inspection disclosed the following objectionable conditions: established sampling plans and test procedures are not documented at the time of performance and laboratory procedures do not

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include the establishment of scientifically sound and appropriate test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality, and purity.

On 08/06/08, at the conclusion of the inspection, an FDA-483 form listing all cGMP objectionable conditions was issued and discussed with Ms. Nuria Ramírez Ordóñez, General Manager, who promised corrections and a written response within 15-30 working days.

No refusals were encountered. No samples were collected during this inspection.

ADMINISTRATIVE DATA**[JL]**

Inspected firm: McNeil Healthcare, LLC
Location: Carretera 183, Km 19.8
Bo. Montones
Las Piedras, PR 00771
Phone: 787-733-1000
FAX: (787)733-7600
Mailing address: P.O. Box 2009
Las Piedras, PR 00771-2009

Dates of inspection: 7/22/2008, 7/23/2008, 7/29/2008, 7/30/2008, 7/31/2008, 8/1/2008,
8/4/2008, 8/6/2008

Days in the facility: 8

Participants: Jorge L Lajara, Investigator
Iraida Ortiz, Chemist

On 07/22/08, We presented our credentials and issued an FDA-482, Notice of Inspection, to Ms. Nuria Ramírez Ordóñez, General Manager (**Attachment No. 1**). She accepted the FDA-482 and identified herself as the most responsible person of the firm. Ms. Ramírez delegated on Ms. Mayra Pujals, QA Manager and Ms. Brunilda González, Compliance Manager, the responsibility of assisting us during the inspection.

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On 08/06/08, we also issued to Ms. Ramírez the form FDA-483, Inspectional Observations (**Attachment No. 2**). Ms. Mayra Pujals, Ms. Brunilda González, and Mr. Eddie Carrillo, Quality Site Leader, were also present during the closing meeting. Mr. Larry Constable, VP Manufacturing, joined the discussion of the observations via conference call. (b) (2)

(b) (2)

(b) (2) FDA-483 which was issued to and discussed with Ms. Ramírez and the other firm's representatives. (b) (2)

(b) (2)

(b) (2) I, CSO Jorge Lajara, personally delivered the amended FDA-483 to the firm on 08/06/08. I discussed the amended FDA-483 with Ms. Mayra Pujals, QA Manager, who received and verified the document on behalf of Ms. Nuria Ramírez. She also provided to me a copy of the amended document which is included as **Attachment No. 3**.

The sections of this EIR written by me are identified by the initials JL after the title. Sections written by Chemist Iraida Ortiz are identified by the initials IO.

HISTORY

[JL]

McNeil Healthcare, LLC is a subsidiary of Johnson & Johnson Company, incorporated under the laws of the state of Delaware. The firm is engaged in the manufacture and package of solid dose non-prescription pharmaceuticals ((b) (4) solid dosage forms and (b) active ingredients) under the name brands of Tylenol, Motrin, Imodium, Roloids, Sudafed, Benadryl, and Pepcid. Their production volume is (b) (4) (tablets, caplets, gel tabs, and gel caps) annually. An aerial picture of the premises of the firm is depicted in **Exhibit No. 1**.

Copy of the current Certificate of Incorporation issued by the Department of State of the Commonwealth of Puerto Rico is submitted as **Exhibit No. 2**.

Any correspondence between the agency and the firm should be addressed to Ms. Nuria Ramírez to the address listed under "Administrative Data". Correspondence should also be addressed to Mr. Bob Miller, VP QA OTC and Global R&D Compliance and to Ms. Ashley McEvoy, President of McNeil Consumer Healthcare, to the following corporate address:

McNeil Consumer Healthcare
7050 Camp Hill Road
Fort Washington, PA 19034

Exhibit No. 3 includes a copy of the corporate and local organizational charts.

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Ms. Nuria Ramírez is the General Manager of McNeil Healthcare, LLC, Las Piedras, P.R. She reports to Mr. Larry Constable, VP Manufacturing OTC, who reports to Ms. María Nieradka, VP North American Supply Chain OTC. Ms. Nieradka reports to Ms. Ashley McEvoy, President of McNeil Consumer Healthcare.

