Establishment Inspection Report	FEI:	**2650141**
McNeil Consumer & Specialty Pharmaceuticals	EI Start:	08/20/2002
Las Piedras, PR 00771	EI End:	09/09/2002

SUMMARY

This unannounced inspection of this OTC drug manufacturer was conducted as per SJN-DO Aug/Sep 2002 Work Plan. Coverage was given under CP 7356.002, Drug Process Inspection, and CP 7356.021A, DQRS. I conducted an Abbreviated Inspection that covered the Quality and Production Systems.

The previous inspection dated 2/13/01 covered the Quality and Laboratory systems and was classified VAI. The inspection revealed deficiencies related to laboratory equipment, calculations, and analyst training. An earlier inspection dated 10/99 conducted as a follow-up to a Warning Letter did not disclose any objectionable conditions.

The current inspection revealed deficiencies in stability sampling plans, investigation reports, implementation of corrective actions, and unapproved changes to written procedures. I issued an FDA-483 to Mr. Oray B. Boston, General Manager, who promised immediate corrections and a written response to the District Director. No refusals were encountered and no samples were collected.

ADMINISTRATIVE DATA

Inspected firm:	McNeil Consumer & Specialty Pharmaceuticals
Location:	Km 19.8 Rd 183 Bo. Montones Las Piedras, PR 00771
Phone:	787-733-1000/ 782-7030
FAX:	787-716-5033
Mailing address:	P.O. Box 2009 Las Piedras, PR 00771-2009
Dates of inspection:	8/20/2002, 8/22/2002, 8/23/2002, 8/26/2002, 8/27/2002, 8/28/2002, 9/3/2002, 9/4/2002, 9/9/2002
Days in the facility:	9
Participants:	Ileana Barreto-Pettit, Investigator

HISTORY OF BUSINESS

McNeil Consumer & Specialty Pharmaceuticals is a Johnson & Johnson company incorporated under the laws of the State of Delaware (**Exhibit 1**) since 1983 under the name of McNeil Consumer Products (P.R.) Inc. McNeil is currently registered with the FDA (1/2002) (**Exhibit 2**). This firm recently changed its registration name from McNeil Consumer Healthcare, Inc. to the current name, McNeil Consumer & Specialty Pharmaceuticals.

The plant manufactures and packages solid dose non-prescription pharmaceuticals under the name brands of Tylenol, Motrin and Motrin Migraine. Their production volume is about (b) (4) (b) (4) (tablets, caplets, etc.) per year. They also package Imodium 30mg caplets, an OTC anti-diarrheal product manufactured by (b) (4) another Johnson & Johnson company. See **Exhibit 3** for a complete list of products.

Mr. Oray B. Boston is the General Manager of McNeil Consumer & Specialty Pharmaceuticals in Las Piedras, PR. He reports to Thomas W. Lapinski, VP McNeil Operations, who reports to Mr. William McComb, President, McNeil Consumer & Specialty Pharmaceuticals Co. Mr. McComb reports to Mr. B.D. Perkins, Worldwide Chairman, Consumer Pharmaceuticals & Nutritionals Group, who reports to Mr. William B. Weldon, CEO, Johnson & Johnson Co. See **Exhibit 4** for corporate and local organizational charts.

Any correspondence to corporate officials should be addressed to:

Mr. William B. Weldon, CEO
Johnson & Johnson Co.
Worldwide Headquarters
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

And

Mr. William McComb, President
McNeil Consumer & Specialty Pharmaceuticals Co.
7050 Camp Hill Road
Fort Washington, PA 19034

Any correspondence to local officials should be addressed to:

Mr. Oray B. Boston, General Manager
McNeil Consumer & Specialty Pharmaceuticals
P.O. Box 2009
Las Piedras, PR 00771-2009

McNeil employs (b) (4) and about (b) (4) Manufacturing operations are conducted (b) (4) Laboratory operations have (b) (4) and (b) (4)

PRODUCT DISTRIBUTION

All pharmaceutical products manufactured and packaged at McNeil in Las Piedras are shipped to three major distribution centers in the U.S. These centers are located in Pennsylvania, Missouri, and California (**Exhibit 5**).

