Summary of Findings:

This pre-approval and GMP inspection of a drug manufacturer was conducted in response to FACTS assignment 83046, and assignment #980165. This inspection was in accordance with CP 7346.832, 7646.843, and 7656.002.

The previous inspection was conducted 10/5,6,13,19/99 for ADE reporting and was classified as [redacted] Corrective actions were not covered during this inspection. b2

Covered during this inspection: Post approvals for ANDA 73-019, NDA 20-476, NDA 19-487, NDA 20-135, and pre-approval for NDA 21-128; equipment maintenance and calibration; training; complaints; stability storage and data; purified water system; on-going upgrade to HVAC; preservative effectiveness and preparatory testing for NDA 21-128 and NDA 19-487; overview of the QA system: Quality Control Lab; R&D Lab.

The current inspection revealed the following, which was placed on an FDA-483 issued to top management on 3/9/00: ANDA 73-019 deviates from the application; reconciliation records are not clear; validation batches do not have failure/deviation investigations by QA; Hold times have not been set; Sugar Charging System qualifications have not been completed; calibration of the load cells is not consistent; no cleaning justification for the [redacted] and sugar charging system; SOP 20-MF-CB is not being followed; no audit trail for electronic maintenance records; qualification protocol plan for the compression machines is missing; melting point apparatus is inadequate; no wavelength calibration for HPLC's in R&D lab; calibration for the IR spectrophotometer is not performed adequately. b4

- [redacted] was recommended for NDA 21-128: Children's Motrin® Cold Suspension; ibuprofen 100mg/5mL and pseudoephedrine HCl 15mg/5mL. b4

Corrective actions from current inspection: batch record corrections; hold time for Imodium AD; qualification final report for Sugar charging system was completed; SOPs for calibration of load cells and RPMs were revised; calibration of the IR. All others the firm promised to correct as soon as possible.

Sample collected: Pre-approval profile sample 55004, Children's Motrin® Cold Suspension.

History of Business/ Individual Responsibility:

According to Paula J. Oliver, Senior Director, Regulatory Compliance, there has been no changes since the last inspection, 10/5,6,13,19/99. Exhibit 1 is an overview of the firm's operations, current renovation status, and organization charts of the facility.

Ms. Oliver stated that **W. Anthony Vernon, President, is the most responsible person and all FDA correspondence should be addressed to him at this location.** She also stated that Mr. Vernon has the knowledge, duty, and power to prevent/correct objectionable conditions. Ms. Oliver explained that responsibility depends on the problem, for example, if it were an application problem then Mr. Chester would be responsible; however, ultimately Mr. Vernon is the most responsible person at the firm.

Key Officials:

GEN SPEC.
RELEASE
F# _____ DATE 10/5/2000
Reviewed by: Robin M. Zimmer

W.A. Vernon, President
V.A. Chester, VP Regulatory Affairs
M.D. Gowen, VP Operations
P.N. Juri, PhD, VP Quality Assurance
C.H. Knerr, VP Information Management

Hours of operations are [redacted] b4

Persons Interviewed/Administrative Procedures:

On 1/28/2000, I contacted McNeil and spoke to Paula Oliver's Secretary and informed her that I would be starting a PAI, Post approval and GMP inspection 2/3/00 and requested selected information to be available at that time. This report was written by Debra Bennett unless otherwise indicated.

On 2/1/00, Ms. Oliver called me and asked to postpone the inspection until 2/9/00 because she was not available.

On 2/9/00 credentials, FDA-482, and small business addendum were presented to Ms. Oliver because Mr. Vernon, President, was not available at the time. Ms. Oliver stated that she has authority to accept the FDA-482. Representing FDA were Debra J. Bennett, CSO, Michael Gurbarg, Chemist and Yvonne C. Wood, Chemist. All information requested was available for review.

The following individuals provided relevant information in their respective area of expertise:

Paula J. Oliver, Senior Director, Regulatory Compliance
Ann C. Rademacher, QC/QA Plant Manager
Lawrence R. Constable, Plant Manager
Elizabeth Boyles, Solid Dose Processing Manager
Richard A. Fontana, Analytical QC Lab Manager
Michael A. Vlasic, Engineering Business Leader
James R. Mossop, Compression Equipment Technician Technical Services
Mark A. Plezia, Staff Engineer, Supervisor
Michael A. Liddy, Project Leader
Manoj N. Shah, Ph.D., Director, New Product Development
David R. Bonilla, Supervisor, Microbiology QC Laboratory
Raju V.K. Vegesna, Ph.D., Team Leader & Senior Research Scientist
John Leahy, Liquids Production Manager
Thomas Markley, Director Support to Marketing
Ed Pfender, Plant Maintenace
Gerald J. Mergen, Manager, Technology Development & Statistics
David H. Rogers, Principal Scientist
Eleanor Freeman, Senior Research Associate
Carmella Walter, Raw Materials Supervisor
Rick Bruce, Research Scientist
James Beahm, Senior Research Scientist
Ted Yeager, Research Scientist
Robert Hausel, Team Leader, QC lab
Craig MacDonald, Senior Analyst

Mong-Lan Wang, Project Manager
Joseph Coleman, Information Systems Manager
Paul Palovcak, Manager of Midrange Applications
Sally Cunliffe, System Administrator and Manager
Pat Zinck, Manager Client Services and Operations
Robert Miller, Supervisor of Computer Operations
Cindy Golini, Manager of Records, Telecom and Administration Services
Robert Gallagher, Records Management Coordinator
[redacted] b4
[redacted] b4

Operations:

Mr. Constable provided the following information.

All material coming into the facility is logged into a computerized inventory system. It's given a part number, a McNeil lot number, and it's recorded when the material was received. The material will then be placed in the warehouse in an open location identified by the computer system.

I challenged the system by identifying three materials in the warehouse. I identified the lot number for the system to query. The system tracks all pertinent information including when it was tested and released for use. It also was able to identify its location in the warehouse. Materials are not tagged as approved, quarantined, or rejected. This process is controlled through the computer system. No discrepancies were noted.

Liquid raw material is received by tanker trucks. I reviewed SOP 20MF-LM-46 dated 9/25/98, "Mixing Operation: receipt/sampling/transfer of bulk chemicals." I reviewed records for the last three shipments received for bulk corn syrup and polyethylene glycol. No discrepancies were noted.

Ms. Rademacher provided the following information.

It was explained to me how the quality assurance (QA) program in the manufacturing areas assure manufacturing is conducted according to procedures. The team leader for each area is responsible for the overall review of the operation and reviewing the batch records for completeness. There are [redacted] QA personnel who patrol the floors and audit [redacted] b4
[redacted] These are random, unannounced audits. Observations are documented and b4
brought to the team leader's attention immediately for correction. Audit observations are pointed out during training sessions as well. QA will conduct comprehensive audits, which are announced.

Corporate Headquarters also audits this facility [redacted] I was informed that these b4
are very targeted, detailed audits.

Renovations are on going. Exhibit #1 gives an overview of the status and the projected completion for each area. Some areas are partially operational like the compression area. Areas that are under construction are sealed from the manufacturing areas. No discrepancies were noted.

Equipment:

Exhibits 2 and 3 are lists of major equipment in the oral dosage form and liquid manufacturing areas. I selected at random several pieces to review qualifications, maintenance and calibration records. The selection was based on common equipment used by products covered during this inspection. Equipment reviewed are as follows: mixing tanks [redacted] b4
holding tanks [redacted] load cells for mixing tanks; timers; [redacted] high sheer granular; b4
[redacted] fluid bed dryer; [redacted] melt tank [redacted] and [redacted] Compression b4
Machines. See observations 5 through 10.