Mr. Eddie Carrillo is the Quality Site Leader of McNeil Healthcare, LLC, Las Piedras, P.R. He reports to Mr. Paul Di Paolo, Sr. Director US/Puerto Rico OTC. Mr. DiPaolo reports to Mr. Bob Miller, VP QA OTC and Global R & D Compliance.

As of July 2008, McNeil Healthcare, LLC has (b) (4) regular employees and (b) (4) temporary employees. According to Ms. Ramírez, during the first half of the year, the firm operates in (b) (4) (b) (4). From 08/04/08, (b) (4)

The firm submitted the annual renewal registration of drug establishment to the FDA on February 25, 2008. It was validated by the agency on 04/15/08 (**Exhibit No. 4**). A corrected form FDA 2656 was submitted on May 09, 2008 since it was discovered that "Division of McNEIL-PPC, Inc." was incorrectly added to the firm name for McNeil Healthcare, LLC. Copy of the corrected form FDA 2656 and the letter sent to the FDA on this respect are submitted as **Exhibit No. 5**.

INTERSTATE COMMERCE

[JL]

Finished products manufactured by McNeil Healthcare, LLC LLC are sent to the following addresses for further distribution:

(b) (6)

(b) (6)

(b) (6)

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The percentage of finished product codes shipped to each distribution center is specified in the document included as **Exhibit No. 6**.

JURISDICTION**[JL]**

The firm manufactures pharmaceutical drugs which are subject to the FD&C Act and Title 21 Code of Federal Regulations. Products currently approved for commercial distribution are described in **Exhibit No. 7**. Current API suppliers are described in the document included as **Exhibit No. 8**.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**[JL]**

On 07/22/08, we presented our credentials and issued an FDA-482, Notice of Inspection, to Ms. Nuria Ramírez, General Manager of McNeil Healthcare, LLC. She identified herself as the most responsible person of the firm. Ms. Ramírez is responsible for the management of all plant operations, assuring compliance with company's procedures and regulations established by regulatory agencies. We observed evidence of Ms. Ramírez's authority when she:

- Accepted the form FDA-482, Notice of Inspection.
- Acknowledged having the duty, power, responsibility, and authority to detect, correct, and prevent deficiencies;
- Delegated on Ms. Mayra Pujals, QA Manager and Ms. Brunilda González, Compliance Manager, the responsibility of assisting me during the inspection.
- Received the form FDA-483, Inspectional Observations, and promised correction to the deviations found.

Mr. Eddie Carrillo is the Quality Site Leader. He is responsible for all activities related to the QA and QC operations. He also has responsibility for the coordination operations which assure product quality through compliance with cGMP as well as company policies and procedures. We documented Mr. Carrillo's responsibilities as follows:

- He identified himself as the most responsible person for the QA/QC operations.
- He acknowledged having the duty, power, responsibility, and authority to detect, correct, and prevent deficiencies;
- He accompanied us during the whole inspection and provided information and records.
- We observed him giving instructions to employees regarding information that we requested during the inspection.

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- He was present during the inspection’s closing meeting and committed to implement corrections to all observations.

The following individuals also participated in the inspection and provided relevant information:

