

Establishment Inspection Report
McNeil Consumer and Specialty
Pharmaceuticals
Las Piedras, PR 00771

FEI: 2650141
EI Start: 01/27/2005
EI End: 02/23/2005

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SUMMARY

The inspection of this human OTC drug manufacturer was conducted as per SJN-DO work plan FY-05 and FACTS assignment 598674. The cGMP inspection covered Quality System, Facilities & Equipment System, Production System and the Laboratory Control System. This inspection also covered NDA application 20-958/S-011 of (Famotidine) Pepcid Complete Tablets. Coverage was given under CP 7356.002 - Drug Manufacturing Inspections, and CP 46832, NDA Pre-Approval Inspection/Method Validation.

The previous inspection dated 09/09/02 covered the Quality and Production Systems. That inspection revealed deficiencies in the areas of stability sampling plans, investigation reports, implementation of corrective actions, and unapproved changes to written procedures. The inspection was classified VAI.

The current 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

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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 objectionable conditions were listed on the FDA-483 issued on 02/23/05 to Mr. Jorge Ros General Manager, of McNeil Consumer & Specialty Pharmaceuticals. Mr. Bob Miller, VP Quality Sciences & Compliance Division promised a written response to the observations within two weeks.

Documentary sample # 220337 for Tylenol Extra Strength Caplets 500 mg was collected to document cGMP violations, mix-ups deviation and interstate movement of the product.

Chemists Miguel Martinez (MAM) and Edwin Martinez (EM) participated on this inspection except on 02/11/2005. I José E. Meléndez was the team leader (JEM) in this inspection, and wrote this EIR except those sections identified with the initials of chemists.

ADMINISTRATIVE DATA

Inspected firm: McNeil Consumer and Specialty Pharmaceuticals
Location: Km 18 Rd 183
Bo. Montones
Las Piedras, PR 00771
Phone: 787733-1000
FAX: (787) 733-7692
Mailing address: P.O. Box 2009
Las Piedras, PR 00771-2009

Dates of inspection: 01/27/28/31 & 02/01-03/08-11 & 23/2005
Days in the facility: 11
Participants: Jose E Melendez, Investigator
Miguel A. Martinez, Chemist Drug Specialist
Edwin Martinez, Chemist

McNeil Consumer and Specialty Pharmaceuticals is registered with FDA under CFN# 2650141. A copy of the most recent registration was submitted on February 04, 2004. Currently, firm's officials are in the process of renewal the registration (**Refer to Exhibit JEM 1**).

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On 01/27/2005 we presented our credentials and issued the FDA-482, Notice of Inspection, to Mr. Jorge Ros, General Manager, who identified himself as the individual with most responsibility in the firm. Other individuals present during the opening meeting are:

- Mr. Walter Maldonado, QA/QC Manager
- Ms. Vilmarie Walker, Plant Manager
- Ms. Edna M. Maldonado, QSC NX Manager

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

On 02/23/2005 we issued the Form FDA-483 to Mr. Ros. Other individuals present during the closing meeting are listed below

- Mr. Walter Maldonado, QA/QC Manager
- Ms. Vilmarie Walker, Plant Manager
- Ms. Edna M. Maldonado, QSC NX Manager
- Mr. Bob Miller, VP Quality Sciences & Compliance Division
- 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) (b) (4) tablets, caplets, geltabs, and gelcaps) annually.

The firm employs approximately (b) (4) employees ((b) (4) McNeil employees and (b) (4) by contract), and operates (b) (4)

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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@corus.inj.com

INTERSTATE COMMERCE

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

For example:

DC 10 Olive Branch,
Mississippi, US.

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 JEM 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. Jorge Ros, General Manager participated briefly during the inspection. Mr. Ros responsibilities include the following: assuring product's availability and business demands; assuring product integrity through compliance programs; establishing training programs and staffing (hiring/firing) plans; and assuring an adequate use of resources and strategic planning, among others. Mr. Ros reports to Mr. Thomas W. Lapinski, VP North America Operations. Mr. Lapinski reports to W.L. McComb, President McNeil Consumer & Specialty Pharmaceuticals North America Operations with offices in Fort Washington. Mr. McComb, reports to Mr. C.A. Poon, Worldwide Chairman Medicines & Nutritional. Mr. Poon reports to Mr. W.C. Weldon, Chief Executive Officer whose offices are located at one Johnson & Johnson Plaza WT 1101 New Brunswick, NJ.

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

Mr. Ros has the decisional power to correct any deficiency encountered in this inspection. Mr. Ros' authority was evidenced through the orders that he gave to Ms. Walker, Plant Manager and Mr. Maldonado, QA/QC Manager during the EI, and by accepting the Forms FDA 482 and receiving the Form FDA 483.

Mr. Walter Maldonado is the QA/QC manager. He is responsible for maintaining laboratory operations in compliance with applicable regulations. He is 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. 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 commitments that he promised at the end of 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, Imodium Advance Chewable Tablets & Tylenol PM Caplets.
- Tablet Extended Release (TTR): Tylenol Arthritis Pain Extended Relief Caplets.

A representative list of the products manufactured and packed in this firm is Exhibit JEM 2.

MANUFACTURING CODES

Management has been using the Standard Operating Procedure "MASTER RECORD OF PRODUCTION, LOTS CONTROL NUMBER AND EXPIRATION DATE" sop # (b) (4) dated 07/30/200 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 (Refer to Exhibit JEM 5 page 4 of 5).

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On the other hand, the expiration date is based on the date that the finished goods are assigned to the packaging line (Refer to Exhibit JEM 5 page 5 of 5).

COMPLAINTS

Most of the complaints are related to mixed product, foreign product/material, color/taste/smell uncharacteristic, and label missing. I reviewed the written procedures and handling of the consumer complaint investigations. Some deficiencies were found and are discussed under caption **Objectionable Condition 5**. Refer to **Exhibit JEM 6** for list of reviewed complaints.

I also conducted follow-up investigation for consumer complaints received by the FDA (See **Exhibit JEM 7**).

MANUFACTURING/DESIGN OPERATIONS**Production/Quality System/Facilities & Equipment System/Laboratory System**

The products described in this section were inspected following the system inspection approach according to the drug inspection program. Tylenol Arthritis Pain Extended Relief Caplets, Tylenol PM Caplets and Imodium Advance Chewable Tablets-D were covered under Quality, Laboratory, Production and Facilities & Equipment System.

- During this inspection I did a walk-through manufacturing area. My inspection of the Production and Facilities & Equipment System included the review and discussion of the firm's validation master plan, the sop for validation, process validation protocols, reports, and the rationale for the selection of the critical manufacturing process parameters for Tylenol Arthritis Pain Relief and Imodium A-D,. I also reviewed the current master batch record, equipment qualifications, and manufacturing cleaning procedures. I found no deficiencies with the exception of the cleaning procedures for the buckets (plastic containers) used in the manufacturing areas, and the procedures and controls for packaging line clearance. These deficiencies are discussed under caption "**Objectionable Condition**" **item # 1**.

Production System

Tylenol Arthritis Pain Extended Relief Caplets is used to treat temporarily relieves minor aches and pains due to: arthritis, headache, muscular aches, menstrual cramps, the common cold, toothache, backache.

Tylenol Arthritis Pain Extended Relief Caplets (TAR) is available in 650 mg for oral administration.

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The shelf life for TAR is thirty-six (36) months. The expiration date begins from the date of the packaging process.

Manufacturing of TAR consists of two granulations sustained & immediate release. Refer to **Exhibit JEM 8** for process description.

In-process testing consists of weight, hardness, thickness, printing defects, and friability among others.

The release testing consists of assay, content uniformity, dissolution, physical evaluations among others.

During the inspection I reviewed the validation protocol & report of Tylenol Arthritis Pain Extended Relief Caplets. This validation was done following the Protocol No. (b) (4) dated 02-(b) (4). The validation lots numbers were (b) (4) and (b) (4). Management defined the sustained release (b) (4) and (b) (4). All results obtained were within acceptance criteria, and were reported in the "PROCESS VALIDATION REPORT TAR" dated 04/30/01.

My review of this system disclosed objectionable conditions, which are discussed under caption "Objectionable Conditions" items 1 & 2.

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).

