

Establishment Inspection Report
 McNeil Consumer & Specialty
 Pharmaceuticals, Division of McNeil-
 PPC, Inc.
 Fort Washington, PA 19034-2210

FBI: 2510184
 EI Start: 05/17/2004
 EI End: 06/07/2004

TABLE OF CONTENTS

RELEASE

Reviewed by: Ro 7/13/10

C.O. DATE

F# GEN. SPEC.

SUMMARY 1
 ADMINISTRATIVE DATA 2
 INTERSTATE COMMERCE 6
 JURISDICTION 6
 RESPONSIBILITY 6
 PRODUCTS 7
 MATERIALS SYSTEM 7
 OPERATIONS AND EQUIPMENT 8
 LABORATORIES 9
 CONTRACTING SERVICES/VENDORS 9
 PRODUCT REVIEWS, DISCREPANCY/FAILURE INVESTIGATION AND REPORTING 10
 TRAINING PROGRAM 11
 MANUFACTURING CODES 11
 COMPLAINTS / PRODUCT DEFECTS 11
 OBJECTIONABLE CONDITIONS 13
 VOLUNTARY CORRECTIONS 37
 EXHIBITS AND SAMPLES COLLECTED 38
 ATTACHMENTS 41

SUMMARY

Inspection of this human drug manufacturer was scheduled as a FY '04 workplan inspection (FACTS Assignment (b) (2)). The inspection was conducted in accordance with CP 7356.002, Drug Process Inspections. Inspectional coverage was given to all six systems. In addition CP 7356.021 was also used for follow-up to both DQRS and NDA Field Alerts. Also covered was the follow-up to an import for export shipment that PHI-DO was alerted to by (b) (2) (b) (2) Import Operations (b) (2). The firm manufactures primarily OTC products with one marketed Rx product.

The previous inspection of this facility was January 04 and covered the Adverse Drug Experience Reporting only. The inspection was classified (b) (2). Prior to the ADE inspection was a limited inspection in December 03 which covered the Labeling problems associated with Tylenol Soft Chews Grape & Fruit Flavor. An incorrect amount of phenylalanine (b) (4) was on the

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Children's Tylenol Soft Chew grape fruit flavor, 80 and 160 mg tablets. The actual amount in the drug product was (b) (4) mg in the grape Soft Chew and (b) (4) mg in the fruit burst flavor Soft Chew. The firm destroyed or correctly relabeled undistributed products but did not recall. An incorrect master formula was used to prepare the R & D Data sheet which resulted in the incorrect labels being printed.

The last GMP inspection was 3/28/02. The inspection also covered a pre-approval for Loratidine 10 mg tablets. This site was identified as performing the stability testing on the clinical batches. The inspection was classified (b) (2) (no 483 issued) Discussion with management covered 2 issues. The first was the concern that a non-conformance investigation was not extended to other lots and the second that there was no non-conformance report generated for a dumping time discrepancy.

The current inspection revealed numerous significant GMP deficiencies. Specifically, documented investigations were not timely, complete nor did they extend to other products, water excursions did not address product impact, retention samples were not evaluated, incomplete annual product reviews. At the close of the inspection FDA-483 was issued and discussed with management. Firm management promised correction. On 6/4/04 firm management stated that they will be recalling 4 batches of children's Motrin that are implicated by the print error on the vendor lot of cartons.

Documentary samples were collected of these lots under CR (b) (2) (b) (2) On 6/4/04 firm management informed me that they will be recalling these lots due to the dosing error on the carton.

The import issue alerted involved R & D investigational material that a trial was being compressed on the (b) (4) presses at Fort Washington. The compressed drug product was shipped back to Canada. The material was for investigational use only. Documents were reviewed, review was unremarkable.

ADMINISTRATIVE DATA

On 5/17/04, Nancy L. Rolli and I presented our credentials and issued a Notice of Inspection to Minnie Baylor-Henry, Vice President Regulatory Affairs. Ms. Baylor-Henry stated that she was authorized to accept the FDA-482 in the president's absence. William L. McComb is the President of McNeil Consumer & Specialty Pharmaceuticals he was off-site on 5/17/04. On 5/21/04 we met with William McComb and presented credentials. Nancy Rolli was present on 5/17 through 5/21/04 only, her role was that of an observer.

Inspected firm: McNeil Consumer & Specialty Pharmaceuticals, Division of
McNeil-PPC, Inc.

Location: 7050 Camp Hill Rd
Fort Washington, PA 19034-2210

Phone: 215/273-7000

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FAX: (b) (4)

Mailing address: 7050 Camp Hill Rd
Fort Washington, PA 19034

Dates of inspection: 5/17/2004, 5/18/2004, 5/19/2004, 5/20/2004, 5/21/2004, 5/24/2004,
5/25/2004, 5/26/2004, 5/27/2004, 5/28/2004, 6/4/2004, 6/7/2004

Days in the facility: 12

Participants: Susan F Laska, M.S., Investigator

The firm is currently registered as a human drug manufacturer; registration was last updated in

(b) (4)

Post Inspectional correspondence should be sent to
William L. McComb, President
McNeil Consumer & Specialty Pharmaceuticals
7050 Camp Hill Road
Fort Washington, PA 19034-2299

On 6/7/04, a 14 item 483 was issued to William L. McComb, President and discussed with management. Also present were the following individuals representing the firm:

Minnie Baylor-Henry, R.Ph., JD
Thomas W. Lapinski, VP North American Operations
Tino Juri, VP Quality Sciences & Compliance N.A.
Elizabeth A. Boyles, Plant Manager
Andrew J. Falkowski, Ph.D. Director US Compliance
Carolyn Parziale, Director of Quality Assurance for Validation
Lynn A. Pawelski, Executive Director Regulatory Affairs
Linda S. Labinsky, Associate Director Regulatory Compliance
Robert J. Haarmeyer, Director QA/ R & D Compliance
Drew Bradley, Manager Solid Dose Manufacturing

During the inspection other individuals provided information related to their areas of responsibilities, those individual will be identified in the report. Attached as EXHIBIT # 29 is the listing of persons interviewed that provided information during the inspection.

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HISTORY

McNeil Consumer & Specialty Pharmaceuticals is a Division of McNeil-PPC, Inc. McNeil PPC was incorporated in New Jersey in 1979. This site in Fort Washington is the Headquarters for McNeil PPC. This McNeil site in Fort Washington was constructed in 1960. Other McNeil Consumer & Specialty Pharmaceutical plants are

Las Piedras Plant:	Road 183 KM 19.8 Barrio Montones Las Piedras, PR 00771
Round Rock Plant:	4001 North IH 35 Round Rock, TX 78664
Guelph Plant	890 Woodlawn Road, West Guelph, Ontario, Canada N1K 1A5
JJMCP Lancaster	Johnson & Johnson Merck Consumer Pharmaceuticals 1838 Colonial Village Lane Lancaster, PA 17601

This site manufactures primarily OTC products along with one currently marketed prescription product, Motrin Oral Suspension, NDA (b) (4). According to Lynn Pawelski, Executive Director Regulatory Affairs they are in the process of validating additional prescription products (b) (4) and (b) (4). The validation protocols have been written the validation has not been completed. The (b) (4) products were not reviewed during the current inspections. Attached as EXHIBIT # 1 is a copy of the firm's current product list.

According to Thomas Lapinski, Vice President North American Operations the firm last year produced (b) (4) total packages of product. Of that, (b) (4) packages, (b) (4) were solid packaged product and (b) (4) liquid packaged products. That represents (b) (4) solid oral dosage units and (b) (4) liquid dosage units.

The manufacturing operations currently occupy approximately (b) (4) square feet including a new liquids manufacturing facility which was commissioned in early 2003. The new liquids area comprises approximately (b) (4) square feet. Production operates (b) (4) days per week for (b) (4) shifts. As needed there is production on the (b) (4) which is a (b) (4) shift.

Total number of McNeil Consumer employees at this site is (b) (4) employees. The total number of quality control and quality assurance employees is (b) (4). QC has (b) (4) employees and QA has (b) (4) employees. The QC employees are split as (b) (4) employees in the QC analytical laboratory and (b) (4) employees in the microbiological laboratory. In quality assurance there are (b) (4) employees in batch record review (b) (4) QA inspection employees and (b) (4) quality assurance employees and (b) (4) employees in

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document control. See report of QC and QA headcount provided by Tino Juri, VP of Quality Sciences & Compliance, North America, EXHIBIT # 2.

The last regulatory action for this firm was a Warning Letter that was issued 1/31/95. The warning letter addressed the failure of QC to reject product that failed assay Children's Tylenol Cherry & Bubblegum; releasing on modified sampling plan, adjusted release criteria, no stability pH specification for Children's Tylenol, inadequate process validation for suspension batch uniformity and all complaints were not reviewed by quality control.

December 2003 inspection was for a labeling issue which covered the Labeling problems associated with Tylenol Soft Chews Grape & Fruit Flavor. An incorrect amount of phenylalanine (b) (4) was on the Children's Tylenol Soft Chew grape fruit flavor, 80 and 160 mg tablets. The actual amount was (b) (4) mg in the grape Soft Chew and (b) (4) mg in the fruit burst flavor Soft Chew. The firm destroyed or correctly relabeled undistributed products but did not recall. An incorrect master formula was used to prepare the R & D Data sheet which resulted in the incorrect labels being printed.