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITIES

On 8/20/02, I presented my credentials and issued an FDA-482, Notice of Inspection, to Mr. Raul Cardona Torres, Manufacturing Plant Manager. Mr. Cardona identified himself as the most responsible individual for the daily operations of the firm in the absence of the General Manager, Mr. Oray B. Boston Jr., who was travelling out of the island. Also present were Ms. Veronica Cruz, QC/QA Manager; Hugh Davis, Materials Manager; and Ramon Labarca, Human Resources Manager. On 8/22/02, I met Mr. Oray B. Boston Jr., who gave a brief presentation about McNeil's history and current operations. Mr. Boston delegated authority to Ms. Veronica Cruz and Mr. Raul Cardona to accompany me during the inspection and provide all requested documents.

Mr. Oray B. Boston Jr. is the General Manager responsible for directing and providing leadership and strategic planning to ensure local operations support corporate's pharmaceutical, business, financial, and marketing goals through the production of high quality drug products. He is also responsible for ensuring that all operations comply with corporate and regulatory agencies' requirements. He reports to Mr. Thomas Lapinski, Vice President of Operations.

Mr. Raul Cardona Torres is the Manufacturing Manager responsible for the administration and development of the manufacturing area and for establishing policies and procedures that comply with product manufacturing objectives established by the corporation. He reports to Mr. Oray B. Boston.

Ms. Veronica Cruz is the QC/QA Manager responsible for quality assurance, quality systems and regulatory compliance. She assumed this position two months ago as a new McNeil employee. She is responsible for ensuring that products and facilities conform to current Good Manufacturing Practices. She is overall responsible for product disposition, validations, sampling and analysis (components, containers, closures, in-process materials, finished product, etc.), annual reviews, product transfers, complaint investigations, evaluation of failure investigations, record review, and approval of procedures and specifications. Ms. Cruz reports to Pedro N. Juri, Vice President, Quality Sciences & Compliance Division, for quality matters and to Mr. Oray B. Boston, for administrative issues (**Exhibit 4**, pages 5, 7-8).

Other individuals that participated in the inspection and/or provided information are the following:

- Carmen T. Andino Colon, QA & Compliance Manager
- Vilmarie Walker, Manufacturing Section Manager
- Iramis Ralat Rivera, Engineering Services Manager
- Armando Fajardo Arzuaga, Validation Manager
- (b) (6) Granulation Supervisor
- (b) (6) Granulation Operator
- (b) (6) Compression Supervisor
- (b) (6) Coating/Printing Supervisor
- Evelyn Montes, Coating Manager
- (b) (6) Coating Operator
- (b) (6) Printing Operator
- Ildefonso Ayala, Gel dipping Manager
- (b) (6) Gel dipping Supervisor
- Ileana Zavala, Packaging Manager
- (b) (6) Packaging Supervisor
- (b) (6) Packaging Supervisor
- (b) (6) Packaging Operator
- Juan C. Lugo, Warehouse Manager
- (b) (6) Comptroller
- Wanda Cancel, Microbiology Laboratory Manager
- (b) (6) Analytical Laboratory Supervisor
- (b) (6) Systems Specialist
- (b) (6) Compliance Specialist
- (b) (6) Senior Product Quality Analyst, Fort Washington, PA
- Andrew Falkowski, Director, Technical Services & Quality, Fort Washington, PA
- (b) (6) Technical Resources Supervisor
- Abiel Lopez, Planning Manager

MANUFACTURING CODES

See **Exhibit 6** for the procedure to follow for assignment of the manufacturing code.

COMPLAINTS / PRODUCT DEFECTS

McNeil's consumer complaint system is managed at the corporate level in Fort Washington, PA, where complaints are received, evaluated, and forwarded to the respective manufacturers for an investigation if necessary. On 8/27/02, I participated in a conference call with Fort Washington's officials, Mr. Galen Engh, Senior Product Quality Analyst, and Mr. Andrew Falkowski, Director, Technical Services & Quality. The reason for the conference call was to better understand and evaluate the consumer complaint system from the time the complaint is received at Fort Washington.

I reviewed 19 consumer complaint investigations and 3 emergency (STAT) complaint investigations in 2001-2002 (**Table 1**). I reviewed the written procedures and handling of the consumer complaint investigations and found no major deficiencies.