There are [redacted] stainless steel granulation bins. Granulation bins are dedicated by active drug b4
substance. [redacted] are dedicated to acetaminophen products and [redacted] for ibuprofen b4
products. Most of these bins hold up to [redacted] Granulations are compressed into large b4
plastic totes. During an initial set-up of a compression run for Motrin IB caplet 100mg batch [redacted] I observed totes [redacted] and [redacted] being used that appeared to have b4
powder residue inside them. I questioned what was in the totes before this. Mr. Clark queried the computer system and told me that the totes were used for bulk IB caplets. The system also had a log that the totes were blown down with air before they were brought into the room. The totes also appeared well used and slightly pitted on the inside. I recommended to the firm that they should evaluate the totes for wear because plastic does pit and can be hard to clean, especially since caplets are shot into the totes from the compression machines. I asked the firm when work is complete, who verifies or checks that the work has been done, as stated in the computer system. The firm did not answer my question.

I was informed that the firm plans to use a matrix approach to validate manufacturing areas, as they become ready for production. I informed the firm that they need to be careful using the matrix approach and recommended contacting the district to review their plan before implementing.

During my review of the liquid manufacturing area for the PAI, I specifically looked at the tanks that involved Children's Motrin Cold Suspension NDA-21-128. I reviewed the current b4
diagrams for mixing tank [redacted] and holding tank [redacted] Tank [redacted] diagram did not show the exact position of the mixing bar. The drawings showed the mixing bar on the right, angled to the center, whereas, the actual position of the mixer was centered straight up and down. There b4
were also two stationary stainless steel blades referred to as [redacted], the depth of the tank on each side that were not on the drawings. Mr. Pfender informed me that there have been no additions to the tank since it was installed.

Balance Flow:

Balance flow is a manufacturing process to utilize the full capacity of the granulation equipment, but where the compression of the granulation is limited by the coating pan capacity b4
of [redacted] For example, a granulation batch is normally [redacted] this granulation will be b4
compressed until it reaches [redacted] where it will be considered a complete compression batch and sent to the coating pans for coating. The rest of the granulation will be compressed under a new compression batch number. The balance of the granulation is not enough to complete the new compression batch, therefore, a new granulation batch will be used to complete the compression batch. If a compression batch can not be completed because a new granulation batch is not available, the cores will be stored until a granulation batch is available for compression. This process is continuous for several products, Motrin IB Gelcaps, Tylenol

Cold, Tylenol Sinus, Tylenol Cold Severe, Tylenol Allergy Sinus, Tylenol Cold ND, Tylenol Flu ND, Sine-Aid, Simply Sleep, Motrin 200, 100, Sinus, Cold & Flu, see exhibit #12. Exhibit #13, SOP 20-MF-GP-07, "General Procedure Compression" section 12 page 11 explains the balance flow or continuous flow process.

Samples of compressed cores are collected for each compression batch at the beginning, middle and the end of the compression run and submitted to the quality control lab but they are not tested according to Mr. Fontana. After the cores are completely coated and ready for packaging, samples are collected for finished product testing. I asked Ms. Rademacher how could they determine that they have collected representative samples of each of the granulation's. Mr. Fontana stated that there would always be finished units from a compression batch made up from one granulation. The batch that comprises of commingled cores (left over granulation) would not be released unless the batch with the pure cores would pass. The commingled batch would receive full testing; however, the firm can not confirm which core came from which granulation or if the sample collected was representative of each of the granulation batches.

Exhibit # 14 is a batch flow diagram; however, exhibit #15 is an accurate picture of current manufacturing practice. According to SOP 20-MG-PG-01, "Packaging Procedure Batch Preparation", section 4.1.3, one packaging batch can have up to [redacted] manufacturing batches, which would make it impossible to trace it back to the active drug substance and/or inactive. See section Recall for more information. b4

According to Ms. Oliver and the approved ANDA 73-019 for Motrin® Gelcaps, this process (balance flow) was approved by CDER, even though, the original deficiency letter stated that this practice was not in accordance with GMP's.

Analytical Research and Development Labs:
M. Gurbarg wrote this section.

Laboratory RB-109D – New product development lab.
No user logbooks are kept for HPLC instruments, but maintenance logs are kept. The only way to determine which instrument is used for which analysis is by product files, which are kept with the batch records. HPLC calibrations are performed every [redacted] Preventative maintenance (PM) is performed [redacted] by an outside contractor, [redacted] from [redacted] stated that their wavelength accuracy check is only to detect one peak at a wavelength of 656 nm using a Deuterium lamp, their check doesn't test the whole UV range. We looked at HPLC system [redacted] which included [redacted] autosampler, [redacted] controller and pump and [redacted] diode-array detector. Linearity is done at 280 nm. (See discussions section) We checked the SOP #99-RDIN-6 for HPLC calibration dated 7/20/99. b4 b4 b4 b4
There are about [redacted] HPLCs, most are connected to LIMS and use [redacted] chromatography software. Chromatograms are stored for [redacted] in LIMS and cannot be reprocessed after that. b4 b4

Y. Wood wrote this section

I observed that the majority of the balances in the Research Laboratory were linked directly to LIMS so that data is automatically stored or can be sent to LIMS by pressing a button. Balances that are not linked to LIMS are attached to small, independent printers to

immediately print results. On two separate occasions, I observed that balances were in need of internal calibrations. This was indicated by signals on the readout screen of the balance. I reviewed the SOP for balance calibrations and noticed that internal calibrations were only to be done when NIST-traceable weights didn't meet specifications. David Rogers told me that prior to the current SOP, it had been standard practice to perform internal calibrations at each weighing and that the balances needed frequent repairs as a result of constant stress on internal parts. Consequently, the lab stopped performing internal calibrations, except as stated in the SOP. I suggested that internal calibrations should be done at the start of the day or when necessary (as indicated by the balance), not at each time of use. David Rogers stated that since the problem was with older balances, many of which had been replaced, the suggestion would be taken under consideration.
I reviewed SOP 99-NAT-AN-LP-004, Transfer of Analytical Methods, which described practices for transferring methods between the Research and Development Laboratory and the Quality Assurance Laboratory and between the company and contract laboratories.

M. Gurbarg and Y. Wood wrote this section

Laboratory RB- 111 – New product development and NDAs
We checked [redacted] pH meter, serial number [redacted] which is calibrated at time of use and attached to a small, independent printer. Printouts are attached directly to a worksheet. b4
We looked at the [redacted] balance and the [redacted] calibration in logbook E017. b4
There was a [redacted] HPLC. b4
Laboratory RC-228 – Raw materials lab
We observed that an [redacted] Melting Point Apparatus was being calibrated while we were there on 2/10/00. The calibration logbook showed the last calibration date as 2-17-98. Carmella Walter told us the apparatus has not been used since that date. She also told us that the USP method using heated oil to determine melting point was performed. No melting point standards are used for comparison. (See observation # 11) We reviewed SOP 99-RD-IN-008, Thermometer Calibration. Carmella Walter told us that in instances where thermometers are calibrated on-site, they are read in stability chambers at [redacted] and [redacted] b4
Most often, the company purchases new thermometers.
Laboratory RC-229
We checked the [redacted] titrator logbook #E-054. This Karl Fischer titrator b4
is calibrated at time of use. We also checked the [redacted] b4
titrators; they have the same logbook and serial numbers, because the components can be used interchangeably for different analyses. The [redacted] is located in a hood and b4
used only for perchloric acid titrations. We noted that the calibration stickers were faded to the point that the serial numbers were not apparent. We suggested that they get new stickers.
We checked HPLC [redacted], which had a [redacted] autosampler, a [redacted] detector, b4
and a [redacted] pump. It had a [redacted] system interface module so that the signals could be b4
sent to LIMS. We reviewed logbook, E-97-1 for this instrument. We looked at a [redacted] b4
[redacted] analytical balance, serial number [redacted] and its corresponding b4
logbook 94-34. Carmella Walter told us that [redacted] services their balances [redacted] b4
We checked the logbook # EQ93-003 for HPLC system [redacted] b4
We noticed that the [redacted] UV/VIS [redacted] serial number [redacted] had not been used b4
since 7/99. We observed a [redacted] IR with a [redacted] microscope attached. There b4
was a diode array HPLC from [redacted] instrument [redacted] using stand-alone software. b4
We checked logbook E072 and noticed no wavelength calibration was performed.

