TABLE OF CONTENTS

SUMMARY

The inspection of this human OTC drug manufacturer was conducted as per SJN-DO work plan FY-06 and FACTS assignment 731288. The cGMP inspection covered Quality System & Laboratory Control System. This inspection also covered NDA Field Alert for Acetaminophen 160 mg corresponding to Jr. Tylenol Meltaways Bubblegum and Grape flavors. 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 dated 06/22/05 reported label deficiencies in the following products: Children's Tylenol Meltaways Tablets 80 mg, Junior Tylenol Meltaways Tablets 160 mg, and Children's Tylenol Soft Chewable 80 mg. As a result, the firm conducted a recall of the aforementioned products. An untitled letter was issued. The inspection was classified OAI.

Previous inspection dated 02/23/05 covered the Quality, Facilities & Equipment, Production and the Laboratory Control System. The inspection revealed deficiencies to the cGMP's including: mix-ups of drug products during packaging operations some of which can be traceable to consumer complaints; incomplete or inadequate inspection of packaging lines; inadequate calibration of a gas chromatograph;

the quality control unit is not involved in laboratory investigations and does not always perform consumer complaint investigations; and lack of stability indicating test methods for certain products containing acetaminophen product. The inspection was classified VAI.

The current inspection found corrections of previous deficiencies and did not disclose any significant objectionable conditions.

No Form FDA-483 was issued.

No samples were collected during the current inspection.

ADMINISTRATIVE DATA

Inspected firm:	McNeil Consumer and Specialty Pharmaceuticals
Location:	Km 18 Rd 183
	Bo. Montones
	Las Piedras, PR 00771
Phone:	787-716-7700
FAX:	(787) 733-7692
Mailing address:	P.O. Box 2009
	Las Piedras, PR 00771-2009
Dates of inspection:	03/23/27-30 & 04/07/2006
Days in the facility:	06
Participant:	Jose E Melendez, Investigator

McNeil Consumer and Specialty Pharmaceuticals is registered with FDA under CFN# 2650141. A copy of the most recent registration was submitted on January 25, 2006. **Refer to Exhibit 1.**

On 03/23/2006, I presented my credentials and issued the Form FDA-482, Notice of Inspection, to Mr. Francisco R. Negrón, General Manager, who identified himself as the individual with most responsibility in the firm. Other individuals present during the opening meeting were:

- Mr. Walter Maldonado, QA/QC Manager
- Ms. Esther Cintrón, Manufacturing Plant Manager
- Ms. Brunilda González, Compliance Manager

- Ms. (b) (6), Compliance Specialist

I explained to them the purpose of the inspection. Mr. Negrón stated that Mr. Maldonado had his authorization to accompany me and provide all information requested during the inspection. Then, Mr. Maldonado coordinated a tour through the manufacturing, laboratory and packaging areas.

The closing meeting was performed on 04/07/2006. No significant deviations were documented during this inspection; therefore, no Form FDA-483 was issued. However, I reviewed and discussed with management all the information covered during the inspection. Individuals present during the closing meeting are listed below.

- Mr. Francisco R. Negrón, General Manager
- Mr. Walter Maldonado, QA/QC Manager
- Ms. Esther Cintrón, Manufacturing Plant Manager
- Ms. Brunilda González, Compliance Manager
- Ms. (b) (6) Compliance Specialist
- Ms. Vilmarie Walker, Procurement & Logistics Manager
- Ms. Wanda Cancel, QA Manager

HISTORY

McNeil Consumer & Specialty Pharmaceuticals 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) under the name brands of Tylenol, Motrin, Imodium and Pepcid. Their production volume is about (b) (4) (tablets, caplets, gel tabs, and gel caps) annually.

Any correspondence to corporate official should be addressed to

Mr. William C. Weldon, Chief Executive Officer
1 Johnson & Johnson Plaza WT 1101 New Brunswick, NJ
08933 US
E-mail: wweldon@[illegible]rus.jnj.com

INTERSTATE COMMERCE

Products manufactured by the firm are shipped to the Continental US distribution centers.
For example:

350 Salem Church Road
Salem #3 Building
Mechanicsburg, PA 17055
Tel. 717-766-0746

11244 South Distribution Cove
Olive Branch, MS 38654
Tel. 901-368-8960

9211 Kaiser Way
Fontana, CA 92335
Tel. 909-350-6980

JURISDICTION

All the products currently manufactured by the firm are subject to the FD&C Act and the Title 21 Code of Federal Regulations Section 211. **Exhibit 2** listed all the commercial products manufactured by McNeil Consumer & Specialty Pharmaceuticals in Puerto Rico.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Exhibit JEM 3 listed the individuals that participated and/or provided relevant information during the inspection:

Mr. Francisco R. Negrón, General Manager participated briefly during the inspection. Mr. Negrón's responsibilities include the following: assures operations comply with the company's and regulatory agencies' regulations; maintains relationship with government agencies; assures product integrity through compliance programs among others. Mr. Negrón reports to Mr. M. Nieradka, VP Operations. Mr. Nieradka reports to Mr. C Watts, Worldwide President McNeil Consumer. Mr. Watts reports to Mr. R. Crane, Company Group Chairman. Mr. Watts reports to Mr. C.A. Poon, Worldwide Chairman Medicines & Nutritional Executive Committee. Mr. Poon reports to Mr. W.C. Weldon, Chief Executive Officer whose offices are located at Johnson & Johnson Plaza WT 1101 New Brunswick, NJ.