The inspection of this system disclosed objectionable conditions, discussed under caption "Objectionable Conditions" items 3, 4 & 5.

NDA 20-958/S-011 of Famotidine Pepcid Complete Tablets

This inspection also covered the process validation study of NDA 20-958 of Pepcid Complete tablets (Famotidine) which lists McNeil Consumer & Specialty Pharmaceuticals, Las Piedras facility as manufacturer of coated Famotidine granulation. (b) (4) and (b) (4) are utilized to manufacture coated Famotidine granulation (See **Exhibit JEM 9**). The coated Famotidine Granulation is (b) (4) and (b) (4) into chewable tablets at the McNeil Lancaster site.

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The three coated famotidine validation lots were (b) (4) and (b) (4). All in-process and release testing results were within specification. The supported data was documented on (b) (4) Famotidine to Las Piedras, PR (b) (4) Report No.: (b) (4) approved (b) (4).

I reviewed the protocol and report, and I found no objectionable condition.

Facilities and Equipment System

During the inspection I covered the following areas as part of the assessment of this system: cleaning procedures including the cleaning and clearance of the packaging lines, and calibration and preventive maintenance for the manufacturing equipment.

The cleaning validation was based on collection of swab samples of hard-to-clean surfaces of the equipment.

Also, I reviewed the cleaning procedures and logbooks for the equipment to the packaging line.

I found discrepancies concerning to the line clearances and cleaning controls established in the packaging area. These discrepancies are discussed under caption "Objectionable Condition 1".

I reviewed and discussed reports for the Tylenol Arthritis Relief critical processing parameters with Ms. (b) (6) Reliability Engineer, and the preventive maintenance SOPs and (See Exhibit JEM 10). I asked Ms. (b) (6) for incidents related to out-of-tolerance events for critical equipment. Ms. (b) (6) told me that there were no incidents reported.

I found no discrepancies during the review of these records.

Laboratory System [MAM]

The Quality Control (QC) unit consists of one analytical laboratory area and one micro-laboratory (See floor plan in Exhibit MAM-01). The analytical laboratory is used for the testing of: stability samples, raw material, in-process and finished products. The QC department consists of one QC Manager (Carlos Nadal), (b) (4) and (b) (4) (See Exhibit MAM-02 for QA/QC organizational chart). The laboratory operates (b) (4). The majority of the instruments are qualified by the firm's personnel and some by outside contractors. The stability samples are stored in climatic chambers located at (b) (4). The samples are transported and tested at the McNeil plant in Las Piedras.

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A new QC laboratory has been constructed and finalized. The laboratory started the movement of equipment from the existing laboratory to the new facility. Mr. Carlos Nadal, QC Manager, indicated that this transition is been conducted by modules in order to maintain laboratory operation (See **Exhibit MAM-12** for floor plan and distribution of new laboratory). Mr. Nadal indicated that the existing laboratory will be eventually modernized and converted completely in to a micro-laboratory.

During my review of this system I observed that the laboratory investigations lacked to include personnel from the Quality Assurance for their evaluation and approval. The investigations are not reviewed by QA to assure that conclusions, root cause of out-of-specification or suspect results have a scientifically sound basis. These discrepancies are discussed under caption "**Objectionable Condition 6**".

The stability sample program for Tylenol common products has been tested with a non stability indicating method. This discrepancy is discussed under caption "**Objectionable Condition 7**".

NDA 20-958/S-011 & NDA 19-872 TAR

The Famotidine Coated Rotor granulator Particles (Pepcid Complete) for NDA 20-958/S-011 and the Acetaminophen Extended Release Caplets (Tylenol Arthritis Pain ER "TAR" NDA 19-872 GLP were evaluated. This evaluation consisted of analytical transfer method protocol, validation batches, procedures, review of analytical worksheets, and instruments used for the validation batches, stability studies (follow up studies), in-process testing and daily use operation for raw materials and Famotidine ^{API tests} (b) (4). The analytical validation batches for Famotidine were (b) (4) and (b) (4). See Exhibit MAM-04), and for TAR were (b) (4) and (b) (4). (See exhibit MAM-14).

NDA 20-958/S-011

The only concern related to this application is that the dissolution tests as per SOP # (b) (4) "Famotidine Coated Rotor granulated Particles" (See **Exhibit MAM-05**) did not consider the sample weight purity, which is obtained from the assay test. There is a (b) (4) result difference when sample correction is conducted (**Refer to Exhibit MAM-06**).

When I discussed with Mr. Maldonado, he acknowledged my concern; however, he delegated to Mr. Thomas J. Markley, Director Support Market Products, to respond. Mr. Markley mentioned that this product was a (b) (4) product that was acquired by McNeil and that procedure were transfer as is by the development group. Nevertheless, he acknowledged that the correction is required to assure the accuracy of results, and he promised to discuss the incident with the development group at McNeil Fort Washington.

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On 02/17/2005, I sent an E-mail to the reviewing chemist Dr. Vispi Bhavnagri related to the aforementioned concern. Dr. Bhavnagri responded on 03/09/2005 and concurred that the firm should be account the granules weight during the dissolution testing calculation. Also Dr. Bhavnagri will be requesting from the company to amend the supplement (Refer to **Attachment 4**) to reflect this change.

NDA 19-872 TAR

It was observed that the firm failed to place on the stability program the first three commercial production batches for the Tylenol Arthritis Pain ER Caplets following the commitment established in the NDA 19-872. This discrepancy is discussed under caption "**Objectionable Condition 3**".

During the review of the validation batches it was found that the Content Uniformity results are questionable or inaccurate. These discrepancies are discussed under caption "**Objectionable Conditions**" item # 6.C.a.

Also, during the review of the dissolution test (Profiles at (b) (4) in the SOP (b) (4) "Tylenol Arthritis Pain ER Caplets" (Exhibit MAM-13) it was noticed that the calculation formula did not include a correction required when the test is profiled Refer to **Verbal Observation 3**.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**Observations listed on form FDA 483**

OBSERVATION 1

Procedures for the cleaning and maintenance of equipment are deficient regarding inspection of the equipment for cleanliness immediately before use.

PRODUCTION SYSTEM

Specifically, the procedures and controls for the line clearance may not be sufficient to prevent mix-ups during the manufacturing / packaging processes as evidence of complaints received in 2004 related to packaging/mix-ups, and non-conformance events involving packaging lines. The following line clearance incidents occurred at the firm by the end of 2002 to 2004 in products that were released and distributed:

A. On 11/01/02, you detected a mix up of Tylenol PM Caplets and three (3) Extra Strength Geltabs shippers in the (b) (4) of the packaging lot FMA 200 of Tylenol PM Caplet. Your investigation (b) (4) identified that this lot was packaged in line (b) (4) after major cleaning was performed. The previous lot packaged in this line was the Extra Strength Geltabs twenty-four (24) counts lot FMA168. The investigation concluded that the (b) (4) stayed in the line after the mayor cleaning and line clearance inspection causing the mix-up. All finished goods packaged as lot FMA 200 Tylenol PM Caplets were approved and released for distribution on 11/13/02.

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B. On 04/10/03 the QA technician observed one bottle with (b) (4) white cap over the line accumulator during the packaging process of lot HDA 037 of Tylenol ES Gelcaps 150's. The Tylenol ES Gelcaps 150's required (b) (4). Your investigation (b) (4) indicates that the packaging plan started on 04/09/03, after line cleaning and clearance was done. This line was previously used to pack Motrin 250, a product that required (b) (4) white caps. This incident was detected after twenty (20) line inspections and one line audit by QA auditor. The investigation concluded that there was a possibility that the cap came from the previous batch. The lot was approved and released for distribution on 04/16/03.

C. On 04/13/03, at the beginning of the packaging production plan for Extra Strength Tylenol Tablets 100's, lot HDA 055, you detected forty (40) Regular Strength Tylenol Tablets over the filler machine. Your investigation (b) (4) identified Regular Strength Tylenol Tablets falling down from (b) (4) that should have contained only Extra Strength Tylenol Tablets. This bucket was used on 04/07/03 during the packaging of the lot HDA 054, Regular Strength product. The investigation concluded as most probable cause that the container was not properly cleaned, and/or not properly inspected before re-use it. On 04/29/03 all finished goods were approved and released for distribution.

