

Mc Neil Consumer Healthcare
Road 183 Km 19.8
Barrios Montones
Las Piedras, PR 00771.
E.I. 01/23-25, 29-30,02/05-08, 13/01
CSO: Jorge L. Guadalupe
ACSO: Marianela Aponte

SUMMARY OF FINDING

The inspection of this pharmaceutical OTC drug manufacturer was conducted in accordance with San Juan District, December/January FY 01 workplans for cGMP inspection to be cover in Compliance Program 7356.002, Drug Manufacturing Inspection (b) (2) This inspection also covers NDA 19-872/011, Acetaminophen Extended Release Caplets, 650mg under Compliance Program 7346.832, NDA Pre-Approval Inspection. See **attachments 1 & 2**. This report was written by Marianela Aponte, Chemist, Acting CSO.

Previous inspection conducted on 09/23-10/13/99 did not disclose objectionable conditions. This inspection evaluated all corrections made to previous deficiencies and Warning Letter which were found to be in compliance with the commitments in the FDA -483 response and further in the response to the Warning Letter. Also, the inspection covered NDA 19-012/019 Motrin IB gelcaps, which revealed the firm capability and control to manufacture the drug product under proposed commitment. No FDA-483 was issued.

The current inspection covered the Quality System and Quality Control Laboratory of the firm according to the pilot program. No objectionable observations were detected in their Quality system and three deviations were found during the inspection of the Quality Control Laboratory. Based on this situation, it was decided to perform an abbreviated inspection.

At the end of the inspection a FDA-483 was issued to Mr. Thomas W. Lapinski, General Manager and discussed with him. The observations were as follows: Failure to calculate manually Vs automatic the result obtained in Wates HPLC Millenium Validation, failure to calculate the minimum weight for the analytical and microbalances and failure to properly train the Quality Control analysts (see objectionable condition caption for more details).

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Profile sample consisting of Pregelatinized Starch, Microcrystalline Cellulose NF, Opradry White YS, Hydroxyethyl Cellulose, Povidone USP APAP USP, Magnesium Stereate NF and Acetaminophen caplets. Samples were submitted to FCC for analysis on 02/14/01, under CR # 95301 (**Attachment 3**).

HISTORY OF BUSINESS

Mc Neil Consumer Healthcare, Las Piedras, P.R. is a Division of Johnson and Johnson Consumer Co. (PR), Inc. The plant manufactures and packages solid-dose non-prescription pharmaceuticals. The facility is located in Rd. 183 Km 9.8, Bo. Montones, Las Piedras, PR 00771. Telephone no. (787) 733-1000; FAX no. (787) 716-5033. The site is approximately (b) (4) and the firm's operations are carried out one building (b) (4). This building encompass all the firm's activity areas such as Manufacturing, Engineering, Quality Control Labs. and Administration.

The firm currently manufactures the following presentation of Tylenol:

1. Extra Strength Tylenol
2. Regular Strength Tylenol
3. Junior Strength Tylenol
4. Children Tylenol Chewable (4 flavor)
5. Tylenol PM
6. Tylenol Sinus

Also, the firm produces Imodium A-D Anti-Diarrhea caplets. A complete list of Mc Neil Consumer Healthcare Products is attached (**Exhibit 1**).

PERSON INTERVIEWED, ADMINISTRATIVE PROCEDURE AND AUTHORITIES

Upon arriving at the firm on 01/23/01, Mr. Jorge L. Guadalupe properly identified himself as FDA representative and explained the purpose of the inspection. Credential was presented and FDA-482 was issued to Mr. Thomas W. Lapinskin, General Manager, who identified himself as the most responsible person in the firm. Also, present were Mr. Raúl Cardona, QA/QC Manager; Mr. Oray Boston, Plant Manufacturing Manager; Mrs. Iris Ramos, Lean Manufacturing Project Manager; Mr. Juan Mendez, Business Improvement Project/ Validation; Mrs. Carmen Andino, QA & Compliance Manger; Mr. Armando Fajardo, Validation Manager; Mr. Vilmarie

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Walker, Rotor Site Project Manager. Mr. Lapimskin delegated to Mr. Cardona to be responsible of the over all handling of the inspection to ensure that all information requested by us was provided.

Mr. Raul Cardona, QA/QC Manager describes to investigator Guadalupe the responsibilities of the main management as follows:

1. Mr. Thomas W. Lapinskin, General Manager, is the most responsible individual for Mc Neil Consumer Healthcare, Las Piedras facility. He is responsible for establish operational procedures and business strategies to assure compliance with corporate objectives. Mr. Lapinski reports to Mr. Michael D. Gowen, Vice President of Operations whose office is located at Fort Washington, PA.
2. Mr. Raúl Cardona, PhD; QA/QC Manager. He is responsible for the compliance of the regulations of the company and regulatory agencies related with the manufacturing of the product. Mr. Cardona reports to Mr. Lapinski in administrative matters and to Mr. Pedro Juri, QA Director in Fort Washington PA.
3. Oray Boston, Manufacturing Manager. Mr. Boston is responsible for the development of strategy plan for the manufacturing area. Also, the he has to establish procedure to assure the compliance with company objectives. Mr. Boston reports to Mr. Lapinski

On January 30, another FDA- 482 was issued to Mr. Thomas W. Lapinskin to include acting CSO and Chemist Marianela Aponte. Credential was properly shown to Mr. Lapinski.