Attached as EXHIBIT # 8 is a listing of the recalls and Field Alerts that have been initiated from March 2003 until May 2004. Field alerts will be discussed later in the report. Following a field alert the firm recalled in March 2002 one lot of Junior Strength Motrin Chewable Tablets. The firm found that some bottles contained Women's Tylenol Menstrual Caplets. The Recall was classified as a class 2 recall. In November 2002 the firm recalled two lots of Children's Tylenol Suspension Grape and Bubblegum because the 4 oz contained metric dosing cups instead of English teaspoon dosing. In April of 2004, the firm notified the agency of a recall of Junior Strength Grape Chewable tablets following 2 complaints of the bottles containing Tylenol 8 hour Geltab. This recall was classified as a class one recall.

On 6/4/04, firm management advised that they will be recalling 4 additional lots of Children Motrin following a complaint, and the subsequent Field Alert which was issued 5/13/04. The complainant received (b) (4) had noted that the dosing on the outer carton of Children's Motrin for children 4-5 years old had a print error where the 3 appeared to be an eight. Complainant purchased the product from Walgreen's, pharmacist found a second carton on the shelf with the same incorrect dose.

The dosing on the bottle, the immediate container, was correct. On Friday afternoon, 5/28/04, Andrew J. Falkowski, Director of US Compliance and Tino Juri, VP of Quality Sciences requested that I facilitate a conference call/meeting with the District regarding their latest Field Alert issued 5/13/04. This latest involved Children' Motrin Grape Flavored Chewable Tablets, 24 count bottle Lot (b) (4). McNeil has been unable to find similar defects in the limited retains they evaluated.

The firm's investigation has revealed that the (b) (4) Printing was done at (b) (4). According to the firm's investigation they believe that this defect appeared in position (b) (4) only on the sheets prior to the cutting of the carton. McNeil

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EI End: 06/07/2004

has quarantined & blocked any further shipments of that lot from their distribution centers. According to distribution records collected, see attached DOC samples on 5/24/04 the firm had shipped the remainder of the lots from the distribution centers to a warehouse in (b) (4) for evaluation. According to Andrew Falkowski the outer cartons were removed and the product in bottles was being stored in bulk totes.

Health hazard evaluation for ibuprofen, "... the lowest weight child (16.4 kg) in the affected age range (4-5 years) taking 8 children's Motrin chewable tablets (400 mg of ibuprofen) instead of 3. In this scenario, such a child would ingest 24.4 mg/kg in a single dose or 97.6 mg/kg/d if 4 doses per day were taken. .. (b) (4)
(b) (4)

This recall has not yet been classified or given a recall number. Attachment B recall information was sent electronically directly from the firm to PHI-DO's Recall Coordinator.

INTERSTATE COMMERCE

Approximately (b) (4) of the drug products manufactured at this site are shipped in interstate commerce. Finished products are shipped to (b) (4) warehouse, which is under the same inventory control system used by the receiving & manufacturing facility. The system is (b) (4) That warehouse is (b) (4) From the (b) (4) (b) (4) warehouse the released products are shipped out to one of (b) (4) distribution centers. The distribution centers are all (b) (4) sites. They are located at

(b) (4)

From these three distribution centers the drug products are shipped out by cases to retail stores.

JURISDICTION

Attached as EXHIBIT # 1 is the current list of human drug products that the firm manufactures. As discussed at the present time there is one marketed Rx product and that is Motrin Oral Suspension. The firm is in the midst of process validation for (b) (4) products, which would also be Rx products. The firm manufactures human liquids, suspensions, immediate release solid oral dosage and extended release solid oral dosage products. The drug products are marketed as bottles, pouches, blister packages and liquids. At the present time the Fort Washington site holds (b) (4) NDAs.

RESPONSIBILITY

During the inspection we were accompanied by Lynn A. Pawelski, Executive Director Regulatory Compliance; after day 2 we were also accompanied by Robert J. Haarmeyer, Director of QA/ R & D Compliance.

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EI End: 06/07/2004

William L. McComb is the President and most responsible individual on site. Mr. McComb has held that position since March 2001. Mr. McComb's office is on site, Mr. McComb informed me that he was directly involved with the Board and the most recent decision to recall the Children's Motrin. Mr. McComb reports to Brian Perkins, Worldwide Chairman of McNeil Consumer Pharmaceuticals & Nutritional Organization see page 2 of EXHIBIT # 3. Reporting to Mr. McComb is the VP of Operations, Thomas Lapinski and the Vice President Quality Sciences and Compliance, Pedro (Tino) Juri. See EXHIBIT # 3 for the management board organizational chart. The organizational chart for Tino Juri, Vice President Quality Sciences & Compliance, North America is attached as EXHIBIT # 4. Reporting to Mr. Juri are Andrew Falkowski, Director Compliance US Operations, Carolyn Parziale, Director Validation US & Puerto Rico Operation and Robert Haarmeyer, Director of QA / R & D Compliance. Mr. Juri is responsible for the quality unit including complaints, see page 3-5 of the organizational charts. At the present time Sean Park is Acting Manager QC/QA Operations Fort Washington overseeing complaints, microbiological lab and the QC laboratory.

Thomas Lapinski is the Vice President for North American Operations. He has held this position since 8/2002 and reports directly to William McComb. Reporting to Mr. Lapinski is Elizabeth Boyles, Plant Manager at Fort Washington. Reporting directly to Elizabeth Boyles are the managers of the various manufacturing operations such as Drew Bradley, Manager solid dose manufacturing, Kate DeGroot-Velez Manager Liquids manufacturing, Rob Schlegel, Manager Product Supply and Mike Vlastic, Manager Plant Engineering, see EXHIBIT # 5. The total number of production employees is (b) (4) full time salary employees and (b) (4) hourly employees. They operate (b) (4) per week. The firm also has (b) (4) shift. Since, the previous GMP inspection in 2002 they have added (b) (4) operators and a new plant manager.

PRODUCTS

The firm manufactures primarily OTC products at this site. The one currently marketed prescription product is Motrin Oral Suspension under NDA (b) (4) EXHIBIT # 1 is a copy of the products manufactured at this site. EXHIBIT # 6 is the listing of the process validations that have been completed since 3/1/02, page 3 of the exhibit are the pending validation protocols. According to Linda Labinski, Associate Director Regulatory Compliance the firm is in the process of validating (b) (4) additional Rx products, (b) (4) tablets. This is covered under a supplement (b) (4) to application (b) (4) which was submitted (b) (4) Page 4 of the exhibit is a listing of current supplemental applications that are in the pipeline. At the present time the validations have been completed although the data has not been reviewed. These validations were not reviewed during the current inspection.

MATERIALS SYSTEM

Raw materials are received by the warehouse. As described by Paul Blacken, Material Services Specialist the materials are entered into the SAP system following inspection of the material and shipping documents. The material is staged in the warehouse area awaiting sampling by the

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EI End: 06/07/2004

Sampling & Inspection Technicians. After sampling the material is moved to a warehouse location defined by SAP system. See discussion of sampling of incoming material under observation 14.

Water

The highest quality water used at the firm is (b) (4) water. Incoming city water is fed through (b) (4). The (b) (4) water passes through a (b) (4) filter, and then through a (b) (4) filter and then passes (b) (4). The purified water is fed to a (b) (4) storage tank which delivers the (b) (4) water through one of (b) (4) (b) (4).

See later discussion of the water system under observations # 12.

OPERATIONS AND EQUIPMENT

This GMP workplan inspection covered all (b) (4). The firm manufactures solid oral dosage products along with liquids and suspensions. The solid oral dosage products are all tablets, caplets or gels. There are no capsule filled products manufactured at this site. The firm does have a new liquid filling area that was commissioned in 2003. At the present time the Tylenol family of products has been (b) (4). The Motrin family of products has not yet been (b) (4). According to Elizabeth Boyles, Plant Manager the plan is that once the Motrin family (b) (4) is complete the (b) (4) (b) (4).

Packaging System

Solid oral dosage packaging is primarily done in (b) (4) packaging lines. The firm does have (b) (4) lines and (b) (4) packaging lines. Inspection of the packaging areas revealed that the packaging lines are (b) (4).

Outside the packaging line is a common staging area that (b) (4) (b) (4). The bottles are emptied onto a (b) (4) and into a (b) (4) (b) (4) and they proceed down the packaging line into a (b) (4) washer through a (b) (4) Filler, capper, and (b) (4) induction sealer. Bottles are (b) (4) weighed offline by production employees to verify bottle count. The line continues with secondary packaging for the outer carton which are over wrapped and placed into shippers.

Attached as EXHIBIT # 9 is the firm's SOP for (b) (4) effective (b) (4). The purpose of this procedure is (b) (4) (b) (4).

(b) (4) This procedure, applies to events such as foreign product, incorrect packaging/processing materials or other forms of contamination located in the processing area or on the packaging line. According to the procedure, the material is (b) (4) which for solid oral dosage products consists of (b) (4). Once the non-conformance event has been noted, the team leader or manager will stop the affected processing

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EI Start: 05/17/2004
EI End: 06/07/2004

area. Prior to the affected processing area resuming operation, the following steps need to be completed. All discrepant material must be (b) (4) (b) (4) Routine line clearance or approval of an area normally does not involve QA.

The typical practice as described by Elizabeth Boyles, Plant Manager is for the drug product to be sampled for release testing (b) (4) (b) (4) The solid oral dosage products (b) (4) (b) (4) There is not a one to one correspondence with the bulk compressed or coated products to packaged products. Bulk products are (b) (4) (b) (4) for packaging.

LABORATORIES

The firm has a microbiological laboratory that is headed by David R. Bonilla, Manager Microbiology. Mr. Bonilla reports directly to Sean Park, Acting Manager QC/QA Operations. The microbiology department analyzes (b) (4) (b) (4) samples. They also perform (b) (4) (b) (4) environmental samples for the (b) (4) (b) (4) areas.