Table 1. Consumer Complaints

(b) (4)		(b) (4)	

I also conducted a follow-up investigation to the following consumer complaint received by the FDA:

- Complaint #: (b) (4) (Attachment 3)
- Date of complaint: 1/1/00
- Product Name: Extra Strength Tylenol gelcaps (500mg)
- Lot #: CLA127
- Description of complaint: Complainant found an odd colored, opened gel cap and white powder in a container of Extra Strength Tylenol gelcaps 500mg.

I found no deficiencies in the investigation and its conclusion (**Exhibit 7**).

OBJECTIONABLE CONDITIONS

Observations listed on form FDA 483

QUALITY SYSTEM

OBSERVATION 1

Established sampling plans are not followed.

Specifically,

1) Stability sampling plan for Motrin IB Gelcaps 100 count for year 2001 was not followed in accordance with NDA commitments and SOP (b) (4) Stability Study Design and Acquisition," in that the first lot (b) (4) of the first three marketed lots was not placed on stability.

2) The first lots of each product packaged with caps with a new liner were not placed on stability in accordance with Change Control record (b) (4) The products involved include:

- Extra Strength Tylenol caplets 24 count, lot FBA 224
- Extra Strength Tylenol gelcaps 24 count, lot FBA 233
- Regular Strength Tylenol 100 count, lot FBA 246
- Extra Strength Tylenol tablets 30 count, lot FBA 247
- Tylenol PM geltabs 24 count, FBA 219
- Tylenol PM gelcaps 24 count, lot FBA 251
- Motrin tablets 24 count, lot FBA 294
- Motrin caplets 24 count, lot FBA 304
- Tylenol Soft Chewable Grape tablets 30 count, lot FCA002

Reference: 21 CFR 211.160(a)

Discussion with management:

1) On 8/28/02 while reviewing a print-out from the Stability Database Report that listed the samples to be pulled for stability testing, I noted that there was a list titled "Samples Overdue for (b) (4) (**Exhibit 8**, page 8) When I inquired about overdue samples of Motrin IB gelcaps Lot ELA 250, I was told that they were switching from a manual stability inventory system to a computerized system and that those samples were entered late into the system. However, after reviewing batch records and stability documents, I was told that Lot ELA 250 was replacing (b) (4) the first lot of Motrin, a new product that should have

been placed on stability but was not. On 9/3/02, Ms. Veronica Cruz told me that they were investigating this case and had generated a Nonconformance Investigation Report on 8/30/02 (**Exhibit 9**) to determine why the first lot of Motrin was not placed on stability. However, I told her that this report should have been generated in June 21, 2002 when Regulatory Affairs first discovered that Lot (b) (4) was not placed on stability as per NDA commitments and stability requirements for new products established in SOP (b) (4) (b) Section (b) (4) (**Exhibit 10**, page 3). Ms. Cruz agreed and committed to evaluate the stability system to ensure all stability samples are properly identified and pulled at the right times.

2) On 6/21/01 Change Control Document # (b) (4) was approved and closed for changing the liner material of the (b) (4) and (b) (4) from vendor (b) (4) to vendor (b) The implementation plan of this change control document required placing on stability the first packaged batch of the lowest and highest packaging configuration of each product packaged with caps lined with the (b) material (**Exhibit 11**, pages 4, 16 & 19). I requested a list of the first batches manufactured with the (b) (4) (**Exhibit 12**). During my review of this list against year 2002 stability inventory list (**Exhibit 13**), I noted that none of the first batches packaged with the (b) (4) were placed on stability. When I questioned why the first batches were not placed on stability, I was told that the new caps remained with the same part number and therefore product packaged with the new caps was not readily identified for inclusion in the stability program. When this failure was identified earlier this year, replacement subsequent batches were placed on stability. Ms. Veronica Cruz committed to evaluate the stability program to prevent similar occurrences.

OBSERVATION 2

Deviations from written sampling plans are not recorded.

Specifically, a Nonconformance Investigation Report (NCR) was not generated after the Regulatory Affairs Department discovered that the first marketed lot of Motrin IB gelcaps, lot EAA 283, was not placed on stability in accordance to NDA requirements and written procedures.