- Ms. Mayra Pujals, QA Manager
- Ms. Brunilda González, Compliance Manager
- Mr. Frazer Costa, Formulation BU Manager
- Mr. Michael Alvarado, Finished Product BU Manager
- (b) (6) Warehouse Attendant
- (b) (6) Incoming QA Supervisor
- (b) (6) Warehouse Operator
- (b) (6) Warehouse Operator
- (b) (6) Warehouse Group leader
- Mr. Héctor Acosta, Granulation Manager
- (b) (6) First Shift Granulation Supervisor
- Mr. Luis Mustafá, Compression Manager
- (b) (6) Compression Supervisor
- (b) (6) Compression Area Engineer
- (b) (6) First Shift Coating Supervisor
- (b) (6) Second Shift Geldipping Area Supervisor
- Mr. Juan Carlos López, Analytical Laboratory Manager
- (b) (6) Senior Analytical Laboratory Supervisor
- (b) (6) Analytical Laboratory Supervisor
- (b) (6) Receiving Sample Coordinator
- Ms. María Selles, Packaging Manager
- (b) (6) Packaging Engineer
- (b) (6) First Shift Packaging Supervisor
- (b) (6) Senior Microbiology Laboratory Technician
- (b) (6) Microbiology Laboratory Supervisor
- (b) (6) Microbiology Laboratory Technician
- (b) (6) Compliance Specialist
- (b) (6) Senior Compliance Specialist
- (b) (6) QA Supervisor
- (b) (6) Microbiology Technician

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- (b) (6) Supervisor
- (b) (6) Chemist
- (b) (6) Chemist

FIRM'S TRAINING PROGRAM

[JL]

Procedure (b) (4) describes the requirements of the firm's training program. No significant training observations were disclosed during the inspection.

MANUFACTURING/DESIGN OPERATIONS

The firm currently manufactures and distributes products in the following profile classes:

- Tablets, Extended Release (TTR)
- Tablets, Prompt Release (TCM)
- Capsules, Prompt Release (CHG)
- Crude Bulk drugs (non - synthesized) [CRU]

We conducted the inspection of the site following the system's inspection approach according to the compliance program CP 7356.002 (Drug Manufacturing Inspections). The following profile classes were covered:

- TTR (Tablets, Extended Release) – Tylenol Arthritis Pain Extended Relief Caplets
- TCM (Tablets, Prompt Release) & CHG (Capsules, Prompt Release) – Motrin IB

We also covered other products while reviewing quality indicator areas such as NDA Field Alerts and complaints. The inspection comprised the following systems:

Quality System:

[JL]

My coverage of this system comprised a review of manufacturing investigations, NDA Field Alerts, batch record documents, training, product release, change control, product rejections, consumer complaints, complaint trends, DQRS complaints, CAPA, and standard operating procedures. No significant deviations were disclosed.

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Laboratory System:

[JL]

During this system's coverage, I visited the microbiology laboratory and covered the following areas: standard operating procedures, sample receipt and storage, training, analysis & report, documentation practices, laboratory investigations, equipment calibration, equipment qualification, culture media preparation, growth promotion testing, and test method validation. **Observations 1 & 2** under the caption "Objectionable Conditions and Management Response", address the failure to document sampling plans and testing procedures at the time of performance as well the failure to have adequate validation data available to support the microbiological swab monitoring technique.

[IO]

During my tour of the analytical laboratory, I observed how the sample receiving clerk receives a sample, enter the sample information in the laboratory electronic system and stores it until being analyzed. I also observed the storage of USP and in house working standards and how equipment out of calibration and/or damaged is identified.

I evaluated some laboratory procedures and verified the analysts' adherence to their requirements. I did not observe deviations. No deviations were disclosed either when I evaluated the calibration of some laboratory equipments.

Regarding investigations, my review included incidents related to analysts, instruments, extraneous peaks, expired standards, and out of specification results. All investigations were conducted as required by the corresponding procedures and focusing on a scientifically rationale. Time extensions were requested in some of them in order to perform a complete evaluation of the identified problem. The review did not disclose objectionable conditions.

The evaluation of laboratory training comprised the verification of training records of (b) (4) analysts in the following areas: Tylenol Severe Allergy Caplet Bulk Assay and Content Uniformity, Ibuprofen USP Chromatographic Purity, Tylenol Severe Allergy Dissolution Test, Tylenol PM Gel tabs Assay and Content Uniformity, and (b) (4). No deviations were disclosed.

My review of the Stability data of different lots of Motrin (Ibuprofen) which I randomly chose to verify the (b) (4) did not reflect objectionable conditions.