Officers of this firm who located in PR are as follow:

Mr. Thomas W. Lapinskin, General Manager
Mr. Raúl Cardona, QA/QC Manager
Mr. Oray Boston, Manufacturing Manager
Mrs. Iris Ramos, Lean Manufacturing Project Manager

Mr. Juan Mendez, Business Improvement Project/Validation Manager

See **exhibit 2** for Organization chart.

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Correspondence to this firm should be addressed to:

Mr. Thomas W. Lapinski
General Manager
Mc Neil Consumer Healthcare Inc.
PO Box 2009, Las Piedras
Puerto Rico 00771
Tel (787) 733-7654
Fax (787) 733-7692

The following personnel joined the inspection to provide information their area of expertise:

Miss. (b) (6) - QC Supervisor
Mr. Nestor Contreras - IM Manager
Mr. John Nadzam - Sr. Reasher Associate
Mr. (b) (6) - System Engineer
Mr. Kevin Bradley - Manager, Support to Market Products
Mr. (b) (6) - Principle Scientist

Mc Neil Consumer Healthcare, Las Piedras plant manufactures and packages solid-doses non-prescription human drug products.

NDA 19-872/011

NDA 19-872/011 Acetaminophen Extended Release Caplets, 650mg Supplement application provides for this establishment to manufacture, packaging, label and test for release and stability.

The manufacturing direction for Acetaminophen Extended Release, 650mg Caplets as follows:

(b) (4)

1. The (b) (4) (b) (4) and (b) (4) (b) (4)
2. (b) (4)

a. The (b) (4) [redacted]
with (b) (4) [redacted]

3. (b) (4) [redacted]

4. (b) (4) [redacted] with
following set up:

(b) (4) [redacted]

5. The (b) (4) [redacted]
(b) (4) [redacted]

6. The (b) (4) [redacted] and the (b) (4) [redacted] with
(b) (4) [redacted] and (b) (4) [redacted]

7. The (b) (4) [redacted]
(b) (4) [redacted]

(b) (4) [redacted]

1. The (b) (4) [redacted] and
(b) (4) [redacted]

2. The (b) (4) [redacted]

3. The (b) (4) [redacted]

4. The (b) (4) [redacted]
under the following conditions:

(b) (4) [redacted]

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5. (b) (4)

6. The (b) (4) and the (b) (4)
(b) (4)
(b) (4)

7. The (b) (4)
or (b) (4)

(b) (4)

1. The (b) (4)
the (b) (4)
(b) (4)
(b) (4)

(b) (4)

1. The (b) (4)

2. The (b) (4)
conditions:

(b) (4)

NDA 19-012/019 Motrin IB Gelcaps, 200 mg Validation Review

Profile: TCM

The three validation batches were reviewed and evaluated. Also, the stability data was reviewed. Validation and stability data were found in compliance. The data of the submission lots of was audit and no deficiency was found.

Supplement application provides for this establishment to manufacture, packaging, label and test for release and stability.

The manufacturing direction for Motrin IB gelcap, 200mg Caplets as follows:

(b) (4)

1. The (b) (4) and
(b) (4)
(b) (4) and (b) (4)

2. The (b) (4)
(b) (4)

3. The (b) (4) and (b) (4)
(b) (4)

4. The (b) (4)

5. The (b) (4)

6. (b) (4)

7. The (b) (4)
(b) (4)

8. The (b) (4)

(b) (4)

9. (b) (4)

10. (b) (4)

Film Coating

11. The (b) (4)
(b) (4)
(b) (4) and (b) (4)

(b) (4)

12. The (b) (4) and the
(b) (4)
(b) (4)

Printing

13. (b) (4)

OBJECTIONABLE OBSERVATIONS

The following objectionable conditions, in **bold**, were noted during the inspection listed on the FDA-483 and discussed with management during the closing meeting.

1. **The firm's Installation and Operational Qualification report of the (b) (4) (b) (4) HPLC Computer System does not verify the calculation for the analytical results (b) (4) as part of the validation.**

The analytical laboratory is using a computerized function of the (b) (4) HPLC Computer System to obtain the results directly from the HPLC. This calculation was not verified manually Vs automatic calculation as part of the validation (**Exhibit 3**). The firm showed me a draft of Verification of (b) (4) Calculation SOP (**Exhibit 4**). This draft addresses the observation.