Reference: 21 CFR 211.160(a)

Discussion with management: See explanation for Observation 1(1).

OBSERVATION 3

Written records of investigations into the failure of a batch or any of its components to meet any of its specifications do not include the conclusions and followup.

Specifically, (b) (4) investigations in years 2001 & 2002 related to out of specification yield values after the reconciliation of Tylenol products lot #'s: (b) (4) and (b) (4) were attributed to an (b) (4) A study titled (b) (4) was conducted and completed on 1/28/02. The study concluded that there was a significant difference between the current cubicle factors and the ones obtained in the study and recommended to change them since this "could be the major cause of the yield values out of parameters." This preventive action of replacing the old cubicle values with the new values in the (b) (4) and (b) (4) has not been implemented.

Reference: 21 CFR 211.192

Discussion with management: The following Nonconformance Investigation Reports from years 2001-2002 were conducted to investigate out of specification yield results for Extra Strength Tylenol caplets:

(b) (4)	**Exhibit 14**)	(b) (4)	(**Exhibit 15**)
			(**Exhibit 16**)
			(**Exhibit 17**)
			(**Exhibit 18**)
			(**Exhibit 19**)

These investigations concluded that the out of specification yield results were obtained as a result of an inadequate cubicle factor used in the calculation of yield. The firm then completed a study in January 2002 to evaluate and determine a correct cubicle factor for (b) (4) (b) (4) (**Exhibit 20**). The (b) (4) values. This (b) (4) (**Exhibit 21**). When I asked when these new factors were implemented, I was told that they were not implemented yet because they wanted to complete the (b) (4) (b) (4) In addition, I was told that the (b) (4) (b) (4) I then asked what exactly they were going to do to resolve the problem with out of specification yield values. I was told that they were planning to eventually (b) (4)

which apparently (b) (4) and do not significantly affect yield values. I commented to Ms. Veronica Cruz that (b) (4) (b) (4) (b) (4) (b) (4) **(Exhibit 22)**.

OBSERVATION 4

Changes to written procedures are not reviewed and approved by the quality control unit.

Specifically, a form to verify major cleaning of equipment was created and implemented in September 2001 by production personnel without the review and approval of the quality control unit.

Reference: 21 CFR 211.100(a)

Discussion with management: When I was reviewing major cleaning logbooks for (b) (4) (b) (4) I noted that major cleaning for 7/29/02 was not fully documented as (b) (4) in the cleaning process were not initialed as being completed prior to the manufacture of Tylenol Extra Strength caplets lot (b) (4) **(Exhibit 23**, pages 12, 13 & 15). When I asked Mr. (b) (6) Compression Supervisor, if this major cleaning was done he stated that they use a form to verify completion of major cleaning prior to manufacturing product **(Exhibit 24)**. When I reviewed this form, I asked him if this was part of their procedure and he stated that they were considering inclusion in their procedure. I pointed out that they have been using this form for all compression machines since 9/26/01 without the review and approval of the quality control unit. I stressed that changes to procedures must be approved by the quality control unit prior to implementation.

OBSERVATION 5

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

Specifically, (b) (4) investigation reports reviewed were generated (b) (4) According to SOP (b) (4) notification.

Reference: 21 CFR 211.100(b)

Discussion with management: While reviewing investigation reports, I noted that many investigations reported two initial dates: the date the situation was discovered and the date the report was initiated. When I inquired about it, Ms. Cruz told me that the initiation date was the official date the investigation was started. I asked her what was their timeframe to initiate and close investigations and she showed me SOP (b) (4) "Documenting Nonconformance Reports" (**Exhibit 25**, page 2) where it states under section (b) that "The investigator is responsible for notifying Quality Assurance within one hour after the situation was notified or observed to assign the nonconformance number. An extension of up to twenty four hours may be accepted depending on the nature of the event…" I reviewed some of the investigations with Ms. Cruz and she recognized that some investigations were generated late and did not meet timeframes specified in the SOP (**Exhibit 26**). The following investigations reviewed from year 2002 did not meet timeframes:

NCR #	Date situation was discovered	Date investigation was initiated
(b) (4)	(b) (4)	(b) (4)

During the closing of the inspection, Mr. Oray B. Boston, General Manager, stated that he believed some of the investigations were initiated on time but were documented later. I agreed that it was possible but I stressed that their documentation needs to be accurate and reflect the actual date the investigation was initiated and completed. Ms. Veronica Cruz committed to make the necessary changes to documentation practices.