D. On 07/19/04, one Tylenol Geltabs was detected in the filler machine during the packaging process of Extra Strength Caplets; lot JHA028 in line # (b) (4). Last packaging Extra Strength Geltabs in line # (b) (4) was on 07/14/04. Since then, five (5) major cleaning, seventy-three (73) visual inspections, and six (6) QA inspections have been performed before and/or during the packaging process of lot JHA028. Your investigation (b) (4) concluded as the most probable root cause that the Tylenol Geltabs detected came from the valve of the buckets used in the packaging process of Extra Strength Caplets.

E. During the packaging process of Motrin IB Caplet 100's, lot JLA 203, you detected a bottle of Motrin IB Tablet 100's, lot JLA 111. A major cleaning and line clearance were performed in line # (b) (4) before started the packaging process of lot JLA 203, also thirteen (13) line inspections were performed with acceptable results reported. Your investigation (b) (4) concluded that this incident was related to the clearance process, since the bottle was hidden in an area not covered by the line clearance procedure "PROCESS OF THE LINE CLEARANCE VERIFICATION OF THE PACKAGING AREA" (b) (4) effective date 07/19/2004. All finished goods were approved and released for distribution on 10/27/04.

F. On 10/27/04 during the packaging process in line # (b) (4) of Tylenol Sinus Caplet lot JMA294, you detected three double printed Tylenol Sinus Gelcaps mixed with the Tylenol Sinus Caplet product. Two of them were falling from (b) (4) through the line, and the third one was detected inside the blister card of package lot JMA294. Your investigation (b) (4) identified as inadequate cleaning of one of the plastic bucket as the most probable cause for this situation.

Reference: 21 CFR 211.67(b) (6)

Supporting Evidence and Relevance: [JEM]

During 2004, this firm identified about nineteen (19) consumer complaints potentially associated to product packaging/mix-ups, which are potentially related with inadequate clearance of the lines, and inspections of the buckets for holding oral-solid dosages to batches manufactured and packed prior or within the same period of time (See Exhibit JEM 11). However, management relied on the adequacy of cleaning and line clearance's controls to conclude that it was unlikely that the situation was originated within the manufacturing and/or packaging area at McNeil-Las Piedras even when incidents aforementioned concluded that the firm's established controls have not been effective.

The customer complaint data related to product mix-ups revealed that until December 31, 2004 135 consumer complaints were reported. From these, thirty-two (32) were excluded because the field

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samples were not sent and/or the lot number of the product was not provided by the customer; therefore, the QA unit did not conduct any investigation. These complaints showed mix-ups of products as well, but not investigated. (Refer to Objectionable Condition # 5).

In addition, management concluded that eighty-two (82) complaints were not related to their facility due to the high quantity of tablets found in the bottle(s) (more than 10 tablets). These complaints were not investigated. Nevertheless, on 04/13/2003, at the beginning of the packaging production plan of Extra Strength Tylenol Tablets, lot HAD 055, line # (b) an employee found forty (40) Regular Strength Tablets. The investigation (b) (4) concluded as most probable cause that the (b) (4) used during the packaging process was not properly cleaned, and/or properly verified, since the tablets were only located in the valve of the bucket, and were not visually detected by the packaging neither the compression operator (See Exhibit JEM 12). This incident indicates that is possible a product mix-up with several tablets.

On November 2004, various initiatives were conducted to assess the process, product and equipment to implement preventive and/or corrective actions to avoid mix-ups incidents. These initiatives were discussed during the inspection with Ms. Vilmarie Walker, Plant Manager and Mr. José O. Vives, Compression Manager. The main areas of potential risk were associated with product residues stuck in the bucket container valve area, bucket container handling during storage, packaging line clearance, and minor cleaning process (See Exhibit JEM 13).

An action plan was developed and corrective actions implemented.

Table # 1 Mixed Product Complaints Retrospective Analysis

<i>ACTION PLAN / STATUS</i>	
(b) (4)	July 19, 2004
	09/2004
	10/26/04
	02/05
	Second quarter 05

Refer to Exhibit JEM 14 page 4 of 9.

However, on 10/27/2004, during the packaging process in line (b) of Tylenol Sinus lot JMA294, the packaging operator detected three double printed Tylenol Sinus Gelcaps mixed with the Tylenol Sinus Caplet product. During the visual inspection of the packaging process, the operator detected two double printed Sinus Gelcaps falling from the (b) (4) through the line mixed with the sinus caplet product. This operator also detected another double printed Sinus Gelcap inside the last blister card package of lot no. JMA294. Until that moment, the packaging line periodic inspections performed by the operator and the QA technician were acceptable and no mixed product was detected. The

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investigation (b) (4) identified as the most probable cause the incorrect cleaning of plastic bucket after the last manufacturing step (See Exhibit JEM 15). This deviation was observed after the corrective actions were implemented.

From January 05 to present management has received fifteen (15) consumer complaints related to mix product packed between Sep/00 to 04/04 (See Exhibit JEM 14 page 5 of 9).

OBSERVATION 2

Routine calibration, inspection, and checking of automatic, mechanical, and electronic equipment are not performed according to a written program designed to assure proper performance.

A. Specifically, packaging critical parameters as (b) (4) and (b) (4) are not always performed and/or documented in the packaging batch record as required packaging procedure (b) (4) "PREPARATION AND START-UP OF A LOT (BATCH) RUN IN THE BOTTLE LINE". The following packaging process deviations occurred at the firm by the end of 2002 to 2004.

1. Your firm failed to document in the batch record the in-process critical parameters during the packaging process for Motrin IB Caplets 250 packaging lots FLA 270, FSA 129, HBA 132, HBA 302, and HJA 247 in line # (b) (4)
2. The mechanical challenges were not performed before starting the production plan for the Extra Strength Tylenol Gelcaps 50's packaging lot, HAA024, and Tylenol PM Geltabs 100's packaging lot, HEA 022 in line # (b) (4) and # (b) (4) respectively.
3. On 03/25/03 the packaging operator approved lines (b) (4) & (b) (4) to start production of Extra Strength Tylenol Gelcaps 100 and Extra Strength Tylenol Caplets 250 packaging lots HCA 195 & HCA 187 respectively, but he/she did not document, the approval of the mechanic challenges in the batch records.

B. Your laboratory GC calibration program is inadequate in that:

1. The GCs (b) (4) has no documented evidence that assure that complete calibration (Noise & drift and linearity for detector, reproducibility test for injector and temperature verification of the headspace oven) was performed. Moreover, this analytical equipment was used to execute the method transfer study for (b) (4) number (b) (4) dated (b) (4)
2. The GC (b) (4) used in raw material, specifically (b) (4) do not have reproducibility test for the (b) (4)

Reference: 21 CFR 211.68(a)

Supporting Evidence and Relevance A: [JEM]

In 2004, McNeil -Las Piedras received approximately thirteen (13) consumer complaints related to missing label (Exhibit JEM 16). Management identified as probable causes the conveyor speed and

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inefficacy of the line's sensor. During the inspection I observed that the in-process packaging test is not always performed or documented to assure that adequate control are in place to prevent mislabeling incidents. However, management continued to rely on the established packaging in-process control testing to release products.

The mechanics and/or line leaders have been failing to follow section (b) (4) of the packaging procedure (b) (4) (b) (4) dated (b) (4) which (b) (4) (b) (4) (See Exhibit JEM 17 page 3 of 6). In addition, there are instances when the packaging operators approved the lines to start production without documented evidence in the batch record that supported that the critical (b) (4) was done (See Exhibit JEM 18).

Failing to do a proper preparation and start up of a packaging line might be implicated to missing label type of complaints. For example, complaint investigation # (b) (4) identified as most probable cause the change in velocity of the conveyor that transports the bottle through the labeler. This change in velocity prevented the sensor to detect a mislabeled bottle and reject the bottle that follows the mislabeling (See Exhibit JEM 19 page 3 & 5 of 6).

On the other hand, complaint # (b) (4) concluded that the label missing incident was an isolated manufacturing occurrence, based on the rationale that the (b) (4) (b) (4) However, this complaint investigation identified that there was a possibility that the affected bottle was detected by the scanner, but not rejected by the system (See Exhibit JEM 20 page 2 of 3).