I also selected different lots of Tylenol Arthritis Pain Extended Release Caplets Finished Product batches and evaluated their raw data, calculations, and report. No deviations were found. During

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this review I observed a common practice of weighting the same amount of standard 1 and standard 2 for the (b) (4) and (b) (4). These weights were performed by different analysts on different dates.

The following table shows the lots, dates, and weights done for the (b) (4)

Lot Number	Date	Weight of Std. 1 (mg)	Weight of Std. 2 (mg)
(b) (4)	04/14/07	(b) (4)	(b) (4)
(b) (4)	05/03/07	(b) (4)	(b) (4)
(b) (4)	04/17/06	(b) (4)	(b) (4)
(b) (4)	01/04/06	(b) (4)	(b) (4)
(b) (4)	05/17/05	(b) (4)	(b) (4)
(b) (4)	07/02/05	(b) (4)	(b) (4)
(b) (4)	10/01/05	(b) (4)	(b) (4)
(b) (4)	10/11/06	(b) (4)	(b) (4)

Lots, dates, and weights for the assay test were the following:

Lot Number	Date	Weight of Std. 1 (mg)	Weight of Std. 2 (mg)
(b) (4)	03/11/08	(b) (4)	(b) (4)
(b) (4)	05/20/08	(b) (4)	(b) (4)

I individually interviewed (b) (4) analysts from the analytical laboratory who performed standards 1 and 2 preparations for the (b) (4) (b) (4) analysts' answers were similar regarding how they perform the weight, preparation, and storage of standards 1 and standard 2. Also, (b) (4) analysts (b) (4) of standard 1 and standard 2 specified in the product method.

I explained to (b) (6) Mayra Pujals and Mr. Eddie Carrillo my concern about this practice since these weights are questionable. I found that the validation of Tylenol Arthritis Pain ER Caplets specifies the following statement for the standard preparation for assay and content uniformity tests: "Transfer 130 mg of acetaminophen, USP RS or WRS accurately weighed". I also observed that for the standard preparation for the dissolution test, a

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statement specifies the following: “Transfer 144.4 mg of acetaminophen, USP RS or WRS, accurately weighed”. Nevertheless, the current laboratory method let the analyst weigh about (b) (4) and (b) (4) for each test. I asked (b) (6) what she understands for the word “about”. Both, (b) (6) and (b) (6) declared that (b) (4) I suggested to (b) (6) to avoid this practice since these weights are questionable and their procedure permits a (b) (4).

Facilities & Equipment System:

[JL]

Coverage of this system included an evaluation of standard operating procedures, equipment cleaning and storage, equipment identification, calibration & maintenance, documentation practices, building conditions, cleaning of facilities, equipment qualification, environmental monitoring, water monitoring & testing, and microbiology trending results. My review did not disclose any adverse findings.

Production System:

[JL]

My coverage of this system included a visit to the manufacturing areas and a review of standard operating procedures, in-process controls, batch record documents, and personnel practices. No adverse findings were disclosed.

MANUFACTURING CODES

[JL]

Lot numbers for commercial products are automatically assigned by the (b) (4) following SOP (b) (4). An alphanumeric packaging lot number consisting of six (6) characters is assigned according to the format “AAANNN”. The first “A” represents the year, the second “A” represents the month, the third “A” represents the plant (A=Las Piedras), and the characters “NNN” represent the sequential number assigned to the batch.

COMPLAINTS

[JL]

Consumer complaints received at the firm are handled following the local SOP (b) (4) (Las Piedras Complaint Receipt and Investigation) and the corporate SOP (b) (4). During the

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inspection, I reviewed the actions taken by the firm in response to the following DQRS Complaints and Consumer Complaints:

- 1) MSB File Number: (b) (4) Extra Strength Tylenol Cool Caplets, Lot # JDA 181,
Expiration Date: 04/06 / Consumer Complaint - Injury Report # (b) (4)

Complainant claimed that her mother purchased a bottle of the above referenced product on 08/14/06; four (4) months past its expiration date. The complainant took one (1) caplet and her father took two (2) caplets at the same time on 08/15/06. They both developed within minutes a burning sensation in their mouths and throats that lasted for at least eight (8) hours. They both were nauseous and the complainant reported that she vomited once. According to her, there was no evidence of tampering to the product bottle.