Correspondence to Mr. Weldon should be addressed to the mailing address under the caption "***HISTORY***".

Mr. Negrón has the decisional power to correct any deficiency encountered during this inspection. Mr. Negrón's authority was evidenced through the orders that he gave to Mr. Maldonado, QA/QC Manager and Ms. Brunilda González, Compliance Manager during the EI, and by accepting the Forms FDA 482.

Mr. Walter Maldonado is the QA/QC manager. He is responsible for maintaining laboratory operations in compliance with applicable regulations. He is also responsible for the coordination of operations to assure product quality; assuring compliance with cGMPs as well as company policies and procedures; and developing strategies to improve efficiency, and control of operations, among others. He reports to Mr. Robert Miller, VP Quality Sciences & Compliance Division. Mr. Maldonado authority was evidenced through the orders that he gave to the personnel that participated during the EI, and the corrective actions that he implemented during the inspection.

Exhibit JEM 4 includes organizational charts for the local and global organization.

PRODUCTS

The firm is engaged in the manufacture and package of solid dose non-prescription pharmaceuticals (b) (4)

During the inspection I covered the following profile classes:

- Tablets, Prompt Release (TCM): Tylenol Common Products, & Tylenol PM Caplets.
- Tablet Extended Release (TTR): Tylenol Arthritis Pain Extended Relief Caplets.

See **Exhibit #2** for a representative list of the products manufactured and packed in this firm.

MANUFACTURING CODES

Management has been using the Standard Operating Procedure "MASTER RECORD OF PRODUCTION, LOTS CONTROL NUMBER AND EXPIRATION DATE" SOP #(b) (4) dated 07/30/2000 to establish the guidance in the assignment of packaging lot numbers. The packaging lot number is alphanumeric and consists of six (6) sequential characters. The first character represents the year, the next two digits represent the month and site (Las Piedras = A) and the last three digits are assigned sequentially at the start of every year. The expiration date is based on the date that the finished goods are assigned to the packaging line.

COMPLAINTS

The firm manages all complaint investigation activities. All complaints are evaluated for adverse trends. I reviewed the complaint procedures and reports received within last year. Management has established as a control procedure "Complaint Investigation" SOP (b) (4) effective 05/23/2005 to confirm and investigate any complaint reported.

Most of the complaints are related to foreign product/material, color/taste/smell uncharacteristic and broken pills. I reviewed and discussed the written procedures and handling of approximately (b) consumer complaint investigations.

Table 1 Complaint Investigation Reports

Complaint Report Number	[illegible]	[illegible]
(b) (4)	(b) (4)	Complainant reported the discovery of tablets described as "dirty, with black marks" in a bottle of Regular Strength TYLENOL tablets, 100's. Firm's investigation (b) (4) concluded that the returned field sample was stored under environmental conditions, which impacted the product's appearance, since no incidents were observed during the manufacturing process of the subject lot product. In addition, retain samples were evaluated and met all the release specification.
(b) (4)	(b) (4)	According to the complainant, one pill of Extra Strength Tylenol Rapid Release Gel caps did not look as the others. Firm's investigation (b) (4) revealed that five additional complaints (b) (4) (b) (4) of the same nature were reported against this lot. Management identified as most probable cause for the reported incidents the remains of the broken gel cap in the carrier link of the laser machine. As a consequence the next gel cap unit to be processed will not be placed in the carrier link causing a misalignment of the laser engraving and the logo impression. Currently, management is in the position of evaluate certain common

		factors such as equipment, manufacturing parameters among others that could be associated with the adverse trend observed by this type of complaint and lot reoccurrence. They initiated a corrective action plan (b) (4) to address the aforementioned incidents.
(b) (4)	(b) (4)	Complainant reported that two (2) gel caps of Extra Strength Tylenol Rapid Release Gel caps were smeared and exhibited holes. Firm's investigation (b) (4) revealed that one prior complaint (b) (4) was reported for the same deficiency. Investigation (b) (4) reported that there was a possibility that this defect occur during the (b) (4) (b) (4) due to the product got trapped inside the (b) (4) The (b) (4) (b) (4) (b) (4) As a corrective action, management will change the current (b) (4) for a new one that according to them will minimize the (b) (4) According to firm's officials, this project will be completed by three phases (03/15/2007), which will include the qualification and validation of the new equipment.