As a result, management performed a retrospective analysis to address the missing label product complaints. One of the potential causes was that labels not fully sealed to the bottle would fall during bottle travel through the (b) (4) (See Exhibit JEM 21 page 2 of 5). I was told by Ms. Ileana Zavala, Packaging Manager that the line only has (b) (4) Therefore, there is no other control implemented through the line that could detect a mislabeled bottle (See Exhibit JEM 21 page 4 of 5). Ms. Zavala told me that a (b) (4) corrective action.

Supporting Evidence and Relevance B-1: [EM]

There is no documented evidence of the last (b) (4) records for Gas Chromatograph (GC) number (b) (4) performed by the outside contractor. Also, the calibration reports dated on 05/06/04 (Exhibit EM-2) and 02/02/03 (Exhibit EM-3) did not stipulate the parameter of reproducibility for the detector and the injector, the linearity of the detector and the temperature verification for the (b) (4) The firm's procedure for GC number (b) (4) 'Use, Maintenance and calibration of the Gas Chromatogram System (b) (4) effective date 09/24/2004 (Exhibit EM-1) and protocols used did not require test nor documented calibration parameters and specifications. This

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GC (b) (4) was utilized for the execution of the method transfer study for Residual Solvent test number (b) (4) for (b) (4) NDA 20-958/S-011 dated on 02/02/03 (see Exhibit EM-4). This method transfer for the (b) (4) study is questionable, because instrument performance was not assured.

Supporting Evidence and Relevance B-2: [EM]

The calibrations of the GC number (b) (4) dated on 10/01/04 (Exhibit EM-7), 04/05/04 (Exhibit EM-8), and 09/15/03 (Exhibit EM-9) were performed with a calibration method protocol provided by the supplier. The supplier performed the calibration using (b) (4) that did not challenge the (b) (4) of the equipment (routinely used).

On 01/31/05 Mr. Maldonado provided to me a document titled "GC Calibrations" (Exhibit EM-5) on this subject. This document disclosed the following: that the noise test was not included as part of the equipment calibration, the (b) (4) did not cover the equipment operational range, and that the reproducibility for the headspace was not performed.

However, on February 9, 2005 (Exhibit EM-6) Mr. Walter Maldonado provided to me an additional memo indicating that the calibration records and the deficiencies identified were acknowledged and would be corrected. Furthermore the GC calibration requirements will be included in further calibration contractors' agreements. The basic requirements will be: (b) (4) and (b) (4) (b) (4) and (b) (4) and the (b) (4). Also, the SOP (b) (4) "Operation, Maintenance and Calibration Procedure for the (b) (4) Gas Chromatography with (b) (4) will be revised to include the required calibration tests, parameters and specification to be effective on April 2005.

OBSERVATION 3

Established sampling plans and laboratory control mechanisms are not followed and documented at the time of performance.

QUALITY SYSTEM

Specifically, as evidence in the following:

A. The stability sampling plan for Tylenol Pain ER Caplets was not followed in accordance with NDA 19-872 commitment in that the validation batches (b) (4) and (b) (4) were not place on the stability program.

B. Your laboratory fails to document on the analytical worksheets and logbooks the sample handling and preparation for all test procedures. The laboratory personnel is being documenting the sample weight only, however, there is no documentation for other sample preparation parameters such as; dilutions, sample transfer to assure that procedure was followed.

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Reference: 21 CFR 211.160(a)

Supporting Evidence and Relevance 3-A: [MAM]

During the review of the application NDA 19-872 “Tylenol Pain Extended Relief Caplet (TAR)” 650mg, it was noticed, that the validation batches (b) (4) and (b) (4) (See COA on Exhibit MAM-14) were not placed in the stability program, even though it was a commitment established on the NDA submission (see NDA commitment on Vol. (b) (4) Sec (b) (4) page (b) (4) on exhibit MAM-07). The firm placed on stability the (b) (4) as per procedure # (b) (4) (b) (4) “Stability Study Design and Acquisition” (See section (b) (4) of Exhibit MAM-10, page 3 of 10) instead of the (b) (4) which were manufactured prior to the marketed batches. Furthermore, when packaging batches are comprised of more than one bulk batch, the first or beginning samples of the packaging run is pulled for the stability program (see section (b) (4) of Exhibit MAM-10, back page 3 of 10). The first three packaging batches for TAR were lots (b) (4) and (b) (4). The “packaging register sheet”, on exhibit MAM-09, evidenced that none of the validation batches were placed on stability except the beginning packaging batch # (b) (4) (See stability monitoring sheet on Exhibit MAM-15). This information was also confirmed by the “Stability Commitment” power point presentation on exhibit MAM-08 that summarizes the concern.

In addition, the firm did not follow procedure # (b) (4). Section (b) (4) indicates that the lot with the oldest month must be packed first in run. However, the manufacture batches (b) (4) (b) (4) and (b) (4) compounded on 05/01 were placed first for the packaging lot (b) (4) even though the validation batches were compounded on 02/01. The compounded dates are evidenced in exhibit MAM-16 and “Stability Commitment” on exhibit MAM-08, page 4 of 6.

Discussion with Management:

Management was aware of this stability deficiency since a similar observation was addressed in previous Form FDA 483, dated 09/09/02, which indicates that “the NDA commitment for Motrin IB Gelcaps was not followed”. Management indicated that they addressed this deviation in the previous response provided to the agency, and promised to conduct additional assessment to identify any similar situation. However, management identified that TAR was missing the stability studies for the validation batches and no documented evidence was submitted to the agency. The corrective action implemented by management was to conduct special tests on a retention sample of TAR from Lot (b) (4) (not from validation batches). Furthermore, the stability procedure # (b) (4) “Stability Study Design and Acquisition” has not been reviewed to correct deficiencies to prevent re-occurrence.

This is shown in the power point presentation “2002 Stability Commitment to avoid missing stability samples” in exhibit MAM-17. Also, Mr. Maldonado provided an official memorandum dated on 02/09/05 (see Exhibit MAM-18) that addressed the concern mentioned above. The procedure # (b) (4) and procedure # (b) (4) “Handling of Stability Sample in the Packaging Area”

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were modified during the inspection as evidenced in change control # (b) (4) and draft procedures presented (see Exhibit MAM-19).

Supporting Evidence and Relevance 3-B: [MAM]

It was noticed during the review of the analytical raw data that the sample preparations were not documented in logbooks and/or analytical worksheets. The analysts' practice is to document the sample weights in the balance logbook. However, there is not documented evidence to show the sample preparations. As examples of this practice can be observed in analytical batch records for (b) (4) (b) (4) batch (b) (4) and (b) (4) on exhibit MAM-04, pages 2-3, 6, 13-14, 17-18, 20, 25-26 & 32 of 34.

OBSERVATION 4

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically, the laboratory investigations generated have not being evaluated and approved by Quality Assurance. The laboratory investigations conducted by the laboratory personnel during 2002 to present were not informed to your quality assurance unit for a proper review and disposition in order to implement proper corrective and/or preventive action.

Reference: 21 CFR 211.22(a)

Supporting Evidence and Relevance: [MAM]

During the review of the laboratory investigations, from 2002 to present, I observed that the investigations did not include the Quality Assurance final evaluation and approval. In addition, the currently procedure (b) (4) "Laboratory Investigation and Retest Procedure" (see exhibit MAM-20) failed to include the approval of the QA unit. These deficiencies mislead the laboratory to assure that the root cause, and conclusions for the OOS results obtained are based on a scientifically sound basis in order to invalidate original data and to implement appropriate corrective and/or preventive actions. Examples of these investigations are discussed under caption "Objectionable Condition # 6".

Discussion with Management:

Mr. Walter Maldonado acknowledged the deficiency and indicated that this issue will be addressed. He added that they were in the process of an implementation of a new position that would review the investigations and recommend approval. However, this position did not exist at time of inspection. During the inspection Mr. Maldonado indicated that the position "QA Specialist" was approved by their upper management and was filled during the inspection and that an external resource with expertise in laboratory investigation will be contracted to provide training. This new person will be reporting to Wanda Cancel, QA Manager (see new QA/QC organizational chart in Exhibit MAM-21)

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In addition, the procedure (b) (4) was modified to include the QA approval (See draft procedure on exhibit MAM-22 page 10 of 13). Mr. Maldonado mentioned that in order to improve the laboratory investigation, a new investigation (b) (4) system will be implemented that would allow (b) (4) and (b) (4). All the mentioned above is addressed in memorandum letter dated 02/09/05 (see Exhibit MAM-23).