Laboratory RC-230

This lab also had a [redacted] FTIR and an LC/MS from [redacted] hooked to a [redacted] HPLC. We checked on a [redacted] Particle size analyzer [redacted]. There are three standards to check calibration, which are NIST traceable, latex polystyrene microspheres from [redacted]. The three were [redacted] certificate date 9/22/97, [redacted] dated 1/19/98, and [redacted] dated 3/9/98. We checked the HPLC [redacted], a [redacted] system with diode array detector, which was set up as a stand-alone system, not connected to LIMS. We reviewed the calibration logbook E-072. There was also a [redacted] and [redacted] GCs [redacted] and [redacted]. We checked logbook E92-129 for calibrations. We observed a [redacted] UV/VIS spectrophotometer.

b4 b4 b4 b4 b4 b4 b4

Quality Control Laboratory:

M. Gurbarg wrote this section:

The QC laboratory was moved to a new area on/about October 1999. The lab has [redacted] team leaders and [redacted] senior chemists. The lab does not use notebooks, only data sheets which are distributed out of LIMS. Analysts cannot access more than one sheet for an analysis. Only the Systems Administrator and the supervisor can print a data sheet. Each sheet has a specific product number and batch number. It has a scan bar to enter data into LIMS. Data from balances, HPLCs, UVs are sent directly to LIMS for calculations.

b4 b4

Laboratory QC19A - prep and wet chemistry lab

We reviewed the calibration logbooks for the [redacted] balance, serial number [redacted] the [redacted] balance [redacted] and the [redacted] balance [redacted] had an OOS result for calibration in 10/99 after it was moved. The OOS result was attributed to the move. Balance [redacted] was moved on 9/20/99, but wasn't qualified until 10/6/99. Richard Fontana told us that the balance was taken out of service until it was qualified. Both balances were calibrated in 12/99.

b4 b4 b4

We checked the calibrations for the [redacted] serial [redacted] a new instrument. Richard Fontana told us that spectra are not stored on the hard drive, they are all printed out. Samples are compared to a working reference standard, vendor standard, previously accepted lot. We asked if they had USP standards available in case there was a questionable result. Richard said they did.

b4

We checked [redacted] UV/VIS serial [redacted] and [redacted] and the [redacted] pH meter serial [redacted]. Another pH meter [redacted] had a sign that said, "Do not use until qualified". Richard Fontana said it was new and had not been qualified yet.

b4 b4

We checked the HPLC system [redacted] serial # [redacted]. This system was labeled as being calibrated for [redacted] and [redacted] runs, however the documentation showed only pump flow rates calibration. There are methods available to test [redacted] delivery for HPLC, but none were performed in this case.

b4 b4 b4

We reviewed the records for calibration of the Karl Fischer titrator, serial [redacted]. The calibration is due every [redacted], but I observed that the instrument was calibrated 3/99 and again 5/99. Richard Fontana told me the reason for this was that the vendor came in to rebuild / refurbish the titrator in 4/99.

b4 b4

We reviewed the calibration records for [redacted] dissolution apparatuses, serial [redacted] and [redacted]. We checked on the availability of the set-up tools and the measuring devices. Robert

b4 b4

Hausel, team leader explained that they use the [redacted] QA station to set up their dissolution equipment. b4

There was a [redacted] hat was new. Richard Fontana explained the [redacted] Viscometer to us. It is qualified by R & D and there is a standard certificate for spindle [redacted] where they obtained [redacted] cps. b4 b4 b4

Laboratory QC11B - instrument lab

We checked on an HLPC [redacted] system, which included a [redacted] pump, [redacted] detector, [redacted] and used [redacted] software. We checked the logbook for LC [redacted] LC [redacted] had a [redacted] dual wavelength detector, a [redacted] Autosampler and [redacted] pumps. b4 b4 b4

There was a [redacted] polarimeter, a [redacted] balance and a [redacted] melting point apparatus. We checked the SOP 20-QA-IPAP-002 for the calibration records of the melting point apparatus. It is calibrated at time of use with the melting point standard closest to the melting point of the sample. Every [redacted] it is checked with [redacted] melting point standards. Richard Fontana explained the [redacted] Viscometer [redacted] which is used for starches. b4 b4 b4

Stability:
M. Gurbarg wrote this section.

Room RC-126
This lab is a research and stability testing room that has chambers for stress testing (including light stress testing and temperature cycle testing). The chambers are controlled by the [redacted] monitoring system with battery backup and extra chambers in cases of power failure or chamber failure. In cases where the alarms are after hours, the system will contact the primary (or secondary, if necessary) responsible personnel. The room has restricted access. b4

Stability Room RC-102
This is the room temperature / humidity controlled stability storage area. This room is controlled by a [redacted] computer software system. The computer controls the temperature and humidity and sends alarms when it varies outside the set points. These alarms go to maintenance and to people's home phones or to pagers during holidays and weekends. Repairs are attended to within two hours. The computer has a uninteruptable power supply and the heater/cooler has a generator for emergencies. There is a tape backup for the computer nightly. We reviewed the stability storage logbook E92-120, which noted an electrical shutdown in the stability chamber on 7-21-99. The corresponding memorandum RR446 described the situation and explained that the occurrence did not negatively impact the samples, the temperature went to [redacted] b4 b4

Computer Validation (LIMS):
M. Gurbarg wrote this section.

There are [redacted] security access levels for the system. There is a [redacted] icon for [redacted] on the lab computers. From there an analyst needs a password to get into LIMS and a user name. When entering laboratory results, once the ENTER DATA key has been pressed, there is no way to edit data. If an error has occurred, a sample investigation must be scheduled. This generates a date and time-stamped audit trail. When retest results are entered (even if it's to b4

correct a typographical error), an explanation must accompany the new results. Once the results are entered, the same username / password combination must be entered to verify that the analyst who logged into the system, is the analyst who is entering test results for that account. The supervisor reviews both good and "bad" data or data that he sees has been changed for some reason. Calculations are done by [redacted] in LIMS for the more simple calculations. [redacted] programs handle complicated calculations that are not handled by [redacted] programs are put through IQ/OQ/PQ processes. These qualifications include "extremes testing" such as outlying results, input challenges and tests at either end of analytical specifications. Analysts and Information Management personnel test [redacted] program codes. Programs are under change control rules, so upgrades and modifications of specification changes have to undergo revalidation. Results of [redacted] program are checked against hand calculations and [redacted] spreadsheet calculations. Joe Coleman said there is a test script to test the calculation programs and they do hand vs. program calculations. He does modifications and upgrades, which are reviewed by a team. Source code for LIMS is controlled by [redacted] and is not accessible by analysts. According to the current contract, someone from [redacted] would be called to fix any problems that may occur. A vendor audit was performed before purchasing software from [redacted]

b4 b4 b4 b4 b4 b4 b4 b4 b4

Y. Wood wrote this section

Backup / Archiving of LIMS:

I reviewed SOP 20-IM-LIM-003, dated 7/15/99, Backup for LIMS Systems. [redacted] backups, [redacted] and [redacted] full-image backups are performed. Tapes for the [redacted] backups are rotated on a [redacted] schedule then [redacted] Hard copies are kept with batch records. Tapes for the [redacted] backups are rotated on a [redacted] schedule then [redacted] The [redacted] backup is performed the [redacted] of the [redacted] and stored [redacted] in a [redacted] by a vendor for [redacted] Records Management department generates a [redacted] destruct report that lists all records (in this case, tapes) to be destroyed. This list is sent to all the "owners" (usually, department supervisors) of these records so they can authorize the destruction. If they want to retain a record, they can highlight that record to prevent its destruction. Once the list has been reviewed, a call is placed to a password-protected voicemail account at the off-site vendor's office. All items to be destroyed are identified and brought to McNeil to be shredded.

b4 b4 b4 b4 b4 b4 b4 b4 b4

I reviewed SOP 99-VAL-CS-001, dated 11/25/98, Validation of Computerized Systems. This SOP covers various stages of the software lifecycle and the quality assurance checks at each stage.