The quality control lab is headed by Caroline Moffa, Acting Manager analytical QC lab sampling inspection. Ms. Moffa reports directly to Sean Park, Acting Manager QC/QA Operations.

During the inspection I reviewed general laboratory procedures and started with a walk through of the laboratory. I reviewed the firm's practice & procedures for identification and receipt of finished product samples reference standards, calibration, adherence to analytical methods, growth promotion, microbial limits, water testing and out of specification investigations for both laboratories.

Attached as EXHIBIT # 39 is the listing of confirmed QC out of specification (OOS) investigations. A sampling of OOS investigations were reviewed from 2004 along with any stability OOS for the period of March 2002 until May 2004 review was unremarkable. Attached as EXHIBIT # 40, are the OOS logs for the microbiology laboratory 2004, 2003, and 2002 see discussions under observations # 2 and 12.

CONTRACTING SERVICES/VENDORS

The firm does use contracting employees from (b) (4) (b) (4) area and to support (b) (4) (b) (4) During the inspection (b) (4) (b) (4) Senior Consultant with (b) (4) (b) (4) provided information regarding the (b) (4) (b) (4) for Tylenol Cold.

Establishment Inspection Report
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EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Other contract services that were noted during the inspection were (b) (4)
(b) (4) This organization was involved in both (b) (4) on site

(b) (4)
(b) (4)
(b) (4) According to Rose Mary Dollard, Validation Project Manager at all times the contract employees are reporting into the McNeil Validation Project Manager.

PRODUCT REVIEWS, DISCREPANCY/FAILURE INVESTIGATION AND REPORTING

During the inspection I had reviewed several of the firm's annual product reviews. The firm's procedure for (b) (4) effective (b) (4) is attached as EXHIBIT #72. According to the procedure the process of the product reviews is as follows: local (b) (4) and (b) (4) will generate, receive, collate and distribute the data. As needed representatives from (b) (4) and (b) (4) will evaluate the data and recommend follow-up activity. These groups do not provide any data or trending to be included in the APR. For example production does not provide data or trending to be included in the APR. The procedure does identify that these key indicators of product quality will be reviewed such as complaints, product returns etc. As discussed later under observation # 6 the review included does not include all complaints only the top 3 complaints.

EXHIBIT #74 is the annual product review for St Joseph Chewable Tablet, Orange Flavor for the review period of 2/1/02 to 1/31/03. Page 5 of the APR is a memo stating that during the previous year's (b) (4) was noticed when comparing the previous years APR (2001-2002) to the current period. This will continue to be monitored and will be addressed in next year's APR (2003-2004 for these product codes. Page 8 of the APR is a graph of the average thickness; the lower limit is (b) (4) EXHIBIT # 75 is the APR for St. Joseph Chewable Tablet, Orange Flavor from 2/1/03 -1/31/04. The discussion on page 2 of the report states that "(b) (4)

(b) (4)

(b) (4) Page 6 of the APR is a graph trending of the (b) (4) The graph shows that from batches (b) (4) the results were closer to the (b) (4) value. Batches (b) (4) were closer to the (b) (4) value. This variability or the out of trend for batches (b) (4) are not addressed. During the inspection I asked Richard Fontana about this variation, he responded they all met specifications.

Other APRs reviewed and attached are APRs for Children's Motrin Suspension Bubble Gum Flavor covering the period of 6/1/02 -5/31/03, EXHIBIT 76. EXHIBIT # 77 is a copy of the Children's Motrin Suspension Berry Flavor, Dye Free covering the period of (b) (4) EXHIBIT # 78 is the APR for Children's Motrin Suspension, Berry Flavor covering the period of (b) (4)

Establishment Inspection Report
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TRAINING PROGRAM

Training consists of (b) (4)

(b) (4)

(b) (4) Richard Fontana, QA Manager provided that listing.

MANUFACTURING CODES

The firm's finished packaged product lot number consists of 6 digits. The first 3 are alpha codes representing (b) (4). The last 3 digits are numeric that represent (b) (4). For example, lot JCM104: (b) (4)

(b) (4)

Batch numbers for in-process material consists of (b) (4) (b) (4)

(b) (4)

COMPLAINTS / PRODUCT DEFECTS

Review of the (b) (2) system for complaints revealed (b) (2) complaints that were dispositioned as (b) (2) see attachment. (b) (2) were complaints regarding Tylenol Arthritis Lot (b) (4) that were missing bottle labels. These complaints were received (b) (4) and (b) (4). These (b) (4) additional complaints predate the time period covered during this current inspection:

(b) (4)

Complaint (b) (4) was received (b) (4). This complaint was for a (b) (4) in a bottle of ER Tylenol. This complaint had also been received by the firm and was the subject of the Field Alert and subsequent recall of Children's Motrin Grape Flavored Chewable Tablets lot (b) (4). See EXHIBIT # 71 for the final field alert submitted 4/14/04.

All other (b) (2) complaints were followed up during this inspection; see reports.

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During the inspection I reviewed the firm's quality complaints, (medical complaints had been covered during the January ADE inspection). I had also requested various sorting of complaints for foreign tablets, mixed product etc. Those print outs are attached as EXHIBIT # 62. During the period of January 1, 2003 through to May 1, 2004 the firm had received (b) (4) complaints for (b) (4) (b) (4) in the bottle. According to Chris Wysocki, Complaint Specialist the (b) (4) product category would represent complaints classified as (b) (4) McNeil product. Some examples of the complaint investigations are listed below.

Complaint # (b) (4) in a bottle of Jr. Strength Motrin Caplets lot (b) (4). This complaint was initially classified as a (b) (4) product and not a (b) (4) product. The correct coding was made on (b) (4) sample was returned (b) (4) (b) (4) lab confirmed that the (b) (4) tablet was a (b) (4). Retain samples were evaluated, no (b) (4) tablets were observed. Batch record review revealed that a batch of (b) (4) (b) (4) was packaged prior to Junior Strength Motrin Caplets lot (b) (4). The complaint investigation was closed (b) (4) see EXHIBIT # 63. During the inspection I had requested a current printout of all complaints for this lot of Junior Strength Motrin Caplets lot (b) (4) see EXHIBIT # 64. To date a total of (b) (4) complaints have been received for this lot. No other complaints of (b) (4) product had been received. (b) (4) complaints were for (b) (4) and the (b) (4) complaint was for the (b) (4) product. The (b) (4) product was received (b) (4) complaint stated that many of the Motrin caplets were (b) (4).

The following observation was inadvertently omitted from the 483 although the inadequate, untimely investigation was discussed at length with management. Complaint (b) (4) was received (b) (4). The complainant stated a bottle of St Joseph Enteric Coated Tablets contained (b) (4) (b) (4). This complaint investigation was closed (b) (4) see EXHIBIT # 65. The following day Christine Wysocki provided the following explanation: This complaint was assigned to a person that was on a temporary detail to complaints. The detail (cross training) was over but this complaint investigation had never taken place and the complaint was closed (b) (4) without further review. This closed complaint was reopened in response to questions during the FDA inspection. The investigation concluded that the complaint sample was never returned, the (b) (4) tablets marked SJ are St Joseph Chewable aspirin tablets. Chewable products are conveyed in dedicated totes during manufacturing. The inspection concluded, on May 27, 2004 that based on the sample evidence a review of the packaging line documentation and the absence of related complaints against this batch, no quality related cause could be determined for this reported condition. This complaint was again closed on (b) (4) see EXHIBIT # 66 and a nonconformance report that was created to document the extended time period for closure. EXHIBIT # 70 is a copy of the nonconformance that was created (b) (4). The NCR states that the complaint was open for (b) (4) days which is in violation of the procedure. (b) (4) (b) (4) The preventive action addresses a procedure revision to require the workflow and other task areas be reviewed for open or pending complaint. The NCR is silent as to searching through other temporary employee workflows to determine if other open complaints are languishing.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FBI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the discussion regarding this event, it was explained that this error of an employee being detailed for training and complaints left opened appeared to be a system breakdown and that a search to see other complaints in the same situation would be warranted. Firm management agreed.

Attached as EXHIBIT # 67 is another (b) (4) product complaint that involved Children's Motrin Grape Chewable lot (b) (4). The complainant explained that purple pills had (b) (4) mixed up in the bottle. This complaint was received (b) (4). The investigation stated that according to the logbook for packaging line (b) (4) on which the lot was packaged on Women's Tylenol Menstrual Relief Caplets ran immediately prior to the Children's Motrin Batch. The investigation was closed on (b) (4) because no complaint sample received; based on available evidence, no quality related cause could be determined for this reported condition. The third page is the screen print from the packaging line showing the product previously packaged.

During the inspection when this was discussed with Christine Wysocki it was pointed out that the packaging line is not the only area where this mix-up could have occurred. The firm does not dedicate (b) (4) etc. (b) (4) for the St. Joseph's product only. Discussed later under observation # 1 is a nonconformance where a foreign tablet from a previous lot was noted in the filling manifold following cleaning of the subsequent batch. On May 27, 2004 Christine Wysocki reopened and closed the complaint the same day to expand the logbook for the packaging sequence, see EXHIBIT #68. There were no other complaints for this lot.

Prior to the inspection DQRS were retrieved both from PHI-DO and CDER Postmarketing Surveillance Group. Attached as EXHIBIT # 69 are (b) (4) complaint follow-ups to DQRS filings.

OBJECTIONABLE CONDITIONS

Observations listed on form FDA 483
Quality System

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been thoroughly distributed.