I found no deviations after evaluated the aforementioned complaints reports.

PRODUCT DEFECTS

Jr. Tylenol Meltaways Acetaminophen 160 mg and Children's' Tylenol Meltaways Acetaminophen 80 mg

On 11/10/2005, McNeil Consumer & Specialty Pharmaceuticals submitted final NDA Field Alert Report (FAR) to FDA pertaining to Children's & Jr. Tylenol Meltaways Tablets 24, 48 & 64 counts. According to FAR's investigation, the initial report was submitted on May 2005. The deviations were associated with a risk of dosing confusion based on existed product labeling. Final firm's investigation

identified as probable causes inadequate product packaging configuration for Children's Tylenol Meltaways and deficiencies in the product labeling of Jr. Tylenol Meltaways. As corrective actions, management performed labeling modification for Jr. Tylenol Meltaways and developed a new product packaging configuration for Children's Tylenol Meltaways. **Refer to Attachment C.**

I reviewed and evaluated the aforementioned corrective actions and appear to adequately address the misbranded incidents.

MANUFACTURING/DESIGN OPERATIONS

Quality System & Laboratory System

During this inspection I did a walk-through manufacturing, packaging and laboratory areas. I inspected and reviewed the products described in this section (Tylenol Common Products, & Tylenol PM Common Products) following the system inspection approach according to the drug inspection program:

Quality System

My review of the quality system included the review and/or discussion of the firm's corrective and preventive action during manufacturing and/or laboratory investigations, QA Alerts, and complaint investigations. Also I evaluated firm's officials rationale during the change control implemented, the SOP for investigation of non-conformances or unplanned deviations; and manufacturing investigation reports (approximately 30 of them).

Tylenol PM Common Products

Tylenol PM temporarily relieves occasional headaches and minor aches and pains with accompanying sleeplessness. The active ingredients are acetaminophen 500 mg and Diphenhydramine HCl 25 mg.

The shelf life of the finished product is twenty-four (24) months. The stability samples are stored at (b) (4) However, the stability testing of the product is conducted by McNeil Las Piedras.

Following is the physical address of the external company providing support to the stability program:

(b) (4)

As part of this inspection I reviewed the Annual Product of Tylenol PM Gel caps (Period 10/01/04 to 09/30/05). A total of (b) (4) were analyzed during this reviewed period cycle. This sample constitutes (b) (4) According to the firm, neither reworked batches nor return goods were reported in this period. In addition, no process and/or formula changes occurred during this review period. Management also reported that all the stability results obtained were consistent with previous stability interval. The (b) (4) (b) (4) The (b) (4) (b) (4)

A total of 16 non conformance reports were initiated during this reviewed period. Ten (10) of them were related to human error, three (3) were related to equipment malfunctions and others three (3) were related to the manufacturing process. Specifically, low results obtained for Diphenhydramine HCl (DPH HCL) in Tylenol PM Products.

Management has been investigating since 2005 incidents related to low DPH HCL assay results (although within USP monograph specifications) in some lots of Tylenol PM common products. The internal release specification for this product is (b) (4) However, the stability and USP monograph specifications are from 90.0 % to 110.0 %.

Table 2 listed the results obtained corresponding to assay testing of DPH HCL in Tylenol PM Samples.

Table 2 **Low DPH HCL Manufacturing Assessment**

2005	(b) (4)
2005	
2005	
2006	
2006	

Also, refer to Chart 1 for the low DPH HCl results obtained.

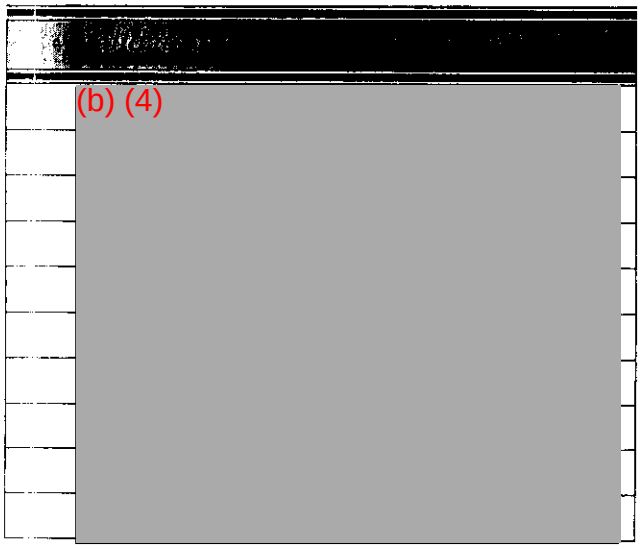
(b) (4)

As result, the firm's officials initiated and conducted laboratory and manufacturing investigations. No root cause was identified for the low results obtained corresponding to DPH HCL active ingredient. The firm destroyed all the lots involved in these incidents.