GENERAL DISCUSSION WITH MANAGEMENT

On 9/9/02 I held a closing meeting and issued an FDA-483 to Mr. Oray B. Boston, General Manager. The following individuals were also present during the closing meeting:

- Raul Cardona, Plant Manufacturing Manager
- Veronica Cruz, QA/QC Manager
- Carmen T. Andino Colon, QA & Compliance Manager
- Vilmarie Walker, Manufacturing Section Manager

- Iramis Ralat Rivera, Engineering Services Manager
- Armando Fajardo Arzuaga, Validation Manager

I explained the new format of the Turbo EIR FDA-483 and discussed every observation. I also discussed the following verbal observations:

1. During my review of laboratory investigations, I noted that some of the investigations lacked sufficient details to fully describe all of the steps taken during the investigation. In addition, not all of the investigations included the final results used for product approval and release. I also recommended to write the names and titles of all individuals signing the investigations as it was sometimes difficult to identify the individuals from the signatures only. Before the end of the inspection, Ms. Veronica Cruz provided a copy of a draft of a revised procedure for laboratory investigations (**Exhibit 27**). I reviewed the SOP and it appropriately addressed all laboratory investigation observations made during the inspection. During the closing meeting, Ms. Cruz stated that the SOP was implemented on 9/6/02.

2. Also during my review of investigations, it seemed that there were many laboratory OOS results attributed to analyst's error. In addition, I noted that corrective actions such as training was usually limited to the analyst who made the mistake and not to other analysts that could benefit from the training. Ms. Cruz agreed and recommended to conduct a quarterly review of investigations to identify trends and conduct appropriate training. This was included in the revised SOP for laboratory investigations (**Exhibit 27**, page 2).

3. Documentation in the equipment major cleaning logbook is not always complete. Ms. Cruz committed during the inspection to evaluate procedures and documentation practices of major cleaning to avoid similar occurrences.

4. Cleaning validation protocol does not have criteria for objectionable organisms. Criteria for microbiological contamination is limited to Total Count.

5. Some Nonconformance Investigation Reports such as (b) (4) contained erroneous information such as incorrect temperature parameters and relative humidity measurement units. I stressed the importance of accurate information and careful review of investigations before approval.

I warned Mr. Boston and those present that the observations discussed were in my opinion deviations from cGMPs and that upon further review FDA may determine if they are violations of the Food, Drug & Cosmetic Act. I also warned them of the possible civil and criminal penalties associated with violations of the Act. Mr. Boston expressed his commitment to correct all deficiencies and to submit a written response to the District.

ATTACHMENTS

1. FDA-482 issued on 8/20/02.
2. FDA-483 issued on 9/9/02.
3. Complaint # DAL09065

EXHIBITS

1. Certificate of Incorporation
2. FDA Registration Certificate (1/10/02)
3. List of Products
4. Organizational charts
5. Distribution Centers
6. SOP (b) (4) "Master and Batch Production and Control Records, Batch Numbers, and Expiration Dates"
7. Consumer Complaint # (b) (4)
8. Stability Samples Pull Schedule, dated 8/23/02
9. Nonconformance Investigation Report (NCR) No. (b) (4)
10. SOP (b) (4) Stability Study Design and Acquisition"
11. Change Control Record # (b) (4)
12. List of first lots packaged with (b) (4)
13. 2002 Marketed Stability Samples to be taken for Testing, dated 8/14/02
14. NCR No. (b) (4)
15. NCR No.
16. NCR No.
17. NCR No.
18. NCR No.
19. NCR No.
20. (b) (4)
21. Compression Equipment Diagram
22. Compression Socks Replacement Project Action Plan, dated 9/3/02
23. 2002 Major Cleaning Logbook, (b) (4)
24. Form for Verification of Equipment Major Cleaning
25. SOP (b) (4) "Documenting Nonconformance Reports"
26. Unplanned (b) (4)
27. Draft SOP "Laboratory Investigations Report"

Ileana Barreto-Pettit, Investigator