The investigation performed by McNeil Healthcare, LLC did not reveal any unusual circumstances during the manufacturing and packaging process of this lot. No adverse findings were disclosed during the evaluation of the retain samples. Analytical testing performed prior to release the lot complied with the specified acceptance criteria. Satisfactory results were as well obtained for the testing performed on the returned complaint sample. I reviewed the complaint trend reports of the firm and no adverse findings were disclosed. The DQRS Complaint and the Complaint # (b) (4) are included in **Attachment No. 4**.

- 2) MSB File Number: (b) (4) Regular Strength Tylenol Tablets, Lot # LPA 120,
Expiration Date: 10/09

This complaint reported the finding of twelve Extra Strength (500 mg) Tylenol tablets in a 100 count bottle of Regular Strength (325 mg) Tylenol tablets (100's).

The complaint bottle was received at the firm without the product carton. It contained 24 Regular Strength (325 mg) Tylenol tablets and 10 Extra Strength (500 mg) Tylenol tablets. The investigation performed by the firm did not disclose any further complaints on the subject lot. The review performed on the manufacturing and packaging batch records did not reveal atypical conditions that could be associated to the complaint. Four bulk lots of Regular Strength (325 mg) Tylenol tablets were used to package lot LPA 120. The product packaged prior to it was Extra Strength Cool caplets and not Extra Strength tablets. No adverse findings were disclosed upon evaluation of the lot's retain samples. No quality related situation could be determined or identified as a potential cause of the reported mix-up.

I reviewed the corrective actions that the firm has implemented through the years to avoid line clearance incidents and mix-up complaints. Among the line clearance improvements made are the following:

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Area	Improvement
SOPs, Guidelines, and Documents	Standardized work between manufacturing and QA / (b) (4) Modified SOPs
Equipment Design	Lights installation to the case packer and cartoner machines / Installation of (b) (4) (b) (4) Installation of (b) (4) (b) (4)
Housekeeping and Facilities	Improvement in the organization of the packaging area.
Employee Awareness	Employee participation in (b) (4) (b) (4) and in the discussion of improvement areas.

The firm's action plan also included the following preventive measures:

- Established a plant-wide awareness program.
- Implemented (b) (4) the manufacturing and packaging area.
- Trained and certified QA personnel, packaging operators and mechanics in the line clearance procedure.
- Revised the packaging line cleaning procedures and (b) (4) to be cleaned and verified by mechanics and QA personnel.
- Improved the (b) (4)
- Revised the cleaning procedure of (b) (4)
- Placed cleaning guidelines in form of visual aids in the processing areas.
- Enhanced packaging lines current partitions.
- Modified the reject stations in the packaging lines to ensure expulsion of bottles from the line.
- Modified the buckets cleaning procedure to include (b) (4)
- Implemented the SOP (b) (4) for manufacturing processing equipment cleaning/clearance process.
- Purchased (b) (4)

I reviewed the complaint trends since 2005 and observed a reduction in the reported mixed-product category. Among the actions taken, the firm continuously focuses in the close monitoring of the

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effectiveness of the implemented corrective actions. **Attachment No. 5** includes the DQRS Complaint.

RECALL PROCEDURES

[JL]

Procedure (b) (4) defines the requirements for assessing any potential product recall promptly and for implementing recall activities at McNeil Healthcare LLC, Las Piedras, P.R. No recalls were covered during this inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

[JL]

Observations listed on form FDA 483

LABORATORY SYSTEM

OBSERVATION 1

Established sampling plans and test procedures are not documented at the time of performance.