During the inspection closeout there were no comments other than the information provided during the inspection and that they would respond in writing

OBSERVATION 5

Written records are not always made of investigations into unexplained discrepancies.

Your firm does not always perform consumer complaint investigations on consumer's complaints that provide the product's name, control number, and expiration date, because of lack of field sample for evaluation.

Specifically, for consumer complaints # (b) (4) of Tylenol PM Gelscaps lot # FJA063, and Imodium A-D Caplets lot # HJA194 respectively, your QA unit failed to conduct an investigation for a possible mix-up by products due to lack of a field sample for evaluation.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance: [JEM]

The QA unit does not perform consumer complaint investigations when the field sample is not provided. I was told by Ms. (b) (6) Compliance Specialist that the SOP "Complaint Investigations" (b) (4) dated 10/09/03 stipulates that investigation may not be required when a product field sample or/batch control number is not available or is incorrectly reported (See Exhibit JEM 22 page 3 of 4). Nevertheless, I explained to Ms. (b) (6) that there are instances (complaints # (b) (4)), when the consumer provided the name of the product, the control number, and the expiration date and no QA investigation was performed. No comments by firm's official (See Exhibit JEM # 23).

OBSERVATION 6

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

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LABORATORY SYSTEM

A. Your firm approved and released for distribution lots of Extra Strength Tylenol Caplets (Lots: FHA204, FHA200 and FHA205), Extra Strength Tylenol PM (Lots: FHA223, FHA124 and FHA055) and Extra Strength Tylenol Gels (Lots: FHA208 and FHA210), which may have been possibly contaminated with micro organisms, as evidence on a supplier's memo dated on 7/18/2002. This memo mentions an investigation due to an off-colored appearance of the (b) (4) raw material lot # (b) (4) used in the manufacturing process of the aforementioned products. The supplier indicated that the off-colored was found to be mold growth. Nevertheless, you released these lots based on the microbial testing results obtained for Motrin number FHA 219, FHA 137, FHA 040 lots manufactured using the same lot of (b) (4) even though you and the supplier observed the off-colored randomly among raw material drums.

B. Validation study "Cleaning Validation Protocol Number (b) (4) on 07-18-1995" for (b) (4) for Extra Strength Tylenol Gels & Gels does not assure that the cleaning process is effective removing micro organism. Your validation study obtained ten (10) Non-Conformance Report (NCR) investigations related to out-of-specification for Total Microbial Count (TMC) in the valves and pumps sample points on the (b) (4). The re-validation conducted on 10/03, showed other seven (7) NCR investigations of OOS for TMC, but the root cause has not been identified.

C. Your laboratory investigations reports lacked to include documented evidence to support your conclusions and scientific rationale used to identify possible root cause, and to invalidate the original data. Your laboratory investigations only address the product disposition and do not extend to other product batches that may have been associated with the specific failure or discrepancy.

For example,

a. Your laboratory obtained an out-of-specification (OOS) result of sample # (b) (4) for content uniformity testing of Tylenol Arthritis ER Caplet Batch (b) (4) (validation batch). Your investigation report # (b) (4) concluded that the OOS result was caused by a wrong stock sample preparation. Nevertheless, the final result, reported from the re-analysis, of the product was obtained from an aliquot taken from the same stock sample.

b. Your investigation report # (b) (4) of Diphenidramine Hydrochloride, USP (DPH) disclosed that assay test were out of specification (b) (4) for batches (b) (4) and (b) (4). This investigation concluded that the results obtained were caused by a (b) (4) in the HPLC system. However, all chromatographic parameters were within specification. In addition, there is no documented evidence that shown that an evaluation was performed to the HPLC injector.

c. Your investigation report # (b) (4) concluded that the (b) (4) for batch (b) (4) and (b) (4) were caused by a wrong sample preparation. However, the batches # (b) (4) (b) (4) and (b) (4) concurrently analyzed were not questioned in the investigation to assure that the results obtained are accurate.

c. Out-of-specification result was obtained for Motrin IB Gels Batch (b) (4). Your investigation report # (b) (4) (b) (4) identified as root cause wrong sample preparation (b) (4). However, batch (b) (4) was re-analyzed and released using the original stock sample solution. In addition, other lots # (b) (4) and (b) (4) analyzed by the same analyst were approved and released without verifying the accuracy of the results obtained.

Reference: 21 CFR 211.160(b)

Supporting Evidence and Relevance 6-A: [MAM

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During the review of the Action Notice (investigation conducted on raw material upon arrival or during the manufacturing process, not related to finished product) it was noticed that the firm released lots of Extra Strength Tylenol Caplets (Lots: FHA204, FHA 204, FHA200 and FHA205), Extra Strength Tylenol PM (Lots: FHA223, FHA124 and FHA055) and Extra Strength Tylenol Gels (Lots: FHA208 and FHA210) without the assurance that the finished product did not contain objectionable micro-organisms. The Action Notice # 2D-091 (Exhibit MAM-24), and NCR # (b) (4) (Exhibit MAM-25) was generated due to large atypical and discolored particles that were found inside the drums that contain (b) (4) Lot: (b) (4) (vendor lot: (b) (4) used as a raw material in the manufacturing process of the aforementioned products.

The investigation and official memo dated on 7/18/2002 provided by the raw material's supplier indicated that the off-colored material was found to be mold growth. The firm had used (b) (4) drums, and found atypical and discolored flakes or chunk material in identified drum (b) and (b) which were not used during the manufacturing process

The investigation disclosed that the chunks were related to the starch containing the suspect appearance that the supplier identified as mold.

Nevertheless, firm's officials did not question the supplier nor conduct any additional testing to confirm that the finished products were within microorganisms specification. Management relied on the micro-organisms test conducted for Motrin finished products that were manufactured using the same starch lot number and that obtained acceptable results.

According to supplier's memo and firm's investigation the flakes or chunks beside the drum (b) and (b) could be found in other drums randomly.

Discussion with Management:

Mr. Maldonado mentioned that the supplier did not assure that the particles contained mold growth, because they were detected with a microscope. It was indicated to Mr. Maldonado and the management team that the supplier's investigation conducted several test examinations of the particles with a stereomicroscope, with a polarized light microscope and infrared tests, and that all tests concluded or suggested that the particles contained starch and mold. In addition, the Non Conformance Report did not have any documentation re-bottling allegations to the supplier. The firm returned all drums not used to supplier because there was no assurance of other particles encountering.

During the inspection closeout, I indicated to the management team that during the review of the Non Conformance Report (NCR) No. (b) (4) I observed a table summarizing additional products, also affected by the starch. The lot: 2A03131 listed the same batch of supplier vendor lot: (b) (4) (same as previous investigated lot). This was noticed when non colored particles were observed also in drums when they were opened (Refer to NRC No. (b) (4)). However, it was voided and attached to NCR

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No. (b) (4) The use of lot: (b) (4) is mentioned in the investigation summary dated on August 6, 2002 and in (b) (4) 'Lots Produced with Reference Materials in the exhibit MAM-25, pages 3 & 47 of 52.