I looked at SOP-VAL-CS-005, dated 11/25/98, System Security. This SOP covers the physical measures taken to assure security and proper authorization for access of LIMS.
I reviewed SOP 20-IM-OPS-003, Computer Room Power Failure Procedures, which was effective 3/3/99. This SOP outlines the steps taken when a power failure occurs, including the order in which portions of the system are shut down and restarted.

I reviewed SOP 99-NAT-LIM-002, LIMS Incident Reporting, which was effective 8/15/97and SOP 99-RD-CR-043, Adding / Modifying / Deleting Users to [redacted] Lab Manager LIMS System, which was effective 4/17/98.

b4

I reviewed SOP 99-RD-CR-054, R & D Laboratory Information Management System Raw Data, which was effective 4/14/98. This SOP describes what is considered raw data.

I reviewed SOP 99-QA-LIM-005, LIMS Data Review and Approval, which described the steps taken by supervisors to review and approve product and sample information in LIMS.

Children's Motrin® Cold Suspension NDA 21-128:

This inspection covered the pre-approval for this product. During my review of the NDA and comparing it to the master batch record I observed that the master batch record was not approved. The master batch record submitted in the application is also not approved. Ms. Oliver told me that this record would not be approved until after the process validation. The reason is that there could be some changes optimizing the process. McNeil considers the process validation batches as R&D batches. Once the validation batches are approved by quality assurance they are converted to commercial batches and marketed. The master batch record is not captured until after validation. See observation #3 for more information. Changes made to the master batch record compared to the pivotal batch are as follows:

Specification	Pivotal Batch	Current Master Batch Record	b4
Water Addition	[redacted]	[redacted]	b4
Sugar Addition			

Dr. Shah explained that the pivotal specifications variation was too tight. The batch must meet a set weight yield in order for the batch to be approved.

Dr. Shah explained to me that R&D will take the product from development to launch, therefore, there is no technical transfer. A cross functional group comprised of folks from R&D to marketing oversees this project.

I reviewed the Development Report Pre-commercialization Phase dated 6/8/99 and the Development Report Commercialized Phase dated 8/27/99. Preservative Effectiveness testing was reviewed. No discrepancies were noted.

I reviewed raw data for the container/closure qualifications and compared it to what was submitted in the application. No discrepancies were noted.

M. Gurbarg wrote this section

I reviewed the test methods for Motrin Drops MS-846 with dates of 9/14/98, a revision on 1/14/99 and the final version dated 1/18/00. The [redacted] is sampled for release testing and the [redacted] are sampled for stability testing. I saw a memo from the reviewer approving the [redacted] testing on 2/8/00. The original version of the assay method was a [redacted] HPLC method that included ibuprofen, pseudoephedrine, isobutylacetophenone and [redacted] but columns were not lasting long enough. The new method dated 1/18/00 is [redacted] but without [redacted] The [redacted] is tested separately by a different [redacted] HPLC method. I reviewed the change control for this method and the equivalence report between the two methods. Batches [redacted] and [redacted] were run by both methods, which showed similar results. I also reviewed the chromatograms for lot [redacted]. This lot was tested [redacted] instead of the [redacted]

b4 b4 b4 b4 b4 b4 b4 b4 b4 b4 b4 b4

due to an analyst's mistake. The analyst was given training on 11/13/98. I reviewed notebook 168, pg. 151 to 162 dated 10/12/98, which included the testing for assay of ibuprofen, pseudoephedrine and isobutylacetophenone (IBAP).

There are specs for IBAP, which is a degradation product of ibuprofen. They use working standards in the lab so I checked the qualification of the ibuprofen and the pseudoephedrine standards. I reviewed the certificate of analysis (C of A) for pseudoephedrine hydrochloride USP and notebook 187, page 67 that detailed the analytical testing and assay results. The assay results of the manufacturer's C of A were similar to the lab's results. Page 72 of that notebook showed the infrared results for the identification test of pseudoephedrine. I reviewed the C of A for 4-isobutylacetophenone and compared the manufacturer's assay results to the lab's assay results.

[redacted] is present in the berry flavor. On sample preparation it oxidizes to [redacted] making the [redacted] results high. [redacted] is added to the sample preparation, which nullifies the oxidation. I reviewed the validation of the [redacted] in validation reports MVH-822(R3) and MVH-846(R3) dated 1/19/00. I reviewed notebooks 322 and 328, which included the [redacted] addition. In notebook 328 the sample chromatograms show the peaks rising when no [redacted] was added. b4

Chromatogram set [redacted] showed a growth of [redacted] at [redacted] was added to the sample preparation, placebo, grape and the berry flavor to check interferences. b4

I reviewed the identification tests for ibuprofen and pseudoephedrine. The IR spectra of pseudoephedrine standard and sample showed too much water vapor, which obliterated some of the drug peaks. (See discussion items)

In looking over the dissolution method, I found that only ibuprofen was tested, pseudoephedrine was not. Manoj Shah said that the pseudoephedrine is all dissolved in the product, but ibuprofen is suspended, so pseudoephedrine will be 100% dissolved immediately.

M. Gurbarg and Y. Wood wrote this section

[redacted] batches were made of the Children's Motrin Cold Suspension, [redacted] (grape flavor) and [redacted] (berry flavor). We reviewed batch [redacted] berry flavor for specific gravity and refractive index. We also checked the sucrose, lot [redacted] that was a different lot than in the berry flavor. We looked at specific rotation and [redacted] [redacted] of room temperature stability had been completed and [redacted] of accelerated. We reviewed [redacted] stability data for bio-batch [redacted] study number [redacted] A contract laboratory performed the stability study for [redacted] b4

We reviewed in-process testing for [redacted] batch number [redacted] samples were taken from the mixing tank, [redacted] from the hold tank and [redacted] samples from the packaging. [redacted] was an investigation of low results for pseudoephedrine and ibuprofen. From the 2nd sample from packaging the results for ibuprofen were [redacted] and [redacted] and the pseudoephedrine were [redacted] and [redacted] The specs are [redacted] to [redacted] The investigation proved inconclusive and the original results were confirmed with a [redacted] for ibuprofen and [redacted] for pseudoephedrine. We then reviewed the dissolution results for the mix tank, the hold tank, and the packaging. b4

We reviewed the raw data for stability of biobatch [redacted] It was only tested inverted which is a worst case scenario because it is in contact with the cap. The dissolution was in notebook 313. We reviewed the data from the [redacted] accelerated stability; dissolution and assay, and the cycle testing which is done for suspensions at [redacted] The [redacted] accelerated stability was not done due to the method change from a [redacted] to an [redacted] method as mentioned above. This is mentioned in the NDA in vol. 2, sec. 4 pg. 266. We reviewed the three-month cycle testing including ibuprofen and pseudoephedrine assay.

We reviewed some OOS reports on this product.

[redacted]

This was during method validation for [redacted] The resolution was not constant and linearity sample, which was supposed to be [redacted] was [redacted] and [redacted] It was attributed to the mobile phase. New mobile phase was made and the samples were reinjected using the same column and the results were [redacted] This was completed 1/20/99.