Specifically, investigations are not always timely, complete, or do they include documentation of quality review, examples include:

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FBI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

1. Nonconformance report (NCR) (b) (4) was created (b) (4) for excess broken and muddled caplets from Tylenol Sinus Severe, batch (b) (4) the event occurred (b) (4). On (b) (4) QA deleted the description on the investigation and entered "(b) (4) (b) (4)". Quality System Report (b) (4) was created (b) (4) there is no documentation of any investigation until the closure of the investigation on (b) (4).
2. The investigation into the follow-up Field Alert submitted (b) (4) for the incorrect dosing for the Children's Motrin Grape Chewable lot (b) (4) fails to include an evaluation of retention samples for all lots packaged with the implicated outer carton vendor lots. Notably, retains of packaged lots (b) (4).
3. Nonconformance report (b) (4) was generated (b) (4) for a weighing error incident that occurred (b) (4). The investigation is silent as to when the error was discovered, other lots previously weighed, and any consideration for additional samples. The investigation was closed by QA on (b) (4).
4. Quality System Reports (QSR) investigations are initiated and remain open without documentation as to the status of the investigation. For example (b) (4) was initiated (b) (4) the extent of documentation was a memo written (b) (4) to cancel the QSR. Notably, (b) (4) investigations were opened in 2003 and remain open.
5. NCR (b) (4) was generated (b) (4) for a foreign product, Tylenol 8 hour Geltab, was discovered on (b) (4) on bottle line (b) (4) after packaging Mylanta Gelcap lot (b) (4). On (b) (4) QA rejected the batch, there was no further documentation of Quality involvement on the NCR although the packaging Team Leader on 11/12/03 had updated the NCR that corrective actions have been completed.

The firm has (b) (4) systems for documenting deviations. The first system is the (b) (4) system and the other is the (b) (4) system reports system. The firm's procedure, (b) (4) (b) (4) is attached as EXHIBIT # 10. This procedure defines the requirements for initiating and investigating a deviation. The non-conformances are categorized as (b) (4) non-conformances. (b) (4) deviations must be reviewed and approved at a minimum by the area manager, QA Compliance Specialist, and Plant Manager. (b) (4) deviations do have specified approvals as defined by the area where the deviation occurred, these are listed on page (b) (4) of the procedure.

The nonconformance reports are assigned a report number from the (b) (4) system although according to Richard Fontana, Quality Assurance Manager the official investigation is the (b) (4) investigation that is (b) (4) from the system. According to the firm's procedure, (b) (4) the non-conformance must be initiated within (b) (4) of determining that an event is a non-

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

rEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

conformance. The procedure also describes that a thorough investigation of the nonconformance will be performed. “..(b) (4)

(b) (4)

(b) (4)”

During the inspection of the material review board storage area of the warehouse it was noted that batch (b) (4) Tylenol Sinus Severe was located in this area. Upon request I was furnished nonconformance report (b) (4) for the investigation as to why this batch was blocked. Attached as EXHIBIT # 12 is copy of the NCR which was according to the print out made on (b) (4) the status was complete. According to the NCR the NCR was created on (b) (4) the description reads “(b) (4) (b) (4)” This same explanation was entered by Tracy Cooper, QA Specialist on (b) (4). During the inspection I requested the audit trail print out of this NCR that is attached as EXHIBIT # 13. According to the audit trail the NCR was created on (b) (4) with a description of “(b) (4)

(b) (4)

I was provided with a copy of QSR draft report (b) (4). According to the QSR, see EXHIBIT # 14 on (b) (4) a Printing operator observed (b) (4) waste (b) (4) for bulk batch (b) (4). Samples of the broken caplets were collected from the sorter and were examined. According to the investigation (b) (4) meetings were held with Plant Projects, Operations, QA & R & D to discuss high waste from both (b) (4). The group concluded that the most probable cause of the defects was a (b) (4) from the connections of the (b) (4). This caused the defects of caplets, (b) (4) (b) (4). The corrective action was for the batch to be (b) (4) moved into the (b) (4) and investigation was initiated. The recommended disposition the batch will be (b) (4) due to the cosmetic defects observed in the batch.

I had inquired as to any ongoing investigation for this deviation. I was provided with copies of emails, see EXHIBIT # 15. The emails dated (b) (4) place the batch in (b) (4) status; (b) (4) repeat to place the material in (b) (4) status in (b) (4) states that the QSR had been opened to investigate; (b) (4) QA has scheduled a meeting “..(b) (4) (b) (4)”; agenda on (b) (4) review data form batches with high waste; (b) (4) to review the QSR.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEL: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the inspection I had inquired as to why this deviation which was noted (b) (4) took until (b) (4) to open a nonconformance report. On (b) (4), the description that was needed to create the NCR was deleted and the NCR was closed. On (b) (4) the QSR was opened yet there was no documented investigation until (b) (4). I was informed by QA specialist Tracy Cooper that it took from (b) (4) because they were deciding the best system of either NCR or QSR to document. Sean Park, Acting QA/QC Manager stated that the yield was actually ok it was the out of trend rejects which was the initial reason for the deviation. There is no documentation as to why this deviation exceeded the specified timeframe in the procedure to initiate and why this QSR remains open with a draft report only dated following the inspectional request.

During the inspection when this was discussed with Richard Fontana, it was explained that certain criteria such as description of the event need to be entered in order to initiate a nonconformance. This required information can be deleted from the nonconformance.

Thursday, 5/13/04, prior to the inspection starting an initial field alert was submitted for Motrin Chewable tablets, 50 mg for lot (b) (4). Based on the review and inspection confirmation of a consumer complaint sample a carton printing defect was evident on the dosing chart caused the (b) (4) to appear as an (b) (4) for the dosing of (b) (4) year olds. The dosing on the bottle was correct. The batch had been in distribution since (b) (4). A second carton was noted on the shelf by the pharmacist at the (b) (4) store. A follow-up Field Alert was submitted (b) (4). The firm's investigation is attached as EXHIBIT # 16. According to the investigation the outer cartons were printed by (b) (4). Batch record review revealed that Batch (b) (4) different carton vendor lots during the packaging. The (b) (4) vendor lots were (b) (4). (b) (4) These (b) (4) vendor lots of cartons were used to package a total of (b) (4) finished batches (b) (4). The lot (b) (4) was the subject of the April class I recall for complaints of 8 hr Tylenol in the bottle labeled as Children's Motrin. Part of the firm's investigation was for retain samples to be evaluated for lot (b) (4) and retains had been evaluated for the recalled lot (b) (4). During the inspection on May 28, 2004 when I was reviewing the investigation I noted that retain samples of the other (b) (4) lots that used the implicated carton printing lots had not been evaluated. Andrew Falkowski stated that retains will be evaluated. On 6/4/04 when I returned to the firm to collect the DOC samples, Andrew Falkowski provided a copy of the retain sample inspection, see EXHIBIT # 17. According to the evaluation no carton defects were noted with the print defect that made the (b) (4) tablets for ages 4-5 years old appear as an (b) (4).

According to the firm's investigation the incident occurred during the (b) (4). The source of the ink could not be determined. The color is inconsistent with the (b) (4) used to print Children's Motrin Chewable Tablet cartons. The investigation has pinpointed the defect to be in position number (b) (4) of the carton prior to die cutting.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

An additional concern with this investigation is the fact that the firm has not evaluated their procedure of accepting labeling and packaging material. See discussion of later objection but the firm's practice is to do a (b) (4). These vendor cartons were not the first shipment received so (b) (4) would not have been performed.

Nonconformance report (b) (4) is attached as EXHIBIT # 18. This nonconformance was generated (b) (4) for a (b) (4) error incident that occurred (b) (4). The error was a result of an incorrect (b) (4) entered for the (b) (4) of dextromethorphan for Tylenol Cold Severe Granulation. The granulation batch was (b) (4). According to the investigation "(b) (4)

(b) (4)

The investigation is silent as to when the error was discovered, other lots previously (b) (4) and any consideration for additional samples. The investigation was closed by QA on (b) (4).

Quality System Reports (QSR) investigations are initiated and remain open without documentation as to the status of the investigation. For example (b) (4) the extent of documentation was a memo written (b) (4) to cancel the QSR. Notably, (b) (4) investigations were opened in (b) (4) and remain open.

The second system that the firm has for deviations is the Quality Systems Reports; the procedure effective (b) (4) is attached as EXHIBIT # 11. According to Sean Park Acting QC/QA Manager, this is the only procedure that describes Quality System Reports. The listed objective is to establish a procedure which will initiate controlled numbers for Quality System reports. The QSR is any report that may be used as additional justification or documentation for a GxP process or investigation, or as supporting documentation for a process change. According to the procedure, (b) (4)

(b) (4)

(b) (4)." The procedure is silent as to responsibility as to follow-up for these reports. During the inspection it was noted that a number of quality system reports were initiated and never closed. The procedure is silent as to any timeframe for closeout of QSRs or periodic review of open QSRs. As discussed later in observation # 6 QSRs are not included in the annual product reviews. In some cases discussed later a QSR was generated to archive all the attachments.

Attached as EXHIBIT # 19 is the listing from the Quality System Reports Database of QSR's from (b) (4). As can be seen from this (b) (4) report (b) (4) QSR that were initiated in (b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

remain open. During the inspection I selected several QSRs from (b) (4) that remained opened according to the database printout. Some examples are as follows:

According to the database (b) (4) was generated (b) (4) for Tylenol Cough Plus Sore Throat Cooling Berry Flavor R & D Notebook (b) (4). See EXHIBIT # 20 for the QSR dated (b) (4) which states a prototype formulation was manufactured and submitted to (b) (4) (b) (4). This was explained by David Bonilla as the system to (b) (4) (b) (4).