I reviewed the results reported for the assay of DPH HCL during the validation process. The results obtained were listed in Table 3.

Table 3 **Validation Assay Results for DPH HCL**

(b) (4)



(b) (4)

I observed that the results obtained for the assay of DPH HCL during the (b) (4) (b) (4) The percent of relative standard (b) (4) (b) (4)

I asked to Mr. Maldonado if he identified any change and/or modification in the Tylenol PM process parameters. Mr. Maldonado told me that all the lots of Tylenol PM have been manufactured using the original validation. However, he explained to me that the firm has preliminary observed that some lots experienced difficulty in achieving (b) (4) Mr. Maldonado said that this may be related to the length of time that the materials are held in the equipment bowl after charging and prior to start processing. He mentioned that currently the materials (b) (4) (b) (4)

McNeil Las Piedras contacted its R & D group to identify the root cause of these events and to prevent further incidents of low assay DPH HCL results. R & D developed a study titled "Process Improvement Development Study for Tylenol PM Caplets Granulation Process". According to management, this study will evaluate all the process parameters that could affect the potency of DPH HCL in Tylenol PM Products. This study will be completed for May 31, 2006.

My inspection of this system did not disclose any significant objectionable conditions.

Laboratory System

The Quality Control (QC) unit consists of one analytical laboratory area and one micro-laboratory. The analytical laboratory is used for the testing of: (b) (4) (b) (4) The analytical laboratory headcount consists of (b) (4) where (b) (4) are assigned to the (b) (4) The other (b) (4) are assigned to different laboratory services areas such as calibration, SOPs, training, investigations, purchasing, stability coordinators among others. The laboratory works in (b) (4) (b) (4) Most of the instruments are qualified by firm's personnel (HPLC, GC and dissolution baths) and some by outside contractors (Balance, Thermometers). The stability samples are stored in climatic chambers located at (b) (4) However, the stability testing is conducted at McNeil plant in Las Piedras.

During my review of this system I evaluated the laboratory investigations, calibrations, trainings, and method validations. Most of the laboratory investigations were related to equipment malfunctions, and analysts' techniques. No laboratory investigation adverse trend was detected.

During the inspection I reviewed the following SOPs and calibration reports related to laboratory equipment:

Table #4 **Laboratory Equipment Calibration Reports**

Analytical Equipment	*Equipment ID*	*SOP ID No.*
(b) (4)		

Most of the instruments are qualified and calibrated by firm's personnel (HPLC, GC and dissolution baths) and some by outside contractors (b) (4)

I reviewed the "Stability Study For Dissolution Standards and Sample Solutions Report" validation Report (b) (4) dated 04/05/06. According to the firm's officials, the objective of this report was to summarize the results obtained during the stability study of dissolution standard and sample solutions for lots of products brands manufactured at McNeil Las Piedras site.

This study consisted in preparing representative samples and standards solutions of the products manufactured at McNeil Las Piedras to determine the suitability of it's for a period of time. According to Mr. Maldonado, this study will prevent the use of expired testing solutions during analytical analysis.

My inspection of this system did not disclose any significant objectionable conditions.

REFUSALS

No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On 04/07/2006, I discussed the outcome of the inspection with Mr. Francisco R. Negrón. Other officials present during the closing meeting were.

- Mr. Walter Maldonado, QA/QC Manager
- Ms. Esther Cintrón, Manufacturing Plant Manager
- Ms. Brunilda González, Compliance Manager
- Ms. (b) (6) Compliance Specialist
- Ms. Vilmarie Walker, Procurement & Logistics Manager
- Ms. Wanda Cancel, QA Manager

I informed them that I did not find any objectionable condition; therefore, a Form FDA 483 was not issued. I discussed with Mr. Negrón and his staff that the records that I reviewed and the systems covered were only a small portion of their firm's operation. Thus, it is the responsibility of firm's officials to continue in compliance with the FD & C Act.

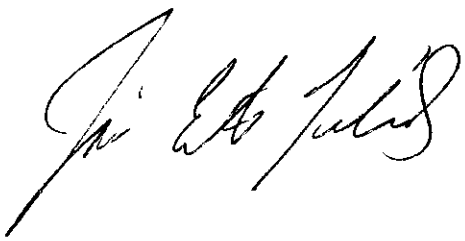
SAMPLES COLLECTED

No sample was collected during this inspection

VOLUNTARY CORRECTIONS

During the inspection, I reviewed and verified the corrective and preventive actions taken as a result of the FDA-483 dated on 02/23/2005.

I confirmed the corrections implemented for previous objectionable conditions. The proposed corrective actions seem to be adequate if they are implemented as firm's officials described.



Jose E Melendez, Investigator