[redacted]

For [redacted] assay results were [redacted] and [redacted] for duplicates on 8/4/99. These were suspect due to a [redacted] deviation. The solutions were reinjected and reprepared from stock and the original results were valid.

[redacted]

Dealt with batch [redacted] One result for the dissolution release analysis was out of trend. The result was unusually high when compared to the other results from the same analysis, but was within specifications. The investigation was inconclusive since the re-measurement of the sample was low and didn't validate the original result. The original result was used since it was still within specifications.

[redacted]

Dealt with batch [redacted] The investigation showed that the irregular peak in the HPLC chromatogram was the result of an air-bubble and/or an electrical spike. The original chromatogram was reprocessed with different parameters to integrate the peak of interest, since it could be separated from the irregular peak.

We reviewed the raw data for the testing of ibuprofen raw material, lot [redacted] that was used in the biobatch. We checked the tests for identification, water, heavy metals, assay, and chromatographic purity. Then we reviewed [redacted] lot [redacted] for tests for identification, congealing range, water, carbonizable substances, oxidizable substances, and assay.

We reviewed SOP 99-RD-AN-003, Reference Standards, which describes the annual re-certification of working reference standards (WRSs) and explains that the company may discard standards prior to manufacturer expiration date if specifications are not met. No standard is retained longer than the manufacturers suggested expiration date.

We reviewed the excipients, which went into lot [redacted] Polysorbate 80, lot [redacted] had expired on 6/12/97 but was requalified on 3/20/97, which extended the expiration to 3/19/99. We reviewed D&C Red no. 33, lot [redacted] FD&C Blue #1, lot [redacted] and FD&C Red no. 40, lot [redacted] We checked Sucrose, lot [redacted] tests for [redacted] and specific rotation, Xanthane Gum, lot [redacted] which had tests for LOD, viscosity, ash, heavy metals

and assay, Starch, lot [redacted] and glycerin, lot [redacted] We reviewed excipient data for Acesulfame K, batch [redacted], Artificial Grape Flavor, and batch [redacted] b4 b4

Children's Motrin® Drops NDA-20-476:

For this commercial product, I reviewed the annual product reviews for the past two years. I also compared the NDA manufacturing process to the process validation and to the current master batch record. Exhibit #4 is a history of this product. I randomly selected three batches to review; [redacted] Each manufacturing batch receives a packaging batch lot number. Non-conformance report [redacted] for batch [redacted] was reviewed. No discrepancies were noted. For this product, batches are not commingled. b4 b4

M. Gurbarg and Y. Wood wrote this section.

We reviewed the raw data for lot [redacted] including assay, dissolution, identification, pH, [redacted] and IBAP. We asked for the OOS results for the past year. b4 b4

OOS [redacted]
This dealt with lot [redacted] that showed no peaks for the dissolution of ibuprofen and high pressure in the column. On investigation it was found that the column was not washed with [redacted] before the run. The reinjected samples had results of [redacted] and [redacted] After the column was washed results were [redacted] and [redacted] I suggested that the method should state wash the column with [redacted] before each run. b4 b4 b4 b4 b4

OOS [redacted]
This dealt with lot [redacted] that was an assay for ibuprofen results of [redacted] and [redacted] for the bulk and end samples. The original vials were reinjected and the original results were confirmed. The original sample preparation was injected and found to have [redacted] and [redacted] The problem was improper mixing of the sample flask. b4 b4 b4 b4

OOS [redacted]
This dealt with lot [redacted] the [redacted] room temperature stability sample. Dissolution results were [redacted] and [redacted] where Q = [redacted] The standard was suspected so it was rerun and obtained [redacted] Two new standards were made and the results were [redacted] and [redacted] Another analyst prepared these. The original standards were invalidated. The new standards were rerun and the results were [redacted] and [redacted] The pH of the dissolution medium was then suspected because it is used to prepare the standards. Th pH was tested in the original standards and was [redacted] the new standards it was [redacted] as it should be. The dissolution was repeated and the values were [redacted] b4 b4 b4 b4 b4 b4 b4 b4 b4 b4 b4

OOS [redacted]
This dealt with lot [redacted] for viscosity the result was [redacted] cps. The specs are [redacted] cps. An alternate method was used using [redacted] instead of [redacted] b4 b4 b4

Imodium A-D Liquid NDA-19-487:

For this commercial product, I reviewed the annual product reviews for the past two years. I also compared the NDA manufacturing process to the process validation and to the current master batch record. There were some discrepancies found between these documents.

Exhibit # 5 outlines the differences, which are mainly [redacted] reduced mix times during the mixing process. Ms. Oliver stated that the amended supplement (exhibit #6) did not specify mix times, therefore, during validation (exhibit #7) mix times were included, which is the current manufacturing process (exhibit #8). Exhibit #9 is the manufacturing directions submitted as amendment #1 for supplement S-008. b4

During process validation, it should be noted that two batches failed because of an overcharge of sugar. Exhibit #7 page 44 is a copy of an investigation that showed the Sugar Charging System failed because of no preventive maintenance for the valve actuators causing them to fail and had to be rebuilt. This document was discovered after the inspection. Ms. Rademacher had informed me during the inspection that the failure was due to operator error.

I randomly selected three batch records for review; [redacted] Cleaning validation and cleaning of the tanker trucks was reviewed. The tanker trucks are used to transport bulk finished product to the contract packager. These tanks are dedicated to McNeil and are cleaned after each shipment. Cleaning is verified before tanks are filled. b4

Exhibit #10 are shipping records for Imodium A-D packaging lot [redacted] which is manufacturing batch [redacted] manufactured on 11/24/99. These documents illustrate that [redacted] skids of commercial product were shipped from McNeil Consumer Healthcare in Fort Washington, PA on 1/7/00 to [redacted] by [redacted] carrier. According Mr. Constable there are [redacted] units remaining in inventory. Each manufacturing batch receives a packaging batch lot number. For this product, batches are not commingled. b4 b4 b4 b4 b4

M. Gurbarg wrote this section:

We reviewed lot [redacted] for the assay of loperamide, identification by [redacted] and pH. We looked at the method validation for the impurities test; the [redacted] is the only impurity. We looked at the forced degradation studies and the SOP for impurity calculations to make sure that the [redacted] was the only impurity and that it was used in the calculations of total impurities. The forced degradation was with heat, light and acid. There were extraneous peaks but they were due to the flavor. No other degradation peaks were found. We reviewed lot [redacted] including assay, dissolution, identification, pH, [redacted] and IBAP. We reviewed supplement 008 and amendment No. 1. b4 b4 b4 b4

Motrin® Chewable Tablet 100mg NDA 20-135:

For this commercial product, I reviewed the past two year's annual product reviews. I also compared the NDA manufacturing process to the process validation and to the current master batch record. Two batch records were randomly selected for review; [redacted] For this product, batches are not commingled. No discrepancies were noted. b4

M. Gurbarg and Y. Wood wrote this section

We reviewed lot [redacted] for assay of ibuprofen and IBAP, identification, dissolution and content uniformity. There were no OOS reports for the past two years due to the fact that there isn't much of the product manufactured. b4

Motrin IB Sinus Headache Caplets, NDA 19-899:

We reviewed compression batch [redacted] for assay for ibuprofen and pseudoephedrine, content uniformity, identification and dissolution. No impurities test is included in the approved NDA. A supplement will be submitted this year for an impurities test. We reviewed stability testing including [redacted] stability testing for packaging lot [redacted] There were no OOS reports for the past year. b4 b4

Motrin® IB Gelcaps ANDA 73-019:

Ms. Oliver stated that this application was consolidated with NDA 19-012 (exhibit #18), Motrin® tablets and caplets, which is currently manufactured by [redacted] McNeil will be transferring all manufacturing operations from [redacted] to the McNeil Puerto Rico facility by the end of the year. b4 b4

For this commercial product, I reviewed the past two year's annual product reviews. I also compared the NDA manufacturing process to the process validation and to the current master batch record. Three batch records were randomly selected for review; [redacted] Three non-conformance reports were reviewed; [redacted] b4 b4

Several issues were discussed with the firm. During process validation in late 1993, all three granulation batches failed particle size, exhibit 16 page 27. I asked the firm how did they determine the specification for the particle size. Mr. Mergen explained that the specification is calculated statistically by predicting the interval to contain all future observations based on previous batch variations. Since blend uniformity, content uniformity and dissolution testing all passed, the validation was approved. See exhibit #17 for the firm's explanation.