2. **The firm failed to determine the measurement uncertainty for the analytical and microbalances according to USP 24 chapter <41> as for example the determination of minimum weight.**

The calibration reports for the analytical and microbalances (**Exhibit 5**) nor the Balance Performance Verification and Maintenance SOP (**Exhibit 6**) address the random and systematic error to determine the minimum weight as indicated in USP 24. Miss. (b) (6) (b) (6) stated that they do not weigh small quantities and they use the balances in the range that they calibrate the balances. I indicated to her that if they need to weigh small quantities of material even at the lower value weight of the calibration, it is needed to determine the precision of the balance. For weighing to be accurate, it is to be performed with a (b) (4) (b) (4)

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The firm showed me a draft of the Procedure for the Calculation of the Minimum Weight for the Laboratory Balances. The draft procedure addresses this observation.

- 3. The firm's analytical laboratory failed to record the temperature of the medium in the individual vessel during the dissolution test.**

Deleted. See DISCUSSION WITH MANAGEMENT section.

- 4. The firm lacks to have an effective training program for the laboratory personnel. Approximately (b) (4) and (b) (4) of the out of specification in the analytical laboratory for the year 1999 and 2000 respectively, were analyst error.**

Review of the analytical laboratory out of specification list from 1999 showed that training to laboratory personnel was not effective. I noticed that most of them end the tracking number end with A. The procedure states the suffix A indicates analyst error. I asked for the analytical laboratory out of specification for 2000 and the same pattern was noticed. The document indicates that during 1999 a total of (b) (4) (Exhibit 7) and during 2000 a total of (b) (4) (Exhibit 8) were due to analytical errors.

DISCUSSION WITH MANAGEMENT

On 02/13/01 we issued a FDA-483 to Mr. Thomas W. Lapinskin, General Manager, Mc Neil Consumer Healthcare, Inc. in Las Piedras. Also present during the closing

meeting were Mr. Raúl Cardona, QC/QA Manager, and Mr. Oray Boston, Plant Manufacturing Manager. Investigator Guadalupe indicated that the specifications and

controls for NDA 19-872/011 were found in compliance, and also the supplemental changes in Motrin Gelcaps NDA 19-012.

All observations were discussed individually.

1. Mr. Raúl Cardona indicated that they have drafted a procedure for observation #1. The draft was shown and a copy was provided (Exhibit 4). Mr. Lapinskin indicated that since they corrected the observation, he

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understood it could be deleted. Investigator Guadalupe clarified him that even though they have drafted a procedure, the observation will stay because the draft was written after the observation was made. Also, CSO Guadalupe indicated that the all the comments, corrections and documents provided would be explained in the report. Mr. Lapinskin agreed.

2. Mr. Raúl Cardona showed the draft procedure for that observation (**Exhibit 9**). Also he indicated that they implemented the procedure and the minimum weight for the balances was calculated.
3. In this observation they indicated that they are recording each individual vessel temperature for dissolution test. I stated that all analytical data that I reviewed did not show individual vessel temperature. (b) (2)
(b) (2)
(b) (2)
(b) (2) Analytical data of a dissolution test from 01/01 was shown. The temperature of the individual vessels was documented. The observation was deleted.
4. Mr. Lapinskin and Mr. Cardona did not agree with the observation. They indicated that the total OOS the analytical laboratory has is less than 1% of the total lot products that the laboratory receives. Investigator Guadalupe and I indicated to them that they have few products and almost the same method for all products, therefore the error should be minimal. Also, it was indicated that when reviewing the laboratory OOS analytical data, the errors were reflecting that analysts need more trainings. They did not agree and
(b) (4)
(b) (4)

The firm was advised that the observation noted were considered deviations to the cGMP regulations and could result in the regulatory action. The management appreciated the work done by the investigators during the inspection for their professionalism.

EXIBITS:

1. Copy of Mc Neil List of Packages Product Presentation

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2. Copy of organization Chart
3. Copy of Installation and Qualification Summary
4. Copy of Verification of (b) (4) Calculation Procedure
5. Copy of calibration report for microbalance (b) (4)
6. Copy of the Balance Performance Verification and Maintenance SOP
7. Copy of analytical laboratory out of specification - 1999
8. Copy of analytical laboratory out of specification - 2000
9. Copy of Procedure for the Calculation of the Minimum Weight for the Laboratory Balances

ATTACHMENTS

1. Request for Inspection Report for Acetaminophen Extended Release 650mg Tablets
2. Mc Neil Notification of Motrin PIA
3. Collection Report # 95301
4. Copy of the FDA-482 Notice of Inspection of 01/23/01
5. Copy of the FDA-482 Notice of Inspection of 01/30/01
6. Copy of FDA-483



Jorge L. Guadalupe
Drug Specialist
San Juan District Office



Marianela Aponte
Acting Investigator
San Juan District Office