Moreover, the manufacturing investigation NCR No. (b) (4) did not include the affected products of lot: 2A03131 manufactured with this starch lot: (b) (4) which are the following:

Extra Strength Tylenol Caplets Lots: FHA245, FHA 169, FHA205, FHA270, FHA272, FHA271, FHA274, FHA275, FHA201, FHA151, FHA155, FHA156, FHA168, FHA157, FHA204, and FHA284

- Extra Strength Tylenol PM Lots: FHA224, FHA296, FHA221, FHA300 and FHA225
- Extra Strength Tylenol Gelcaps Lots: FHA212, FHA211, FHA284 and FHA283
- Tylenol Arthritis Pain ER Lots: FHA235, FHA234, FHA233 and FJA015
- Extra Strength Tylenol Tablets Lots: FHA192, FHA262, FHA191, FHA261
- Motrin Products: Lots: FHA238, FHA139, FHA135, FHA136, FHA220, FHA216, FHA215, FHA214, FHA214, FHA207

Supporting Evidence and Relevance 6-B: [EM]

The firm obtained OOS results for cleaning samples on (b) (4) manufacturing equipment during (b) (4). The OOS results obtained were observed specifically on valves and pumps of the (b) (4) cleaning sampling points. The cleaning validation of this equipment was performed on 07/18/1995. However, this validation study has shown to be questionable since the following Non Conformance Reports were generated and no root cause was identified:

- (b) (4) dated (b) (4) Exhibit EM-10)
- (b) (4) dated (b) (4) (Exhibit EM-11)
- (b) (4) dated (b) (4) (Exhibit EM-12)
- (b) (4) dated (b) (4) Exhibit EM-13)
- (b) (4) dated (b) (4) Exhibit EM-14)
- (b) (4) dated (b) (4) Exhibit EM-15)
- (b) (4) dated (b) (4) Exhibit EM-16)
- (b) (4) dated (b) (4) (Exhibit EM-17)
- (b) (4) dated (b) (4) (Exhibit EM-18)
- (b) (4) dated (b) (4) Exhibit EM-19)

As a result, a re-validation "Cleaning Validation Report for the (b) (4) Protocol number (b) (4) Revision No. (b) (4) dated (b) (4) (Exhibit EM-20) was executed. However, the firm continues obtaining OOS results for microorganisms (Refer to (b) (4) dated (b) (4) (Exhibit EM-21), (b) (4) dated (b) (4) Exhibit EM- 22), (b) (4) dated (b) (4) (Exhibit EM-23) and (b) (4) dated (b) (4) (Exhibit EM-24), and no root causes have been identified.

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Discussion with Management:

Mr. Walter Maldonado provided an official memo dated on February 9, 2005 responding to the concern that arose from the cleaning validation audit. In this memo, firm's officials indicate that the annual certification of the effectiveness of the cleaning procedure for the manufacturing equipment will be addressed. The master validation plan for the cleaning of pharmaceutical manufacturer and packaging equipment will be updated to include: product contact manufacturing equipment, swab samples for active ingredients, cleaning agent and bio-burden levels will be taken in addition to visual inspection. In addition, a monitoring procedure will be established annually, unless a different monitoring interval is established after final evaluation. A new SOP (b) (4) "Microbiological and analytical monitoring of equipment cleaning" (see draft on exhibit EM-25, pages 1-3 of 14) was developed that will encompass the annual cleaning monitoring for bio-burden.

Supporting Evidence and Relevance 6-C: [MAM]

During the review of the laboratory investigation reports, I observed that management lacked to include documented evidence to support their conclusions and scientific rationale used to invalidate original data.

Evidences of these deficiencies are:

- a. During content uniformity testing of Tylenol Arthritis ER Caplet Batch (b) (4) (validation batch) the laboratory obtained an out-of-specification result for sample # (b) (4). The investigation report # (b) (4) (Exhibit MAM-11) concluded that the OOS result was caused by not (b) (4). However, the laboratory re-analyzed sample # (b) (4) and re-injected the other samples using an (b) (4). (b) (4) The laboratory released the test based on the results obtained. Furthermore, the other validation batches (b) (4) and (b) (4) concurrently tested were not questioned nor verified to assure the accuracy of the results.
- b. The investigation report # (b) (4) (Exhibit MAM-27) for Diphenidramine Hydrochloride, USP (DPH) disclosed an out-of-specification limit results for batches (b) (4) and (b) (4) in the (b) (4). The investigation concluded that the low results were caused by a (b) (4) (b) (4) in the HPLC system; even though; the investigation revealed that the system suitability and overall standard control were within specification. Furthermore, the assay is injected in duplicate and both batches replicate injections confirmed the results. The proposed corrective action did not address an evaluation of the HPLC injector to prevent re-current events.

Investigation reports evaluated that show the failure to have adequate scientific justification are as follow:

- i. The invalidation of data for investigation report # (b) (4) (Exhibit MAM-28) for Tylenol Sinus Caplets Batch (b) (4) is not justified. The investigation disclosed an out-of-specification result (b) (4) for sample # (b) (4) of the content uniformity testing. The most probable cause was related to loss of sample (approx. (b) (4)) caused by a

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glassware crack not detected during analysis and/or re-measurement testing. The investigation lacked to document the incident such as; loss of volume, glassware crack, spills, etc. to support probable cause.

- ii. In the investigation report # (b) (4) (Exhibit MAM-29) for Tylenol PM Geltabs Batch (b) (4) the laboratory invalidated original data with no scientific justification. The investigation disclosed that the assay results were out-of-specification. The results were confirmed by re-measurement. A re-test was performed by second analyst obtaining results within specification. The investigation concluded that there was an assignable cause. However, did not address which one. Moreover, the original results were invalidated with no justification, probable cause and conclusion. The corrective action indicated that the situation was discussed with original analyst to prevent re-current discrepancies, but did not indicate what situation was. In addition, the associated batches were not questioned during this investigation.
- iii. The investigation report # (b) (4) (Exhibit MAM-30) for (b) (4) (b) (4) disclosed an out-of-specification-result for batches (b) (4) and (b) (4). The investigation concluded that the (b) (4) results were caused by (b) (4). A (b) (4) for both batches were conducted to invalidate the original based on the rationale of "handling problem that occur during the sample preparation".

Evidence of corrective actions that only address the product disposition rather than to correct or prevent the cause were observed in the following:

- i. The investigation reports # (b) (4) (Exhibit MAM-31) and (b) (4) (Exhibit MAM-32) concluded that the cause of the OOS results were caused by a wrong volume (b) (4) for product HPLC acquisition template. Nevertheless, the correction was not made until the third incident was originated in investigation report # (b) (4) (Exhibit MAM-33).
- ii. The investigation reports (b) (4) (Exhibit MAM-34), (b) (4) (Exhibit MAM-35), (b) (4) (Exhibit MAM-36) and (b) (4) (Exhibit MAM-37) identified as most probable causes such as (b) (4) and (b) (4). However, there is no documented evidence of the corrective actions implemented.

Evidence of investigations that had no proper assessment of other batches involved or related to investigations was noted in observation 6.C.c. and d.

- c. The investigation report # (b) (4) (Exhibit MAM-30) for (b) (4) concluded that the (b) (4) for batch (b) (4) and (b) (4) were due to "handling problem that occurred during the sample preparation". However, the batches # (b) (4) and (b) (4) concurrently tested were not questioned in the investigation.
- d. The investigation report # (b) (4) (Exhibit MAM-27) for Motrin IB Gelcaps Batch (b) (4) disclosed an OOS result for the (b) (4). It was concluded to be poor

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(b) (4) of the stock sample that causes the high results. The laboratory re-analyzed and re-injected the sample using an (b) (4) (b) (4). Nevertheless, the laboratory released the test based on the new results obtained. In addition, other lots # (b) (4) (b) (4) and (b) (4) concurrently tested were not questioned to assure the accuracy of results.

Other investigation reports evaluated, that failed to have proper assessment of other batches during the investigation, are the following:

- i. The investigation report # (b) (4) (Exhibit MAM-38) for Acetaminophen USP Batch 2A05134 disclosed that the (b) (4) was out of specification (b) (4). The investigation concluded that the most probable cause was due to a bad pipetting or fills to volume technique used. However, the other batches (b) (4) and (b) (4) concurrently tested were not questioned to assure the accuracy of results.

Discussion with Management

Mr. Maldonado agreed with the aforementioned concerns and mentioned that the proposed corrective actions will be addressed in **Objectable Condition # 4** in order to avoid further deviations.

OBSERVATION 7

The written stability program for drug products does not include reliable test methods.

Your firm lacks a stability indicating test method capable to detect (b) (4) in stock sample matrix for the following marketed products: Extra Strength Tylenol Caplets (ESK), Extra Strength Tylenol Geltabs (ESJ), Extra Strength Tylenol Gelcaps (ESG), Extra Strength Tylenol Cool Caplet (ESK COOL), Regular Strength Tylenol Tablet (RST), Extra Strength Tylenol Tablet (EST), Extended Release Tylenol Gelcaps (ERG).