Attached as EXHIBIT # 21 is (b) (4). According to the database print out this QSR was initiated (b) (4) for Tylenol Arthritis Pain Extended Relief Geltab (b) (4). According to the QSR dated (b) (4) which is titled (b) (4) “(b) (4)

(b) (4)

Attached as EXHIBIT # 22 is a copy of (b) (4). This NCR was generated (b) (4) for a foreign product, Tylenol 8 hour Geltab that was discovered on (b) (4) on bottle line (b) (4) after packaging Mylanta Gelcap lot (b) (4). According to the investigation, page 1, the packaging line leader recommended to (b) (4) and that was approved by QA on (b) (4). The problem was that following the cleaning of a Mylanta batch (b) (4) it was discovered that a Tylenol 8 hour Geltab was discovered in the filling manifold. The official copy of the investigation has that the (b) (4) following the QA closeout of the investigation on (b) (4) and the SOP was updated to include an (b) (4). There was no further documentation by QA on the investigation. This was discussed with the firm at the daily wrap-up. Richard Fontana QA Manager stated that although not on the copy of the official investigation a review of the audit trail would reveal that following the initial QA sign-off and the subsequent entry by packaging line leader there would be a QA approval of the corrective action. Attached as EXHIBIT # 23 is the audit trail print for this NCR. According to page (b) (4) of the audit trail QA did review approve the subsequent change on (b) (4). In this investigation the description of the event, root cause, the corrective action and the preventive action are all completed by the initiator of the nonconformance the packaging team leader. The extent of QA documentation consists of “(b) (4)” and a signature and date. There is no documentation as to the deviation from the procedure in that the NCR was created on (b) (4) when the foreign tablet was discovered on (b) (4).

Additional examples of investigations include the following:

Attached as EXHIBIT # 24 is a copy of (b) (4) according to the database printout this QSR was generated (b) (4), according to the QSR, it was created to archive all the attachments listed in the NCR (b) (4). NCR (b) (4) was created (b) (4) for a (b) (4) that

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

was noted upon completion of a (b) (4) campaign of Tylenol Arthritis Pain Extended Relief Caplets. During the rework/re-inspection of the batches involved with NCR (b) (4) of the isolated skids that were set to be destroyed were reworked and dumped into totes containing reworked bulk; this was documented in NCR (b) (4) attached as EXHIBIT # 25. The root cause for this error was that (b) (4) skids were incorrectly listed in the bulk recovery procedure. The employee who wrote the bulk recovery procedure mistakenly listed the incorrect skids. As a result (b) (4) of the skids were reworked and dumped into totes containing reworked bulk.

Out of specification investigation (b) (4) was generated following suspect results for pH on (b) (4). The testing was on Batch (b) (4) Infants Tylenol Cold Drops. The release limits are (b) (4) for pH. The OOS was closed (b) (4) and NCR (b) (4) was created (b) (4). The NCR was closed on (b) (4). The root cause for the (b) (4) pH could not be determined. The NCR was closed (b) (4) was created as further documentation of this nonconforming event and to document the continued investigation of the root cause. The QSR is dated (b) (4) and the root cause remains undetermined. See EXHIBITS #26, 27, 28.

NCR (b) (4) was created (b) (4) for the out of specification dissolution for St. Joseph Enteric Coated tablets batch (b) (4). The limit at stage (b) (4) dissolution is not more than (b) (4) the results for this batch failed at (b) (4) for the (b) (4) stage dissolution, see EXHIBIT # 30. The date of the suspect results was (b) (4) the NCR was created (b) (4) and closed on (b) (4). The investigation into the root cause dated (b) (4) attributes the most probable cause to be a (b) (4) (b) (4) of the tablet that was tested. This bulk lot was rejected along with (b) (4) skids of packaged product due to the bulk packaging practice. See page 18 of EXHIBIT # 30 for a schematic of the bulk packaging. Bulk (b) (4) was the (b) (4) bulk batch to be dumped into the hopper for packaging at (b) (4). Prior to that bulk being dumped there were (b) (4) skids of finished product packaged. (b) (4) of product were packaged following the bulk being dumped in the hopper all (b) (4) skids were rejected. This investigation was completed by Jack Wysoczanski, Production. QA approved the disposition on (b) (4). The investigation is silent as to the delay of (b) (4) until the investigation on (b) (4) and closure also on (b) (4).

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

r-EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

NCR (b) (4) was generated following the OOS result for Tylenol Cold Severe Caplet lot (b) (4) which failed to meet assay and content uniformity for (b) (4). The assay results were (b) (4) initially and the resonication, remix results were (b) (4). The initial content uniformity average was (b) (4) and the repeat was (b) (4) see EXHIBIT # 31. The NCR is attached as EXHIBIT # 32, it was created (b) (4). The most probable cause of the failure according to operations was that the (b) (4) was carried over from the granulation batch and raw material slipped off the rim of the drum between the liner and the drum. (b) (4) batches were granulated together (b) (4) had assay results of approximately (b) (4) for assay, content uniformity and dissolution. The corrective action was to (b) (4).
(b) (4)
(b) (4) The batches evaluated as part of the investigation was limited to batches that were granulated and compressed during this campaign.

Six days following the above suspect results on (b) (4) Tylenol Cold Severe Caplet lot (b) (4) had an out of specification (b) (4). According to the OOS, EXHIBIT # 33, the variability is also present in the dissolution results. NCR (b) (4) was created (b) (4) see EXHIBIT # 34. The documented investigation was (b) (4). The investigation failed to determine a definitive root cause. The investigation evaluated Guaifenesin active granulation manufacturing, Tylenol Cold Severe Granulation manufacturing and Tylenol Cold Severe Caplet compression manufacturing. According to the investigation an "(b) (4)
(b) (4)
(b) (4) " This investigation in the corrective action section dated (b) (4) states "(b) (4)
(b) (4) " The NCR was closed (b) (4). The investigation is silent as to the rejection of the (b) (4) compression batches that were rejected as part of NCR (b) (4) that had OOS results (b) (4) prior on (b) (4) for assay and content uniformity for (b) (4).

OOS (b) (4) due to the (b) (4) failure of packaged Infants Tylenol Cold Decongestant and Fever Reducer Drops lot (b) (4). The initial results were (b) (4) the release limits are (b) (4). The laboratory OOS was closed (b) (4). NCR (b) (4) was created (b) (4). The NCR was closed (b) (4) and a QSR (b) (4) investigation was opened (b) (4). The QSR was closed (b) (4). No root cause for the (b) (4) failure was ever identified.

During the discussion with management, Mr. McComb stated that they are exploring the NCR system to determine the full capabilities of documenting form various departments. In addition they are planning training for operations and quality on documentation practices.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

OBSERVATION 2

Investigations of an unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy.

1. Out of specification investigation (b) (4) for the microbiological excursion, identified as (b) (4) on the purified water system sample from (b) (4) fails to include among other items an assessment of product impact.

2. Out of specification investigation (b) (4) for the (b) (4) of Children's Motrin Suspension Grape Flavor lot (b) (4) that was analyzed on (b) (4). The documented investigation evaluated released Children's Motrin Suspension Grape Flavor lots only. NCR (b) (4) was created (b) (4) and closed (b) (4) the root cause of the (b) (4) contamination was undetermined.

3. Out of specification investigation (b) (4) was initiated (b) (4) for the out of specification (b) (4) media that was discovered on (b) (4). The investigation failed to identify the (b) (4) lots of finished product that were tested with the out of specification (b) (4)

Out of specification investigation (b) (4) was initiated (b) (4) for the microbiological excursion, identified as (b) (4) on the purified water system sample from (b) (4). The investigation is attached as EXHIBIT # 35. The investigation fails to include among other items an assessment of product impact or how the water was used from the loop. According to page 2 of the investigation the sampling point was from (b) (4) produced the results of (b) (4). According to the investigation the out of specification was caused by the (b) (4) by the microbiology laboratory. In conclusion the organisms were most likely introduced into the (b) (4) sample at the time (b) (4). Although page 1 of the investigation states, "... (b) (4) (b) (4) (b) (4) samples tested that day showed growth. Growth was discovered on (b) (4) that (b) (4)". This organism was not identified. See discussion under observation # 12. The results are reported as (b) (4). In the firm's procedure if (b) (4) have been recovered from the (b) (4) The reported plate count would be (b) (4)

During the inspection when this was discussed I asked David Bonilla, Microbiology Manager how

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

they concluded that poor technique or contamination occurred during (b) (4). Mr. Bonilla stated that the temperature of the water at (b) (4) degrees F would not permit the (b) (4). (b) (4) I asked Mr. Bonilla how the determination was made that earlier in the documented investigation it states the microbiologist was well trained and has demonstrated good aseptic technique yet the conclusion was that it was (b) (4). (b) (4) There was no documentation that the analyst was interviewed etc.

The point of use (b) (4). The water would be used to make the gel coating base and subsequent colors. EXHIBIT # 36 is the printout that was generated (b) (4) for the hot water use on (b) (4). The highlighted yellow batch numbers refer to the (b) (4) and subsequent pages refer to the (b) (4) were used. For example page 6 shows that batch (b) (4) was manufactured using water from drop (b) (4). This (b) (4) was used to manufacture gel solution (b) (4) which was used to manufacture Tylenol 8 hour gel-tab bulks (b) (4). (b) (4) There is no finished product micro testing on the gel coated tablets. The only micro testing is on the (b) (4) which is tested for total (b) (4). According to the micro raw data results attached as EXHIBIT # 37 all gelatin solutions were within normal specifications. The only recovery was (b) (4) recovered on the (b) (4) this was not identified, see page 11, 12 and 14.