Specifically,

Procedure (b) (4) describes the requirements for the microbiological surface monitoring program of manufacturing equipment. (b) (4) and (b) (4) are the methods allowed in the procedure to perform the sampling. I reviewed documents related to the 2007 & 2008 monitoring of the (b) (4) and packaging areas, which was conducted using the swab technique. I observed that the elapsed time between the monitoring of different equipment parts was (b) (4). An interview held with an employee who performs the monitoring revealed that the required sampling is not documented immediately in the corresponding laboratory worksheet. Details such as sampling time, sampling date, location, and equipment are documented in the (b) (4) which contains the swab. The (b) (4) is discarded upon (b) (4) into the laboratory worksheet. Based on the detailed explanation provided by the employee regarding the sampling procedure, as well as other steps that would be necessary to take the sample, such as moving from one part of the equipment to another, the inspection disclosed that it is physically impossible to have an (b) (4) between different swab samples.

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Reference: 21 CFR 211.160(a)

Supporting Evidence and Relevance:

The firm follows the SOP (b) (4) for the microbiological monitoring of equipment cleaning (**Exhibit No. 9**). According to the procedure, the monitoring can be conducted using swab samples (**Exhibit No. 9, page 8**), (b) (4) (**Exhibit No. 9, page 10**) or (b) (4) (**Exhibit No. 9, page 10**). According to (b) (6) the laboratory always uses the swab method to perform the sampling. Submitted as **Exhibit No. 10** are copies of the monitoring conducted at the (b) (4) and packaging areas during 2007 & 2008. It can be observed that for the sampling conducted by (b) (4) different employees, the elapsed time between the monitoring of different equipment parts was (b) (4). On 08/04/08, I interviewed (b) (6) who is a Microbiology Technician that performs the surface monitoring of manufacturing and packaging equipment. (b) (6) told me that when he conducts the monitoring, he brings with him a picture manual which depicts the specific equipment parts that he needs to sample. He also brings with him the (b) (4) containing the sampling swab. The interview disclosed that information such as sampling date, sampling time, location, and equipment monitored is not documented immediately in the corresponding laboratory worksheet. According to (b) (6) he documents such information on the test tube and then transcribes it to the worksheet once he arrives at the laboratory. The test tube is discarded upon documenting the information in the laboratory form. (b) (6) also provided a detailed explanation on the procedure that he follows to conduct the sampling. It included steps such as moving from one part of the equipment to another, which would be necessary to take the sample. Based on the explanation provided by (b) (6) it is physically impossible to have an elapsed time of one (1) minute between different swab samples.

Discussion with Management:

Mr. Eddie Carrillo and (b) (6) acknowledged the observation and promised to implement corrective measures. During the closing meeting of the inspection, Mr. Carrillo and (b) (6) told me that the SOP will be changed to require that all sampling/testing must be documented in the corresponding worksheet immediately. In the meantime, employees were alerted to bring the reporting document with them when performing the surface monitoring.

OBSERVATION 2

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that components and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

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The microbiological surface monitoring of equipment is conducted following the frequencies and sampling methods specified in the SOP (b) (4) The monitoring conducted using the

(b) (4)

(b) (4) Once a sample is taken, the swab is returned to the (b) (4) and (b) (4) and (b) (4)

(b) (4)

However, the validation data available to support the swab monitoring technique is inadequate since it comprises the processing of the sample using the (b) (4)

(b) (4) described in your test procedure.

Reference: 21 CFR 211.160(b)

Supporting Evidence and Relevance:

Pages 8-9 of Exhibit No. 9 describe the swab method used by the firm to conduct the microbiological surface monitoring of manufacturing and packaging equipment. The method does not specify the type of swab used. (b) (6) told me that the laboratory uses a (b) (4)

(b) (4)

(Exhibit No. 11). The method requires the

(b) (4)

Upon sampling a (b) (4)

(b) (4)

(b) (4)

(b) (4)

I requested to see the validation data

that supports this swabbing method. (b) (6) gave a copy of the Validation Report #

(b) (4)

which was approved on 01/24/00 (Exhibit No.12). I observed that the procedure

followed for this validation exercise comprised the evaluation of the commercial sampling kit

(b) (4)

and the (b) (4)

However,

the (b) (4)

Exhibit

No.12, page 12). The (b) (4)

Exhibit

No.12, page 9) and not the (b) (4) described in the SOP (b) (4) (Exhibit No. 8,

pages 8-9). Also, the study revealed that the cotton swab showed a lower recovery of the challenge

(b) (4)

(Exhibit No.12, page 4). The conclusion of the study

recommended the (b) (4) Exhibit No.12, page 4).