Reference: 21 CFR 211.166a) (3)

Supporting Evidence and Relevance: [MAM]

During the review of the stability program it was noticed that all Tylenol common products used the same assay method to test the finished product and stability samples (UV spectroscopy). However, this method has not been demonstrated to be a stability indicating, since is not capable to detect the (b) (4)

The following analytical procedures used the UV spectroscopy technique:
(b) (4) "Extra Strength Tylenol Caplets" (Exhibit MAM-39, page 4 of 6)

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- (b) (4) 'Tylenol Geltabs" (Exhibit MAM-40, back page 4 of 6)
- (b) (4) 'Tylenol Gelcaps" (Exhibit MAM-41, back page 4 of 6)
- (b) (4) Extra-Strength Tylenol® Cool Caplet" (Exhibit MAM-42, page 4 of 6)
- (b) (4) Regular Strength Tylenol Tablets" (Exhibit MAM-43, page 4 of 6)
- (b) (4) "Extra-Strength Tylenol Tablets" (Exhibit MAM-44, page 4 of 6)
- (b) (4) 'Tylenol Extra-Strength Rapid Release Gels" (Exhibit MAM-45, back page 4 of 6)

Discussion with Management:

Mr. Maldonado provided a study conducted on 9/22/99 that allegedly demonstrates that the UV testing method used for the common Tylenol is a stability indicating (See "Stability Indication of the Adult Tylenol Ultraviolet Spectroscopy Assay Methods" in exhibit MAM-03, page 2 of 5). However, it was indicated to Mr. Maldonado that the study did demonstrate that the (b) (4)

(b) (4) and that the acetaminophen (b) (4) can be accurately quantified in the presence of (b) (4) with no discernable change in UV spectrum (b) (4) is not detectable in sample matrix).

Furthermore, the study revealed that the (b) (4) was measured in a (b) (4) and gave an (b) (4) and that the (b) (4) (sample matrix or sample active ingredient) measured in a (b) (4) (sample is (b) (4) gave an (b) (4)

Therefore, this study clearly demonstrates that whether the (b) (4) was in the same matrix of the sample it could not be possible to detect by the UV testing method, since the (b) (4) (b) (4) of sample matrix would be significantly over the (b) (4)

Finally, Mr. Maldonado and Mr. Miller acknowledged the concern, and promised to evaluate and develop a new methodology that meets the stability indicating method requirements.

OBSERVATION 8

The use of recording devices not meeting established specifications was observed.

The (b) (4) and (b) (4) Software used by your firm to record all chromatographic raw data were found deficiency in that:

A. Your firm lacks a test procedure for the (b) (4) qualification, and criterion established and/or a periodically Operation Qualification (OQ) to assure instrument performance.

B. The OQ for the lace is deficient in that it was performed using a non certified standard.

C. Your firm lacks to include on the validation protocol (b) (4) for the (b) (4) Software, the mathematical calculations and formulas for content uniformity and dissolution test by HPLC technique for all products

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D. The (b) (4) current in use are not properly identified and stickers of current calibrations are not placed indicating that these instrument are qualified and ready for use.

E. Your firm lacks to have the current diagram or layout for the (b) (4) approved with detailed connectivity between the (b) (4) to patch panel and to the drops in order to trace information and qualification of (b) (4) and (b) (4)

Reference: 21 CFR 211.160(b) (4)

Supporting Evidence and Relevance 8-A, B &D: [MAM]

The laboratory uses a (b) (4) to store, transfer and process the analytical raw data generated by their HPLC's to (b) (4). In the evaluation of this system it was found that there was no test procedure for the operation qualification and specification of the (b) (4). During the review it was found that the (b) (4) were qualified when installed; however, no other OQ has been conducted even though the supplier's recommendation is at least annually. Moreover, the (b) (4) performed was deficient in that the qualification was conducted with an in-house standard and not with a certified standard or a certified peak generator. Example of this is evidence in OQ conducted of (b) (4) exhibit MAM-46. In addition, it was observed during the laboratory walk through that the (b) (4) are not properly labeled with a calibration sticker that would assure instruments are qualified for usage.

Supporting Evidence and Relevance 8-C: [MAM]

In order to review the mathematical calculations of the (b) (4) and the (b) (4) Software a validation protocol (b) (4) (Exhibit MAM-47) was developed. This report includes the mathematical calculations and formula for the assay of all products. However, it did not include the mathematical calculations and formula for content uniformity and (b) (4). The protocol (Exhibit MAM-47, page 6 of 6) concluded that the templates can be used for other tests, even though; the mathematical calculations for each product are different.

Supporting Evidence and Relevance 8-E: [MAM]

During my revision of the (b) (4) and network connectivity I observed that the current diagrams and/or layout for the network and (b) (4) provided for review (See exhibit MAM-48) were not approved and did not contain details of the network connection. Also, it did not compare with the physically observed at (b) (4). The diagram for the (b) (4) previously provided did not include a patch panel (where all the drop connections are placed), interfaces panels related to business connections (used for office and network) and detailed connectivity between the (b) (4) connected to the patch panel in order to trace information and qualification of (b) (4) and (b) (4)

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Discussion with Management:

All deficiencies mentioned above were explained and acknowledged by the management team and assistant engineering. Mr. Adalberto Betancourt, Engineering Sector Plant Manager provided during the inspection an acceptable draft layout (Exhibit MAM-49) of detailed network connectivity and infrastructure between the (b) (4) and the servers used in the entire plant. Also, Mr. Walter Maldonado provided an official memo dated on 2/9/05, and a (b) (4) acceptable layout in order to address the concern (See exhibit MAM-50 for the memo and (b) (4)). This memo addressed the layout drawing for (b) (4) which was updated to reproduce the connection between the network devices, and a commitment that similar action will be taken for all the other (b) (4) (b) (4).

REFUSALS

No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On 02/23/05, we issued the Form FDA-483 to Mr. Jorge Ros, General Manager. Other individuals present during the closing meeting are listed below:

- Mr. Walter Maldonado, QA/QC Manager
- Ms. Vilmarie Walker, Plant Manager
- Ms. Edna M. Maldonado, QSC NX Manager
- Mr. Bob Miller, VP Quality Sciences & Compliance Division
- Ms. Wanda Cancel, QA Manager

Since the observations were fully discussed during the inspection, the firm officials did not ask any questions. However, Mr. Miller and Mr. Maldonado were interested to know the district policy regarding **Objectionable Condition # 3** listed on Form FDA 483, since similar deviation was found in previous inspection. However, I told to Mr. Maldonado & Mr. Miller that the TAR NDA19-872 had not been covered in a previous inspection; therefore, the deficiency has to be cited.

In addition Mr. Ros and Mr. Miller asked about the ranking of the observations and the impact in terms of a regulatory perspective. I told firm's officials that the conditions listed may, after further review by the Agency, be considered to be violations of the Act, and different regulatory actions are available to FDA depending on the significance of the deviations and corrective actions. Mr. Miller promised a written response to the observations in the next two or three weeks.

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Also, Mr. Maldonado mentioned that verbal observations discussed below will be addressed. However, the management team will evaluate if they would be addressed in the written response.

ADDITIONAL INFORMATION [MAM]

1. During the walk through of the laboratory, I found inside a refrigerator, volumetric flasks of (b) (4) and (b) (4) standards that were not properly labeled. The standards were prepared and stored in the refrigerator; however, there was no information to trace standard preparation, lot number, analyst and date.

It was indicated by Mr. Carlos Nadal, QC Manager that standard solutions were disposed immediately after my observation and that he will re-emphasize to the personnel to comply with proper standard identification and storage.

2. The analytical results are not documented to comply with specifications. This was observed with the content uniformity and (b) (4) results that are not documented individually in the analytical worksheet or in the Certificate of Analysis (COA), only the ranges. It was indicated to Mr. Nadal that each result obtained should be documented individually. The deficiency was also noticed in the Identification testing by IR and Retention time. Example of these deficiencies can be found in validation batches (b) (4) and (b) (4) for Famotidine (Exhibit MAM-04 pages 1, 3, 12, 14, 24 & 26 of 34).

Mr. Maldonado, QA Manager acknowledged the deficiency and promised to review the procedures to incorporate all results as part of the analytical batch records and the COA's.