The ambient loop that had the recovery of (b) (4) was used for cleaning only. Specifically the cleaning involved the (b) (4) solution tanks, glatt and coating solution prep tanks (b) (4). See EXHIBIT # 38 for the ambient water loop (b) (4) usage for cleaning. Neither of these points of use or loop feeds the (b) (4).

Micro investigation (b) (4) was created (b) (4) for the analysis of Children's Motrin Suspension Grape Flavor Lot (b) (4). The investigation is attached as EXHIBIT # 43. A total of (b) (4) liquid products and (b) (4) solid products and (b) (4) raw materials were analyzed on (b) (4). Finished product Children's Motrin Suspension Grape Flavor Lot (b) (4) micro analysis revealed (b) (4) species and (b) (4). The investigation from the micro lab looked at water that was tested on the loop from (b) (4) when the batch was actually manufactured (b) (4). The micro investigation was closed (b) (4) NCR (b) (4) was initiated (b) (4) the batch was (b) (4). The NCR is attached as EXHIBIT # 41. The investigation is silent as to an evaluation of operators involved in the production of this batch or other suspension or liquid products with micro contamination. This product is manufactured on multi-use equipment and by employees who are not dedicated to this product only. EXHIBIT # 42 are 5 pages that were copied from the liquid finished product log book testing thus far in 2004.

Children's Motrin Suspension Bubblegum lot (b) (4) species recovered (b) (4)
Tylenol Flu Nighttime liquid Max Strength Cherry Lot (b) (4) species (b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FBI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the discussion with management there was no discussion regarding this observation.

OBSERVATION 3

Evidence of reserve drug product sample deterioration was not investigated.

Specifically, there has been no evaluation or summary reports generated in (b) (4) for the category "(b) (4)" results of visual inspections, which includes product or packaging material exhibiting noncritical irregularities or retained samples not found.

On 5/18/04, inspection of the raw data for the 2003 annual visual inspection revealed that not all entries were completed, see EXHIBIT # 49. Inquiry to Patricia Woods, QA specialist most responsible for retention samples and annual visual inspection revealed that search of the (b) (4) data base had no entry for the results of this examination. Ms. Woods explained the process as the following: The (b) (4) data base generates a listing of retain samples that are due for visual inspection, that sheet (exhibit # 49) is given to the QA Specialist, samples are evaluated according to the procedure which is attached as EXHIBIT # 50. The criteria is listed on page 3 of the procedure. The QA Specialist records (b) (4) '(b) (4)' according to the procedure is product or packaging material that exhibits a noncritical irregularity. This data is then entered into the (b) (4) system. A report is generated when all the (b) (4) samples have been inspected, a QC Team Leader will review and approve the data. Patricia Woods provided as a sample the report for the 2002 (b) (4) see EXHIBIT # 51.

The following day Patricia Woods provided the following information. According to the firm's procedure for annual visual inspection results of the inspection are recorded as (b) (4) (b) (4) category is a product or packaging material that exhibits a noncritical irregularity. The printout summary report from (b) (4) does not print out the (b) (4) categories. If the samples are not found or not evaluated that would also fail into the (b) (4) category. The (b) (4) categories have to be '(b) (4)' otherwise they do not print out on the report. According to Patricia Woods this has been the case for the report generated in 2004 for the 2003 inspection, also for the report generated in 2003 for the 2002 inspection EXHIBIT # 51, and also for the report generated in 2002 for the 2001 inspection. EXHIBIT # 52 is a copy of the print out for the retain samples pending (b) (4) validation report. These samples would represent samples destroyed and samples not found etc. Attached as EXHIBIT # 53 are the results of the (b) (4) for the samples that were found during the inspections for the 2003 (b) (4) The results show that the samples passed the criteria.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the inspection this was discussed at length with the firm. The fault in the (b) (4) system to report only the passing results and the fact that these samples of concern the fail and warn category have not been evaluated. In addition, the results of the annual visual inspection are not included in the annual product reviews. Firm management responded that they reference the stability program in the annual product reviews to support marketed product.

During the discussion with management there was no discussion regarding this observation.

OBSERVATION 4

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Specifically, the 2003 (b) (4) for the following lots was not performed for Children's Tylenol Strawberry Lot (b) (4), Children's Tylenol Strawberry Lot (b) (4) Simply Sleep 24 caplets Lot (b) (4)

As discussed in observation # 3, review of the raw data for the 2003 (b) (4) revealed that no results had been entered for the samples listed above, see EXHIBIT # 49. After this was discussed at the daily wrap-up I was presented with the following report, EXHIBIT # 53 which identified (b) (4) additional samples that were not evaluated. These samples were due for (b) (4) (b) (4) in 2003 that was conducted (b) (4) samples were not found in the retain sample area. No non-conformance or deviation was generated. These samples were omitted from the print out summary report of the annual visual inspection. The firm's procedure for retain samples is attached as EXHIBIT # 54.

It was discussed at length with the firm the program for (b) (4) The reports generated for the (b) (4) are not trending changes to the product over the shelf life. The firm responded that they are using their stability program for that. The (b) (4) system randomly generates the lots that will be evaluated for the (b) (4) It was explained to the firm that the (b) (4) increases the sample size over the limited stability program.

During the discussion with management there was no discussion regarding this observation.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

OBSERVATION 5

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically, (b) (4) procedure, effective (b) (4) is not followed in that (b) (4) (b) (4) investigations fail to include complete documentation. Among other items the investigations fail of to include documentation from the "(b) (4)" and notification to the Johnson & Johnson affiliates possibly impacted by the field alert condition.

Review of the most recent (b) (4) Investigation was provided with the (b) (4) dated (b) (4) in response to my request for the complete investigation with all supporting documents. This summary was written by Christine Wysocki, QA Complaints. The summary covers the consumer complaint that was received on (b) (4). The consumer stated that a sealed box and bottle of Children's Motrin Grape Chewable Tablets Batch (b) (4) had no grape chewable inside. The product inside the bottle was red and white geltabs, Tylenol 8 hour extended release Geltabs. The complaint investigation began (b) (4) physical sample was received (b) (4). The product inside was confirmed to be Tylenol 8 hour Geltabs. The investigation evaluated several possible root causes; the actual root cause could not be confirmed. (b) (4) was filed on (b) (4) (b) (4) is sent on (b) (4). The preventive actions initiated are as follows:

(b) (4)

According to Sean Park and Richard Fontana this Executive summary, EXHIBIT 58 was the extent of the documented investigation, other than the actual complaints see EXHIBIT 59 and 60. A second complaint was received (b) (4) that identifies the same problem. Sean Park provided me a copy of the inspection protocol and the current inventory at the (b) (4) see EXHIBIT # 61. According to the firm's procedure for (b) (4) attached as EXHIBIT # 57 page 3 discusses Director of Central Compliance will (b) (4)

(b) (4)

There was no documentation, as to (b) (4) or documentation of any contemporaneous investigation.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the 483 discussion William McComb stated that on occasion he requests that no notes be taken due to the investigational aspects of the meetings. It was pointed out that there is no documentation that meetings even occurred. It was also pointed out that investigations rarely start with Executive Summaries.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Additional discussions regarding Quality: During the inspection on several occasions I had articulated my concerns for the lack of documented Quality Unit involvement in both documented investigations, approval of line clearance support to manufacturing etc. Among other items I had requested the mechanism for quality issues to be relayed to upper management. Robert Haarmeyer and Tino Juri provided the following purged documents (b) (4). According to Robert Haarmeyer the redacted information was in the realm of financial/business information. The reports dated (b) (4) are attached as EXHIBIT # 85. Attached as EXHIBIT # 86 is the firm's SOP regarding significant event reports. According to the procedure the scope of the events include but are not limited to the following: any out of specification, any product non-conformance that occurs that could result in recall or field alert notice, any GMP issues that are realized either through routine assessment or as a result of changing regulation. The procedure specifies that these are reported on a (b) (4) basis in the (b) (4) Report. The report is sent directly to the Director, US Compliance and/or Vice President of Quality Sciences & Compliance. The procedure is silent as to the most responsible individual at the site being notified, specifically the president.

On June 4, 2004 Robert Haarmeyer provided EXHIBIT # 87 which is a memo dated (b) (4) which was constructed "... (b) (4)

(b) (4)

(b) (4)". Notable, is that these are not included or referenced in the documented investigation.

Again on 6/4/04 I asked to Robert Haarmeyer what procedure does the firm have to satisfy that responsible firm officials are notified in writing of investigations specifically to satisfy the requirement under 211.180(f). Mr. Haarmeyer returned with the following explanation: The specific

(b) (4)

These procedures are attached as EXHIBITS # 88, 89, 90, and 91. Exhibit # 88 the recall procedure states on page 4 in the communication of condition states "(b) (4)

(b) (4)

(b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

FEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Exhibit 89 is the complaint procedure. Page 13 states “ (b) (4)

(b) (4)

(b) (4)

(b) (4)

” EXHIBIT # 90 is the Compliance
Procedure. The purpose of this procedure is “ (b) (4)

(b) (4)

(b) (4)

” The procedure is silent as to documentation, distribution and
notifications. EXHIBIT # 91 is the Fort Washington Plant Quality (b) (4)

(b) (4)

The responsibilities include

“ (b) (4)

(b) (4)

(b) (4)

” The procedure is silent as to authority to

insure that discrepancies (other than QC) are fully investigated and authority to approve/reject
discrepancy investigations and the procedure is silent as to documentation requirements to notify
Senior Management.

OBSERVATION 6

Written procedures are not established for evaluations done at least annually and including
provisions for a review of complaints, returned or salvaged drug products, and investigations
conducted for each drug product.