The firm tested [redacted] gelcaps per batch for dissolution to conclude that the out of specification particle size had no impact. I asked Mr. Mergen if [redacted] samples were representative of over [redacted] gelcaps. He replied that they were representative because they were collected throughout the run. If they were from one time point they would not be representative. b4 b4 b4

Exhibit #19 is the current in-process testing. According to Ms. Rademacher, QA does not review any in-process testing results until the records are reviewed for releasing finished product for distribution.

M. Gurbarg wrote this section.

We reviewed lot [redacted] for assay of ibuprofen and IBAP, impurities, identification, dissolution and content uniformity. We reviewed the validation report; Analytical Method Report MV-224 dated 2/16/93 to see that IBAP was included in the total impurities. Also moisture determination results were included in the analytical data, but not in the original method validation. Karl Fisher water determination was added for information only in 6/13/94 and there are no specifications. b4

We reviewed room temperature stability testing for batch [redacted] The initial testing is the same testing done for the finished product, except that a dissolution profile is added. b4

We looked at the [redacted] stability testing due to a problem that Johnson & Johnson had with the cotton in the bottles of tablets. The cotton manufacturer added an additional purification step, which inadvertently released hydrogen peroxide from the cotton. One of Johnson & Johnson's products was effected. The stability studies were run on the bottles of McNeil's products, which contained the same type of cotton. None of McNeil's products were effected but they were running the stability studies to make sure. We reviewed assay, impurities and dissolution. b4

Tylenol Extended Relief Caplets:

We reviewed compression batch [redacted] and granulation batch [redacted] including assay, content uniformity, and dissolution. Impurities testing was not done because Tylenol is mostly acetaminophen which according to literature degrades into para-aminophenol. The lab has never seen it under stressed conditions. We reviewed room temperature stability studies including; [redacted] testing for batch [redacted]. b4 b4

Y. Wood wrote this section

OOS [redacted] b4

This dealt with batch # [redacted] generating an OOS result for dissolution testing. Non-conformance report (NCR) [redacted] was also generated. At dissolution stage L2, one caplet was OOS. During the investigation, it was determined that L3 testing was inadvertently deleted from the method in a previous revision but was permitted. The sample passed L3 testing and was released. I observed that the NCR was generated four days before the OOS result was obtained. Richard Fontana told me that since this batch was associated with another batch [redacted] that had an OOS result, a NCR is started for every associated batch if a wide-scale problem is suspected. Ultimately, all batches were released. b4 b4 b4 b4

OOS [redacted] b4

This dealt with batch # [redacted] The OOS result was a value of [redacted] for the [redacted] dissolution time point for one caplet. The results for dissolution testing at [redacted] and [redacted] were acceptable. The investigation determined that the dissolution media blank was mixed up with the actual dissolution sample when UV/VIS readings were taken. b4 b4 b4 b4

OOS [redacted] b4

This dealt with batch [redacted] A high OOS result was obtained during content uniformity testing. The investigation invalidated the result and replacement results were accepted. The assignable cause was determined to be a sample dilution (pipetting) error. b4

M. Gurbarg wrote this section

OOS [redacted] b4

This dealt with lot [redacted] for a content uniformity result of [redacted] for APAP. A remeasurement showed that the instrument was in error and the result was [redacted]. b4 b4

OOS [redacted] b4

This dealt with lot [redacted] and [redacted]. Stage three dissolution at the [redacted] aliquot had an avg. of [redacted] and a range from [redacted] to [redacted] for lot [redacted] and [redacted] to [redacted] for lot [redacted]. The specs are for an average of 24 tablets is not to be less than [redacted]. Two other lots associated with [redacted] granulation went to stage 2 dissolution. [redacted] NCR report rejected all 4 b4 b4 b4 b4 b4

batches. QA investigated the process equipment, particle size and bulk density of the granulation, sampling of the uncoated cores, coating of coated cores and the coating solution.

Objectionable Conditions/Discussion with Management:

On 2/9/00, an FDA-483 was presented to Mr. Frank W. Hatch, PhD, Executive Director Research & Development because he stated that he was the most responsible person available at the time. Exhibit #11 is a list of attendees from McNeil. Representing FDA were Debra J. Bennett, CSO, Michael Gurbarg, Chemist, and Yvonne Wood, Chemsit.

1) The Motrin IB Gelcap manufacturing process deviates from the ANDA 73-019 in that most of the time [redacted] granulations are used in one compression batch of cores and they are not always sequential. The ANDA states, "At times, portions of [redacted] granulation batches are sequentially used to make one compression batch." For example: b4 b4

a) In 1999, [redacted] compression batches used [redacted] granulations and [redacted] compression batches used only one granulation, about [redacted] b4 b4

b) Compression batch [redacted] was initiated on 8/24/99 using granulation batch [redacted] and wasn' t completed until 11/24/99 using granulation batch [redacted] These are not sequential batches. b4 b4

c) Compression batch [redacted] was initiated on 11/24/99 using granulation batch [redacted] and wasn't completed until 12/9/99 using granulation batch [redacted] These are not sequential batches. b4 b4

d) In addition, the current batch record allows space for up to [redacted] granulations to be used for one compression batch. b4

Exhibit # 19a page 1 is a copy of page 426 of ANDA 73-019, which states, "At times, portions of [redacted] granulation batches are sequentially used to make one compression batch". Page 2 is the flow diagram of the process. Exhibit #20 is an account of how many compression batches contained [redacted], [redacted] or [redacted] granulations for the year 1999. Adding [redacted] granulations to one compression batch occurred about [redacted] of the time. b4 b4 b4

Exhibit #21 is compression batch record [redacted] It was initiated on 8/24/99 with granulation batch [redacted] however, it was not completed until 11/24/99 using granulation batch [redacted] see page 2. On 8/24/99 the compression was conducted using compression machine [redacted] and on 11/24/99, compression machine [redacted] was used, see pages 10-13. These are not sequential batches. b4 b4 b4 b4

Exhibit #22 is compression batch record [redacted] It was initiated on 11/24/99 with granulation batch [redacted] however, it was not completed until 12/9/99 using granulation batch [redacted] see page 1. Again, compression machine [redacted] was used to start the batch and compression machine [redacted] completed the batch, see pages 22-29. These are not b4 b4 b4 b4

sequential batches. In addition, this record was reviewed by QA on 10/30/99 before the record was complete. Ms. Rademacher could not explain how that happened.

Exhibit #22 is the most current batch record. On page 1, the batch record allows for [redacted] granulation batches to be used on this record, which the ANDA states that only [redacted] granulations will be used at times. In addition, there are no additional verification signatures that the equipment is cleaned and set up properly the [redacted] time. b4 b4 b4

At the summation meeting, item #1d was corrected, exhibit #23. The firm promised to respond in writing to the District Director in two weeks. They also stated that they would call for a meeting to define "at times" and "sequential".

2) Reconciliation records for compression batches of Motrin IB cores are unclear in that compression batches do not clearly identify what granulation and how much was utilized, including samples collected and waste.