Discussion with Management:

(b) (6) and Mr. Eddie Carrillo acknowledged that the validation report shown to me does not support the swabbing method currently described in the SOP (b) (4) Both firm representatives promised to take immediate corrective measures. During the inspection's closing meeting, Mr. Carrillo told me that the firm will perform a revalidation of the swab recovery method.

REFUSALS

[JL]

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No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT**[JL]**

On 08/06/08, we held an exit meeting with Ms. Nuria Ramírez Ordóñez, General Manager, to discuss the results of the establishment inspection. We issued to her a form FDA-483 containing two (2) objectionable observations (**Attachment No. 2**). The following people were also present:

- Mr. Eddie Carrillo, Quality Site Leader
- Ms. Mayra Pujals, QA Manager
- Ms. Brunilda González, Compliance Manager
- Mr. Larry Constable, VP Manufacturing (joined the discussion via conference call)

Each observation had been fully explained during the inspection. Upon reviewing and acknowledging the observations written in the FDA-483, (b) (6) and Mr. Carrillo promised a written response to agency within 15-30 working days.

We explained to the firm officers that the processes that we reviewed covered only a small portion of the firm's operation. We reminded them that it is their firm's responsibility to assure compliance with established regulations during the day-to-day operations. We told them that the prime purpose of the discussion was to call the attention to objectionable practices or conditions. We also warned them that the conditions listed in the FDA-483 may, after further review by the Agency, be considered to be violations of the FD&C Act or other statutes. We explained as well that legal sanctions available to FDA may include seizure, injunction, civil money penalties, and prosecution, if establishments do not voluntarily correct serious conditions.

The closing meeting was then adjourned.

ADDITIONAL INFORMATION**[JL]****I. NDA Field Alerts:**

The following NDA Filed Alerts were covered during this inspection:

Establishment Inspection Report

McNeil Healthcare, LLC
Las Piedras, PR 00771

FEI: 2650141
EI Start: 07/22/2008
EI End: 08/06/2008

1) NDA Field Alert on NDA 19-012, dated 08/09/07, Motrin 200 mg IB Caplets, Lot MDA 081, 100 Count, Expiration Date: 01/09

During a retrospective evaluation of manufacturing investigations issued during 2006, it was found that investigation # (b) (4) was issued due to a missing coating solution batch record for Motrin IB Caplet, material # (b) (4) batch MDA0000862. That investigation was approved on 05/19/06, recommending the release of the lot based on the absence of problems during the coating and printing process and the satisfactory results of the analytical finished product release tests. On 08/02/07, it was identified that the investigation could be enhanced to include additional supporting data that could demonstrate that the coating solution was prepared according to the established formula. It was also decided to notify the findings to the agency through a field alert report.

The firm performed an evaluation which comprised the following aspects:

- (b) (4)
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The results of this evaluation revealed that the coating solution was prepared according to the established formula. The firm supported this conclusion with the satisfactory visual inspection results of the coated product, the satisfactory analytical testing results, and the absence of complaints on this lot. As established in the original investigation, the incident's root cause was correlated to human error. Preventive actions taken to avoid recurrence included:

- Evaluation of the controls established in the SOP (b) (4) Procedure for the Creation, Handling, and Control of Log Books and Checklist)
- Procedures (b) (4) and (b) (4) were modified to include the instruction to maintain the packaging batch record in use inside the labels cage.
- Manufacturing operators and supervisors were retrained in the requirements of the SOP (b) (4) (b) (4) Issuance, Handling and Control of Manufacturing Batch Records), emphasizing in the batch records pick-up and delivery process.
- QA technicians were retrained on the SOP (b) (4) section (b) (4) which focuses on batch records pending investigations and the correct handling of these records.