Specifically:

1. Annual product reviews fail to include among other items; an evaluation of all returned
goods, a documented review of all complaints, quality system reports, all analytical
investigations into out of specifications results and an evaluation of the retention samples.
2. The procedure for (b) (4) fails to include, among
other items, a requirement that all returns, all investigations and all complaints are evaluated.

Annual Product Reviews (APR) do not include all investigations into out of specification results.
The return goods section of the APR evaluates only (b) (4) Discussed
and confirmed with Robert Haarmeyer is the concern that the firm has returns from other areas.
Specifically, the (b) (4) returns and the returns from the sister McNeil facilities, these
returns would be returned through the (b) (4) The annual product review does not

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

address returns from these areas. Product of concern would be returns from (b) (4) sites, etc. The only returns addressed in the APR are the returns from (b) (4)

The procedure, EXHIBIT # 72, does identify that these key indicators of product quality will be reviewed such as complaints, product returns etc. The review of complaints does not include all complaints only the top (b) (4) complaints. For example EXHIBIT # 73 is a copy of the most recent APR for Children's Motrin Suspension Grape Flavor covering the period of (b) (4). There were a total of (b) (4) complaints received during this review period and the report addresses a total of (b) (4) see page 42 of the EXHIBIT # 73. (b) (4) complaints.

During the inspection it was pointed out that often single complaints are significant indicators of quality issues.

In addition, the annual product reviews address (b) (4) if they become (b) (4); out of trend or unconfirmed OOS results are not addressed in the annual product reviews according to Richard Fontana, QA Manager. Evaluation of retention samples is also not included in the APR. Also any Quality System report investigations are not addressed in the APR.

During the discussion with management, management stated that they were revising the APR procedure.

OBSERVATION 7

Strict control is not exercised over labeling issued for use in drug product labeling operations.

Specifically, labels for drug product are staged (b) (4)

(b) (4)
During the inspection assorted roll labels were observed in a caged area on 5/18/04. It was explained by management that this caged area, (b) (4) for (b) (4) to come pick up the labels that have been requisitioned. During the inspection of the area a (b) (4) arrived with a copy of the (b) (4) of material and the label set-up that had been delivered to the label Room. He was retrieving the labels/essential brochures from the staging area of the (b) (4). It was explained by Marcus DeVaughn, the (b) (4) (b) (4) that he was there to verify quantities, batch numbers and the material number and to pick up roll labels for the second shift packaging operation. The labels were staged on several shelves, Mr. DeVaughn was examining the labels to select the appropriate labels that he had the paper work to collect. He would initial and date in the verification of the set-up amount. Approximately (b) (4) different product labels were staged in this area including (b) (4). This locked cage access is by the (b) (4) that is provided with a certain (b) (4). This area is adjacent to the (b) (4) area. The batch record review office is

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

rEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

located through the (b) (4) (b) (4) employees would also have access to the label staging area. The people trained to pick up labels would be a subset of those able to access the area. Labels are staged in this area, picked up by (b) (4) employees. Attached as EXHIBIT # 79 is the listing of employees that have the same security clearance to enter the label room. During discussions with Elizabeth Boyles, Plant Manager this listing of employees identifies who has the same security access to the area. This staging area is accessed from the common walkway that leads from the (b) (4). The firm's procedure for (b) (4) (b) (4) is attached as EXHIBIT # 92.

During the inspection this was discussed at length, the fact that the firm has strict label control up to the point of (b) (4) the labels. Strict control is not maintained for the (b) (4) of labels. According to the procedure for (b) (4) EXHIBIT # 93 states that sampling and Inspections employee will receive (b) (4). As explained by Patricia Woods this procedure is the actual issuance procedure. The procedure is silent to this staging area.

During the discussion with management they stated that they believe the cage access is limited and that they have to have access (b) (4).

OBSERVATION 8

Labeling and packaging materials are not representatively sampled and examined upon receipt and before use in packaging and labeling of a drug product.

Specifically, complete incoming label inspection is conducted on the first receipt only of a vendor lot.

EXHIBIT # 80 is the firm's procedure for (b) (4) Patricia Woods, Analytical Team Leader responsible for labeling explained that upon the first receipt of a vendor lot, a complete (b) (4) is performed on one sample using the (b) (4) as a reference. On subsequent receipts container label identification is performed. For example EXHIBIT # 81 is the packaging material inspection record for the Children's Motrin Chewable Tablet Carton that is subject of the most recent Field Alert (b) (4) and product recall. The exhibit shows that this is the "(b) (4)" for Vendor (b) (4). A container label has been checked as reviewed and the copy meets requirements are checked as reviewed on (b) (4). Subsequent receipts see EXHIBIT # 82 on (b) (4) show that the container label has been checked but the copy has not been examined and samples are not attached of the label. EXHIBIT # 83 is the second shipment of cartons from (b) (4) for the cartons subject of the most recent Field Alert. Again no copy verification is performed for this receipt, it is identified that (b) (4) times previously this part number has been received from this vendor. EXHIBIT # 94 is a copy of the receipt of Simply

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Sleep Caplets label that was received on (b) (4). It was the (b) (4) receipt from this vendor. The container label ID was checked. The copy of the label was not checked.

During the inspection it was discussed that in light of the recent series of labeling problems in (b) (4) there has been no discussion or evaluation whether the inspection sampling size is adequate, or appropriate or if the inspection practices needs to be evaluated.

During the discussion with management, management stated that finding the chances of finding the print error in position (b) (4) appeared to be an (b) (4) would be very slim.

Packaging System

OBSERVATION 9

Reprocessing was performed without the review and approval of the quality control unit.

Specifically, bottles removed from the packaging lines are placed in rework bins and reworked by packaging operators without the review and approval of the quality control unit. On 5/17/04 the following unlabeled bottles were in re-work bins awaiting rework; unlabeled bottles of St. Joseph's Aspirin lot (b) (4) were for rework on line (b) (4); unlabeled bottles of Tylenol Arthritis lot (b) (4) were for rework on line (b) (4). Notably, there is no in-process trending for the amount of reworks generated during packaging.

During the inspection of the packaging lines on 5/17/04, it was observed that the packaging lines contained various bins labeled as reworked. As explained these rework bins are available for bottles and drug product that have been removed from the packaging line. In some cases these bottles were rejected from the line and in some cases the drug product was from an in-process check. It was explained that the rework bottles would be examined or emptied and drug product would be put back on the line.

Sean Park, Acting QA/QC Manager stated that as part of the corrective action from the April Field Alert and subsequent recall of (b) (4) they have changed the rework bins from stainless steel to translucent containers to facilitate and aid in the line clearance. As explained, the translucent containers provide for better visibility and assurance that no bottles remain in the packaging area.

These reworks are not approved by Quality, in fact there was no Quality Unit presence on the packaging floor. There is no trending of the amount of reworks generated or actually performed. During the inspection this was discussed as to the lack of in-process trending as an indicator of quality/equipment problems.

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Attached as EXHIBIT # 102 is a copy of the firms procedure for (b) (4). One of the recent changes to the procedure is that any component or bulk product found on the packaging line (b) (4). In addition, it has also been decided that an NCR would be required in the (b) (4) see page 16. Reworks allowed for include (b) (4).

(b) (4)
(b) (4) Page 8 of the procedure discusses that packaging operator or packaging technician will (b) (4). Page 9 of the procedure states that on a (b) (4).
(b) (4)

Post-inspection review of the procedure reveals that it is silent as to requiring non-conformance documentation for all reworks.

During the 483 discussion Thomas Lapinski, VP North American Operations requested clarification regarding the point of the observation reworking or the fact that they are not approved by Quality. It was explained that the GMPs are quite clear that reworks must be approved by the Quality Unit. In addition, the fact that there is no data collected as to how much of the batch is reworked.

OBSERVATION 10

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically,

1. There was no documentation in the packaging records for St. Joseph's Aspirin lot (b) (4) for the (b) (4) scale set-up which was used to verify the bottle count.

2. Uncontrolled records are issued to the packaging line without complete information for example; on 5/17/04 lot (b) (4) was being packaged, pages 8 through 14 of the packaging production record failed to include batch numbers or product codes.

During the inspection of the packaging area on May 17, 2004 it was noted that a (b) (4) scale was being used to verify counts in the bottle. As explained by Farid Sanders, Solid Dose Packaging Team Leader the scale set up was performed according to a work aid, see EXHIBIT # 95. This would have been performed during the set up of the packaging line. This set up is not documented in the packaging batch record, see EXHIBIT # 96 which is the packaging record for the St Joseph's Aspirin that was being packaged. Page 2 has the record for the start-up, the bottle count verification scale set up is not addressed. Page 7 contains the record for in-process checks which include bottle count. The bottles are weighed (b) (4) to determine bottle count. Farid Sanders explained that the scale set-up would actually be specified to be performed during the (b) (4).

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

(b) (4) He provided a copy of the record for the change over from (b) (4)
(b) (4) see EXHIBIT # 97. The checklist is silent as to scale
set-up for the new product.

Review of complaints revealed that short count is often in the (b) (4) complaints listed in the APRs.

After this was discussed during the daily wrap-up, Elizabeth Boyles, Plant Manager provided a copy of a revised packaging record. Page 2 of the record now has a provision for scale set-up for in-process count verification, see EXHIBIT # 98.

Inspection of packaging Line (b) (4) which was running Tylenol 8 hour Caplet lot (b) (4) revealed that the packaging records are issued to the packaging line as uncontrolled documents, without complete information. EXHIBIT # 99 is a copy of the packaging record, pages 8 through 14 have no product codes or batch numbers. According to Richard Fontana this packaging record was issued by Timothy Kulp whose title would be Batch Coordinator who works in scheduling which is a function of Operations. A copy of the procedure for batch preparation that was effective at the time is attached as EXHIBIT 100. Following the discussion the firm committed to revising the procedure and new SOP was circulated hence the print of the procedure states obsolete. The revised SOP is addressed in the voluntary corrections

During the discussion with management, management stated that the records and procedure have been specified.