3. The (b) (4) for TAR is profiled at (b) (4) per SOP (b) (4) "Tylenol Arthritis Pain ER Caplets" (See exhibit MAM-13). It was noticed that the procedure did not include the corrective factor when a test is profiled.

The firm's officials promised to address the issue and will review the procedure to include the formula and the corrective factor.

4. The (b) (4) was being used below the acceptance level that was intended for use in the qualification. The balance was used several times for the weighing of standards (b) (4) which is the (b) (4). An example of this deficiency was observed in a balance logbook (Exhibit MAM-26) where the weight of Povidone USP for the Nitrogen Content Determination limit test is below the minimum weight determination.

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Mr. Walter Maldonado acknowledged the deficiency and indicated that this incident was going to be addressed and that will make necessary adjustment in order to prevent re-occurrence.

SAMPLES COLLECTED

DOC Sample # 220337 for Tylenol ES 200 caplets 500 mg packaging lot JHA028 was collected to document cGMP deviations and interstate movements. The sample consists of affidavit, manufacturing and packaging records with copies of labels, invoices and shipping documents.

The Form FDA 463a was issued to Mr. Maldonado; however, Mr. Maldonado refused to read, listen and sign the form based on firm's policy.

VOLUNTARY CORRECTIONS

During the inspection, I reviewed the firm's corrective actions from the previous inspection. Management implemented and reviewed several SOPs to address the Objectionable Conditions. I found no deficiencies except **Objectionable Condition # 3** previous discussed in this report.

During this inspection management also generated Change Control Requests to modify the following SOPs:

Table # 2 Voluntary Corrections

Description	Description of the Change
SOP (b) (4)	Modify SOP to include the QA unit approval as the final as the final approval to the lab investigations.
SOP (b) (4)	Modify SOP to include the operator's name and shift to the Non Conformance Report investigations, (b) (4)
SOP (b) (4)	Modify SOP to add a statement that will describe the details on how to document in the (b) (4)
SOP (b) (4)	Modify SOP to specify that the first three (b) (4)

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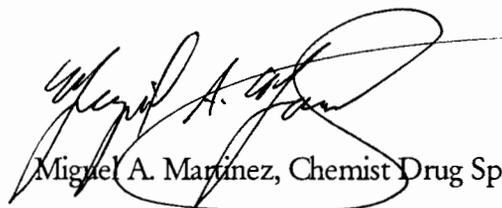
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These proposed corrective actions appear to be adequate if implemented and monitored as stated.



Jose E Melendez, Investigator



Miguel A. Martinez, Chemist Drug Specialist



Edwin Martinez, Chemist

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EXHIBITS COLLECTED

JEM

1. Current registration dated February 04, 2004
2. Products List
3. Employees contact list
4. Organizational Chart
5. SOP "Master for lot number and expiration date"
6. Firm's Complaints reviewed list
7. FDA Complaints reviewed list
8. Process Description for Tylenol Arthritis Pain Extended Relief Caplet
9. Famotidine Manufacturing Process Flow Diagram
10. TAR Critical Processing Parameters Instruments Calibrations
11. McNeil LP 2004 Mix-up Complaints
12. Investigation Report (b) (4) dated on (b) (4)
13. Summary Report for Product Mix-up Prevention Strategy
14. Mixed Product Complaints retrospective analysis
15. Investigation report (b) (4) dated on (b) (4)
16. Missing labels complains list
17. Copy of SOP (b) (4) "Preparacion e inicio de la corrida de un lote"
18. Investigation report (b) (4) dated on (b) (4)
19. Complaint report # (b) (4) dated on (b) (4)
20. Complaint report # (b) (4) dated on (b) (4)
21. Missing labels product complaints retrospective analysis
22. SOP (b) (4) "Complaint Investigation"
23. Complaint reports # (b) (4) dated on 06/23/2004 & 06/09/2003 respectively

MAM

1. Laboratory floor plan with identified drops
2. QA/QC Organizational Chart
3. Study "Stability Indication of the Adult Tylenol Ultraviolet Spectroscopy Assay Methods"
4. Validation Batches (b) (4) and (b) (4) for Famotidine
5. SOP # (b) (4)
6. Result difference when sample correction is conducted for (b) (4)
7. "Stability Commitment" established for NDA 19-872
8. TAR Stability Presentation
9. The "packaging register sheet" for Lot (b) (4)
10. SOP # (b) (4) Stability Study Design and Acquisition
11. The investigation report # (b) (4)
12. New QC Laboratory floor plan and distribution

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13. SOP # (b) (4) "Tylenol Arthritis Pain ER Caplets"
14. COA of validation batches (b) (4) and (b) (4) for Tylenol Arthritis Pain ER Caplets.
15. Batch # (b) (4) Stability Monitoring Sheet
16. The compounded dates of TAR validation batches and other TAR batches
17. 2002 Stability Commitment to avoid missing stability samples
18. Memorandum letter dated on 2/9/05 related to TAR Stability Validation
19. Change Control Document # (b) (4) and Revised Draft SOP# (b) (4) Stability Study Design and Acquisition & SOP# (b) (4) "Handling of Stability Sample in the Packaging Area".
20. SOP (b) (4) Laboratory Investigation and Retest Procedure
21. New QA/QC Organizational Chart
22. Revised SOP (b) (4) Laboratory Investigation and Retest
23. Memorandum Letter dated 02/09/05 related to QA not evaluating investigation
24. The Action Notice # (b) (4)
25. Non Conformance Report No. (b) (4)
26. Page copy of balance (b) (4) logbook
27. The investigation report # (b) (4)
28. The investigation report #
29. The investigation report #
30. The investigation report #
31. The investigation report #
32. The investigation report #
33. The investigation report #
34. The investigation report #
35. The investigation report #
36. The investigation report #
37. The investigation report #
38. The investigation report #
39. SOP # (b) (4) Extra Strength Tylenol Caplets
40. SOP # (b) (4) Tylenol Geltabs
41. SOP # (b) (4) Tylenol Gelcaps
42. SOP # (b) (4) Extra-Strength Tylenol® Cool Caplet
43. SOP # (b) (4) Regular Strength Tylenol Tablets
44. SOP # (b) (4) Extra-Strength Tylenol Tablets
45. SOP # (b) (4) Tylenol Extra-Strength Rapid Release Gels
46. Operation Qualification of Lace01
47. (b) (4) software a Validation Protocol (b) (4)
48. Actual Diagram or Layout for the Network and (b) (4)
49. Draft Layouts of Network Connectivity and Infrastructure Between the (b) (4) and the Servers
50. Memorandum letter dated on 2/9/05 related to (b) (4)

EM

1. Calibration Procedure # (b) (4) dated 09-24-04

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2. GC calibration report dated 05-06-2004
3. GC calibration report dated 02-02-03
4. Method transfer study number (b) (4) A dated 02-02-03
5. Presentation from McNeil on GC observations dated 01-31-05
6. Memorandum from Carlos Nadal to Walter Maldonado McNeil on GC observations dated Feb 9, 2005
7. Calibration report for GC # (b) (4) dated 10-01-04
8. Calibration report for GC # (4) dated 04-05-04
9. Calibration report for GC # (b) (4) dated 09-15-03
10. Investigation report (b) (4) dated (b) (4)
11. Investigation report (b) (4) dated (b) (4)
12. Investigation report (b) (4) dated (b) (4)
13. Investigation report (b) (4) dated (b) (4)
14. Investigation report (b) (4) dated (b) (4)
15. Investigation report (b) (4) dated (b) (4)
16. Investigation report (b) (4) dated (b) (4)
17. Investigation report (b) (4) dated (b) (4)
18. Investigation report (b) (4) dated (b) (4)
19. Investigation report (b) (4) dated (b) (4)
20. Re-validation protocol (b) (4) dated (b) (4)
21. Investigation report (b) (4) dated (b) (4)
22. Investigation report (b) (4) dated (b) (4)
23. Investigation report (b) (4) dated (b) (4)
24. Investigation report (b) (4) dated (b) (4)
25. Memorandum form McNeil dated on 2-10-05

ATTACHMENTS

1. FDA 482 dated 01/27/2005
2. FDA-482 dated 02/23/2005
3. FDA-483 dated 02/23/2005
4. E-mail from Dr. Bhavnagri regarding NDA 20-958/S-011