Establishment Inspection Report

McNeil Healthcare, LLC
Las Piedras, PR 00771

FEI: 2650141
EI Start: 07/22/2008
EI End: 08/06/2008

My evaluation of the annual product review of Motrin IB Tablets and Caplets and the product's complaint files did not disclose any adverse trend. The NDA Field Alert Report is included as **Attachment No. 6**.

2) NDA Field Alert on NDA 19-012, Motrin 200 mg IB Caplets; 50, 75, and 150 Counts and NDA 19-872, Tylenol Arthritis Extended Release Caplets (TAR); 24, 50, 100, 225, and 290 Counts

Batches manufactured between February 18 to April 16, 2008 / Expiration Date: Between November 2010 and April 2011.

This field alert was issued in response to a programming mismatch detected between the (b) (4) and the (b) (4)

It was (b) (4)

(b) (4)

(b) (4)

The investigation performed by the firm disclosed that only the (b) (4) had the temperature mismatch. The incident's root cause was correlated to a human error during the replacement of the temperature transmitter on 02/18/08. Specifically, it was found that the

(b) (4)

(b) (4)

The (b) (4) A technical assessment and an in-depth evaluation of all batches coated in the (b) (4) since (b) (4) to (b) (4) were conducted. Among the areas appraised were: compliance with manufacturing parameters, in-process quality attributes, analytical results (assay, impurities, dissolution profiles), and consumer complaints. As a result of this assessment, it was concluded that the exposure to the elevated coating process temperature did not affect the quality and integrity of the product lots involved. Personnel involved in the incident were retrained in the corresponding standard operating procedures. As a continuous preventive action, the firm will continuously monitor any customer complaints on the impacted batches. In addition, packaging lot 08EMC041 of Tylenol Arthritis Extended Release Caplets and packaging lot SBA305 of Motrin 200 mg IB Caplets were placed on marketed stability. These are representative batches from the period impacted by the incident.

I reviewed the complaint files and the annual product review for TAR Caplets and Motrin IB Caplets and did not observe any adverse trend. The NDA Field Alert Report is included as **Attachment No. 7**.

II. Investigation Report on ES Tylenol Rapid Release Gel Caps

Establishment Inspection Report

McNeil Healthcare, LLC
Las Piedras, PR 00771

FEI: 2650141
EI Start: 07/22/2008
EI End: 08/06/2008

I reviewed the investigation performed by the firm on March 2007 regarding 446 cases of ES Tylenol Rapid Release Gel Caps, Lot PBA023, which were stolen from a trailer while being delivered from Jacksonville, FL to one of the firm's distribution centers located in Olive Branch, MS. According to the investigation, the incident occurred while the driver took a four (4) hours rest.

The firm put on hold and later destroyed the remaining portion of lot PBA023 (1,934 cases). The cases of three additional products (ES Tylenol Caplets Lot PBA014, Imodium AD Caplets Lot PBA096 & Imodium AD Caplets Lot PBA111) which were being transported in the same vehicle were also put on hold. These were later release upon careful examination and confirmation that there were no tampering signs. Up to date, no complaints that could be related to this incident have been received.

As actions to prevent recurrence, the firm revised the internal procedures to increase the security for the transportation of products. No further diversion issues have been reported. Copy of the notification sent to the SJN-DO is included as **Attachment No. 8**.

SAMPLES COLLECTED

[JL]

No samples were collected during this inspection.

VOLUNTARY CORRECTIONS

[JL]

During the inspection, (b) (6) showed to me a revision of the SOP (b) (4) (b) (4) which was made in order to (b) (4) (b) (4)

Establishment Inspection Report

McNeil Healthcare, LLC

Las Piedras, PR 00771

FEI:

2650141

EI Start:

07/22/2008

EI End:

08/06/2008



Jorge L Lajara, Investigator



Iraida Ortiz, Chemist