Laboratory System

OBSERVATION 11

Laboratory records do not include a description of the sample received for testing, the source or location from where the sample was obtained, the quantity of the sample, the date the sample was taken, and the date the sample was received for testing.

Specifically, there is no documentation either in the log book for samples entered into the laboratory or on the analyst worksheets for the quantity of samples received, source of the sample and the date the sample was taken.

Inspection of the sample accountability in the QC laboratory on 5/18/04 revealed the following: Finished product samples are logged into the "(b) (4) Logbook". The current book in the lab is book (b) (4) see excerpts attached as EXHIBIT # 7. According to Caroline Moffa, Acting Director of the QC Lab the samples are brought over by (b) (4) Samples are logged in by the laboratory and are entered into the (b) (4) which generates the analytical work sheets. For example EXHIBIT # 84 is a copy of the analytical raw data for Tylenol Sinus Severe

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

Congestion Caplet lot (b) (4) Page 3 is a copy of the worksheet generated by (b) (4) when the sample is logged in. Neither the QC logbook nor the worksheet contain the quantity of samples received, source of the sample and the date the sample was taken.

During the inspection when this was discussed Richard Fontana, QA Manager stated that the date the sample was taken and the quantity of samples are recorded in the batch record.

During the discussion with management, management stated that the log book has been corrected to allow for additional entries.

OBSERVATION 12

The establishment of specifications including any changes thereto, are not reviewed and approved by the quality control unit.

Specifically, the alert level specifications of (b) (4) for the purified water use points and non use points have not been evaluated or adjusted based on the historical results.

EXHIBIT # 103 is the firm's procedure for sampling water. EXHIBIT #104 is the firm's procedure for Analysis of Water. According to the firm's procedure water is sampled (b) (4) from each point of use for (b) (4) analysis. This sampling procedure is silent as to quantity of sample to collect. EXHIBIT # 104 analysis procedure identifies that (b) (4) is the amount filtered. This procedure states that for total (b) (4) a samples must be a minimum of (b) (4). If total (b) (4) count, (b) (4) are to be tested the sample size must be a minimum of (b) (4). According to the procedure after (b) (4) recovered on the (b) (4) Results are reported as (b) (4). The example in the procedure states if the filter has 9 colonies and the quantity of sample filtered is (b) (4). The reported plate count for this example would be (b) (4). (b) (4) The specifications for the purified water are

(b) (4)

According to the procedure all alert/action level excursions are formalized in written investigations to management. Review of the micro investigations for 2002 through 2004 revealed (b) (4) investigation which is discussed in observation #2. This was confirmed by David Bonilla that there was only one out of specification report generated for water micro excursions over this (b) (4) period. EXHIBIT # 105 is a copy of the water trending. Page 1 of the report is for the month of (b) (4). The highest cfu recovered was (b) (4). Review of the (b) (4) monthly reports of trending for (b) (4) revealed that this recovery of (b) (4) cfu was the highest. The

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

AEI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

results for 2003 are attached although not in a monthly trending format. Attached as **EXHIBIT # 106** is a listing or library of microorganisms isolated from Fort Washington.

During the inspection when this was discussed I had inquired as to whether any consideration had been given to decreasing the alert level. Identification is normally performed with excursions only although the firm's procedure states, on page 16 quarterly for a (b) (4) all organisms isolated from routine testing will be identified. I explained that lowering the alert level reflective of actual results would give an indication of concern of different organisms or greater bioburden of the water. It was stressed that specifications should be realistic.

Firm management had no comment when this was discussed.

Facilities and Equipment System **OBSERVATION 13**

Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, the dirty hold time of (b) (4) prior to cleaning, had been exceeded on 3 occasions from liquids holding tank (b) (4) to packaging line (b) (4) in the new manufacturing area during the period of (b) (4)

As discussed earlier, in (b) (4) was commissioned. (b) (4) (b) (4) assisted with the cleaning validation protocol & report.

EXHIBIT # 107 are excerpts from the final report for the cleaning of the equipment and transfer lines from the (b) (4) area to the packaging area. Based on the data collected the data supports that the cleaning is effective when the dirty hold time has not exceeded (b) (4) The time that the equipment is in use and cleaning is recorded electronically. There was no mechanism in place for the system to alert the operator if the dirty hold time has been exceeded. Steve Minacci, Sr. Team Leader Liquids had explained that the system provides a count down timer to ensure that the clean hold time is not exceeded prior to manufacturing. According to a print from Packaging Line (b) (4) from Hold Tank (b) (4) the dirty hold time was exceeded following the manufacture of batch (b) (4) **EXHIBIT 108**. This was one of three examples where the dirty hold time had been exceeded. As discussed during the inspection during these times that the dirty hold time was exceeded no data was collected to verify that the cleaning was effective. As described by Steve Minacci no samples are taken routinely to verify the equipment is clean, approval is visual only. These incidents involved the hold tank (b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

During the inspection following this discussion, Steve Minacci, Sr. Team Leader had explained that they will be (b) (4) for the dirty hold time to ensure that an alarm is raised if the validated times have been exceeded prior to cleaning.

During the discussion with management, management reiterated that the timer will be installed.

Materials Handling System

OBSERVATION 14

Representative samples are not taken of each shipment of each lot of components for testing or examination.

Specifically, samples of incoming material are not collected randomly. For example 30 drums of Pregelatinized Starch lot (b) (4) were received on 3 pallets on (b) (4) all six samples were collected from 1 pallet.

During the inspection of the warehouse receiving area it was noted that 3 pallets of Pregelatinized Starch lot (b) (4) See EXHIBIT # 55 for the (b) (4) print out of this receipt. It was explained that samples would be collected by QC receiving and submitted to the QC laboratory. Samples would be collected from various drums based on the (b) (4) of the total drums received. In this case (b) (4) drums should have been sampled. Inspection of the lot revealed that all six samples were taken from 1 pallet.

Attached as EXHIBIT # 56, is the firm's procedure for (b) (4)
The firm's procedure does not require that the samples be representative of the lot received.

During the inspection this was discussed with management. The concern that the SOP does not specify that the samples be representative of the lot and the fact that the observed sampling practice was not representative of the lot with all the samples being collected from one pallet only.

VOLUNTARY CORRECTIONS

Attached are the voluntary correction documents that the firm provided during the inspection. As explained to firm management these voluntary corrections were noted although not reviewed due to time constraints on the inspection. They are attached to this report as EXHIBITS 109 although not reviewed. It was also explained to the firm that they will need to include these items as part of the 483 response. Corrections include the following SOPs

(b) (4)

EXHIBITS AND SAMPLES COLLECTED

1. Product listing
2. Head count of QA
3. Organizational chart for the management board
4. Organizational chart for the Quality Sciences & Compliance
5. Organizational chart for Operations
6. Process validation reports/protocols generated since 3/2002 & pending applications
7. QC sample logbook
8. Listing of Recalls and Field Alerts

9. (b) (4) (b) (4)

10. (b) (4)

11. (b) (4)

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26. (b) (4)

27. (b) (4)

28. (b) (4)

Children's Motrin Grape Flavored Tablets

29. Listing of people interviewed

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EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

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(b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
PPC, Inc.
Fort Washington, PA 19034-2210

EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

65. not used

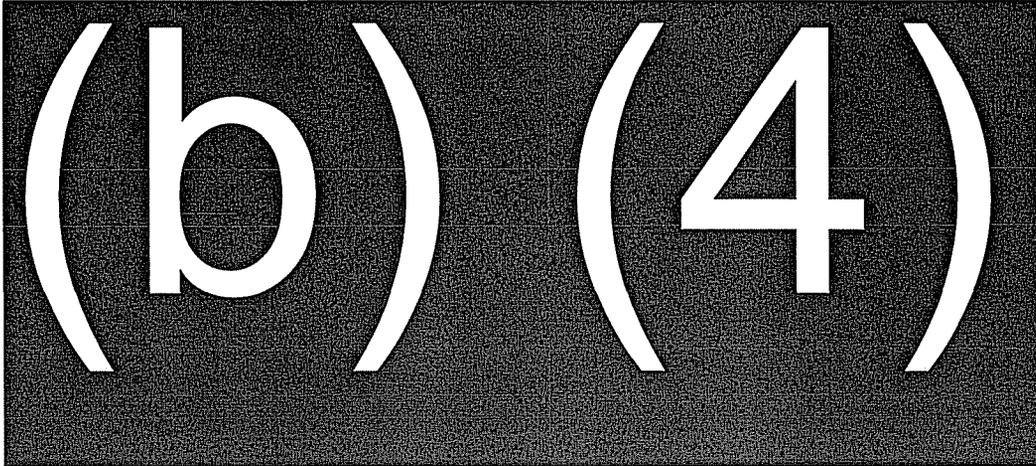
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(b) (4)

Establishment Inspection Report
McNeil Consumer & Specialty
Pharmaceuticals, Division of McNeil-
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EI: 2510184
EI Start: 05/17/2004
EI End: 06/07/2004

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ATTACHMENTS

Memo dated 4/8/04 from (b) (2)
FDA-482 dated 5/17/04
FDA-483 dated 6/7/04
DOC 286424
DOC 286425
DOC 286426
DOC 286427

A handwritten signature in cursive script that reads "Susan F Laska". The signature is written in black ink and is positioned above the printed name.

Susan F Laska, M.S., Investigator