Exhibit #24 is a copy of granulation batch [redacted] Page 15 is the reconcilation for the granulation batch. Page 16 is compression material reconciliation. On this page there is not one annotation for granulation batch [redacted] Exhibit #21 is compression batch [redacted] which utilized granulation batch [redacted] Exhibit #22 is compression batch [redacted] which also utilized granulation batch [redacted] however, no weights are associated with the compression batches. The total yield for granulation batch [redacted] was [redacted] Only [redacted] are accountable. The material input on page 16 references granulation batch [redacted] According to Ms. Boyles, this is the beginning batch for the campaign. The firm pulled all the records for this campaign and I still found it difficult to follow. b4 b4 b4 b4 b4 b4

At the summation meeting the firm promised to correct by 4/1/00.

3) Failures and deviations associated with process validation batches are not documented and investigated by Quality Assurance.

During my review of batches submitted in the Children's Motrin® Cold Suspension NDA 21-128 application I observed an overcharge of sugar. I also observed an overcharge of sugar in the process validation for Imodium AD Liquid. In the application a letter was written stating that the overcharge had no effect on the batch. In the process validation report two batches were rejected and destroyed, see exhibit #7 page 4 paragraph 2. I asked Dr. Shah if a non-conformance report was written and investigated. He informed me that for R&D batches it's reported in the development report or the validation report. I stated that validation batches are typically marketed. He stated that initially process validation batches are considered R&D batches and after QA review they are converted to marketed product. I explained to Dr. Shah that batches are either R&D or commercial batches. They can not be converted to commercial batches. Commercial batches must follow GMPs, which include conducting failure investigations and deviations from the procedures. SOP 99-VAL-PRO-001, "Outline for Manufacturing Process Validation Protocol and Report" section 5.2.3 states, "All exception, deviations, problems or departures, e.g., taking extra samples, should be discussed here." exhibit # 24a.

At the summation meeting the firm promised to correct this as soon as possible.

4) Hold times have not been established for the following:

a) Bulk Imodium AD Liquid before packaging.
b) Unfinished oral dosage form cores before they are coated and before they are packaged.

Bulk hold times for Imodium AD Liquid before packaging have not been established. Exhibit #8 is the current batch record. Hold times were established for holding bulk in the tanker trucks but not for the total hold time before packaging, see page 10.

Unfinished oral dosage form cores can be held up to [redacted] before the compression batch is completed, see observation #1. The firm has not established hold times for any oral dosage form whether it is an in-process material or finished product. b4

At the summation meeting the firm explained that they evaluated all the data and established hold times for Imodium, see exhibit #25. Hold times for oral dosage forms is on-going.

5) Qualifications for the Sugar Charging System are incomplete in that the Qualification Final Report was not prepared as required by the protocol. The Installation and Operational Qualifications were conducted by an outside vendor and signed off on 4/10/98 but were not approved by QA until 2/7/00. This system has been in place since 1987. In addition, there is no justification for the [redacted] cleaning of the Sugar Charging System. b4

"The Sugar Charging System is used to automatically transport the required quanitities of granular sugar from the dispensers to the manufacturing mix tanks from the central Sugar Charging control system.", exhibit #26 explains the system. This equipment is used in the liquids manufacturing area. Page 2 outlines qualification method and documentation required. The second to last paragraph explains that a qualification final report must be written. In addition, it required the installation and operational qualifications to be approved, which only the vendor approved on 4/10/98. QA did not approve the report until 2/7/00, almost two years later, exhibit #26 page 5. And the final report was not written.

Page 3 of exhibit 26 the maximium weight utilized in validation was [redacted] The current practice is to transport up to [redacted] see exhibit #27 section 6.5. Ms. Rademacher informed me that this system is not meant to be an accurate method of the addition of sugar to the batch. The mixing tank load cell is the final weight verification. b4 b4

The firm has no procedures in place for cleaning the sugar charging system. Ms. Rademacher informed me that the system is cleaned [redacted] with micro swabs done after cleaning. I asked her what is the justification for the [redacted] cleaning. She could not answer my question. b4 b4

At the summation meeting the qualifacation final report was completed, see exhibit # 28. The [redacted] cleaning procedure is being evaluated. b4

6) Calibration of the load cells for weighing contents of the mixing tanks are not consistent and written procedures are not specific to calibrate the load cells for the range of use. For example, load cell [redacted] has a capacity of [redacted] and the calibration record of 1/27/00 shows that this load cell was calibrated at [redacted] and [redacted] b4 b4 b4

Calibrations are conducted by outside vendors. Vendors are required to follow McNeil's written procedures. Calibrations for load cells were not specific for weight ranges used. SOP 20-MF-CB-40, "Calibration Procedure Scales", exhibit #29, does not specify how to calibrate the load cells for the mixing tanks. Exhibit #30 and 31 are copies of calibration records load cell [redacted] and [redacted] for the last two years. The calibrations are not consistent for the range of use. b4

At the summation meeting the corrected this observation, see exhibit #32.

7) There is no justification for cleaning the [redacted]. This is a dedicated piece of equipment for transporting gelatin powder into the mixing tank. b4

During my review of the geldipping operations it was explained to me that the [redacted] is used for transporting pre-weighed gelatin powder into the mixing tanks for manufacturing of the gelatin solution used to coat cores. I was told by Ms. Rademacher that the equipment is cleaned [redacted] and swabbed for microbiological contamination after cleaning, exhibit #33. I asked what was the justification for the [redacted] Ms. Rademacher could not answer my question. She also stated that it is not advisable to introduce water into the system and that gelatin powder does not support micro growth. b4 b4 b4

At the summation meeting the firm promised to evaluate the cleaning schedule as soon as possible.

8) SOP 20-MF-CB-71, "Calibration Procedures Revolutions Per Minute (RPM) Readings is not being followed in that calibration specifications for calibrating mixers are not printed on the calibration work order. In addition, fixed speed mixers are not being calibrated.

Specifications for main mixer RPM are hand written on the calibration sheets at the time of the calibration and they are not specified in the SOP (exhibit #34) or on the calibration sheets, exhibit #35. The SOP states that tolerances are to be printed on the calibration work order, section 5.5. In addition, fixed speed mixer are not being calibrated.

At the summation meeting the firm corrected this observation, see exhibits #36 and 37.

9) There is no audit trail or documentation for when and who changed the Fluid Bed Dryers preventive maintenance procedures in the [redacted] Computer System. This system monitors, schedules, and maintains all maintenance records for manufacturing equipment. b4

During my review of the maintenance records for the fluid bed dryer, [redacted] observed that the preventive maintenance procedure changed 1/11/00 with an additional step to be b4

performed. All preventive maintenance procedures are maintained in the [redacted] Computer System. I reviewed the change control and training records for this change. I asked when and who changed the procedure in the computer. I was told the mechanic changed the procedure but later was told the system administrator. I replied by asking to see the audit trail. According to [redacted], there are no audit trails for this system. In July 1999, the firm identified this system as not having audit trail capabilities.

At the summation meeting the firm promised corrections by either upgrading the system or replacing it.

10) The approved Qualification Protocol for qualifying the new and upgraded [redacted] compression machines is missing.

The new compression area currently has [redacted] rooms operational. I reviewed the qualifications for [redacted] three pieces of equipment. All are [redacted] compression machine [redacted] is new. Compression machines [redacted] and [redacted] were upgraded to be equivalent to [redacted] The upgrades included new software, increasing the height of the mezzanine that holds the granulation bins and the angle of the shoots were decreased, which is referred as the Tote System Bulk Transfer Discharge Station. Only machine [redacted] had IQ/OQ/PQ. Each of the others had IQ/OQ. Mr. Liddy stated that they used a matrix approach to validating this equipment. I reviewed the qualification protocol plan and associated reports; however, the qualification protocol plan was not signed as approved for use. Mr. Liddy stated they are currently looking for the approved signed report.

I asked Mr. Constable if any manufacturing process was revalidated for using this new equipment. The reply was no and there were no plans to do so. He explained that this equipment was only upgraded and slightly modified, which would not require any revalidation at the product level.

At the summation meeting the qualification protocol plan was re-issued, exhibit #38 and a revised SOP 99-QA-DC-002, "Security Control & Retention of Documents" was rewritten so documents would not be lost again, exhibit #39.

11) The melting point apparatus in the R & D lab, which is used to qualify standards for the QC lab such as Pseudoephedrine HCl, lot [redacted] is not adequate to determine accurate melting points. The lab sets up a beaker with oil in it, on a stirring hot plate with a calibrated thermometer. No USP melting point standards are run and the heat is not adequately controlled. The USP states that a controlled heat source be used to raise the heat by 1 to 2 degrees per minute when the temperature is near the melting point.

M. Gurbarg wrote this section.

I asked Carmella Walter if there was a melting point apparatus. She said that they don't have one in the R & D lab, but they put one together. They use the USP description with an oil bath and a calibrated thermometer. I found that raw materials that are used in McNeil products and have melting ranges in their monographs, are qualified using this technique.

On my last day of inspection, Carmella said she was ordering a [redacted] melting point apparatus for R & D. At the closeout meeting, David Rogers said that they are purchasing a new [redacted] Melting Point Apparatus with a printer. They will change their SOP and do training in the raw materials group. Now they are using the apparatus in the QC lab. b4 b4

12) No wavelength calibration is being performed on the HPLCs in the R & D lab. [redacted] does not include wavelength calibration in it's [redacted] preventive maintenance check and McNeil only performs internal diagnostics, linearity and reproducibility, which is done at only one wavelength. SOP # 99-RD-IN-006 dated 7/20/99 does prescribe wavelength calibration. HPLCs are used for method development of almost every product including, Motrin Oral Suspension, Motrin Drops, Children's Motrin Suspension, etc. b4 b4

M. Gurbarg wrote this section.

In investigating the lab instrumentation, Yvonne and I found that no wavelength calibration is being performed. I asked if the PM checks included them. I reviewed [redacted] alibration documents and there was no clear description of the tests that are performed. I spoke to [redacted] and he said that the wavelength test looks at one line at 656.4 nm., which is the literature line for deuterium lamps. No testing is done in the UV range. The contract between [redacted] and McNeil is mostly verbal and then checklists and service reports are given to McNeil. I reviewed the maintenance logs and the calibration notebooks, which did not contain wavelength calibration. b4 b4 b4 b4

(Exhibit 2A-L and 3A-C)
David Rogers said that they would develop a method for wavelength calibration in the near future. He took my suggestion to use euracil as the calibration standard. At the closeout meeting, David Rogers said that [redacted] would do a wavelength calibration as part of their performance verification using [redacted] b4 b4

13) Calibration for the IR spectrophotometer is not being performed adequately. The specifications for the calibration of the [redacted] Fourier Transform Infrared Spectrophotometer in the R & D lab, are too wide. SOP # 99-QA-IPAP-020 dated 3/24/1993 states that at [redacted] the tolerance is [redacted] the tolerance is [redacted], and at [redacted] the tolerance is [redacted] The accuracy for the entire range of these instruments is [redacted] The IR is used for identification test of new products and raw material standards. b4 b4 b4 b4 b4

M. Gurbarg wrote this section.

When we looked at the calibrations of the FTIR, we discovered that the specifications for wavelength accuracy in SOP# 99-QA-IPAP-020 were too wide. The instrument collects spectra at [redacted] b4

(Exhibit 4A-4C)
David Rogers said they are going to change the specs to a more narrow accuracy limit due to the fact that they will have to meet the Japanese Pharmacopoeia specs, which are tighter than the US specs.

At the closeout meeting David Rogers handed me a copy of the new SOP which includes tighter specifications for calibration.

Discussion items:

M. Gurbarg wrote this section.

Method and specifications for impurities:

NDA 19-899 for Motrin IB Sinus Caplets has no method or specifications for impurities. During the inspection Paula Oliver told me that they are working on a method for impurities and it will be submitted as an NDA supplement.

Dissolution methods for suspensions:

Sample volumes of suspensions are not accurate for dissolution. The dissolution methods for suspensions introduce the samples into the dissolution vessels with a 5 cc. syringe. More accuracy is required; i.e. syringes are not volumetric. I suggested that the weight of the syringe plus sample be measured and after introducing the sample the empty syringe should be used as the tare weight as per USP 24, pg. 855.

David Rogers said they would use weights of the syringe and sample in the future.

Identification test for Pseudoephedrine:

The infrared spectrum of Pseudoephedrine HCl was too noisy and some of the drug peaks were not well resolved. Spectral noise was present at [redacted] and [redacted] probably due to moisture, which obliterated some of the small drug peaks. I suggested that more than one dosage unit weight be used so that more Pseudoephedrine could be extracted and hence a more concentrated spectrum. b4 b4
The R & D lab worked on improving the method during the inspection. David Rogers showed me the results of changing the amount of sample and the amount of base needed to extract the sample. The spectra showed more of the drug peaks and had less moisture.

UV absorbance Readings:

The UV absorbances taken for Salicylic Acid Tablets for dissolution calibration determinations were sometimes less than [redacted] and sometimes more than [redacted] I suggested that a different size flow cell for the autosampler be used to yield absorbances of between [redacted] and [redacted] a more ideal range for good linearity. b4 b4

Chromatography problems in dissolution test:

Problems occurred in the chromatography in Method MS-300; Children's Motrin Suspension Drops for dissolution test. Investigations showed that washing the column with [redacted] would remedy these problems. I suggested that there should be a "wash" step in the method. b4

Samples Collected:

Sample number 55004 was collected in response to CP 7346.832 to collect a pre-approval profile sample for NDA 21-128: Children's Motrin® Cold Suspension.

Complaints:

Several complaints were covered during this inspection: (FDA) DET-0991, PHI-9-0635, NWJ9-1161, SAN-4217, NEW-1923; (McNeil) [redacted] b4 b4

All complaints are handled at this facility and then given to the respective site for investigation. After the investigation the complaint is returned to this facility for further processing.

NWJ9-1161: was never received by McNeil even though the letter cc FDA was to McNeil.

PHI-9-0635: McNeil claims they only got a copy of the empty blister pack and not the original as the letter stated. This batch was manufactured in Puerto Rico and an investigation could not be conducted without the package.

NEW-1923: a complaint for Nictrol, which is manufactured by [redacted] b4
McNeil only distributes this product. This should be forwarded back to NWJ-DO to follow up b4
at [redacted]

SAN-4217: There were 26 complaints for Lactaid lot [redacted] however, all complaints were b4
received just before the product expired 6/99. According to McNeil it appeared that the product was exposed to excessive heat. Since the product expired the investigation was closed.

Distribution:

Exhibit #40 is a description of McNeil's distribution network.

Training:

I randomly selected three employees training records for review. All records contained GMP training documentation but no training records for SOPs. Ms. Boyle showed me a department meeting agenda where SOP training was done. I recommended that records be kept for SOP training. The firm promised to document individual SOP training.

M. Gurbarg and Y. Wood wrote this section

We checked employee records for training in analytical techniques, in SOPs and in GMPs. Training is performed by senior chemist, team leaders, vendors, and outside seminars and courses. There is a
J & J Certification Program Group, which performs a two-week training course on laboratory GMPs. Analysts are trained in the particular techniques that they are to perform. As they expand to different methods and techniques, they are trained in that technique before they run samples. A new employee gets training for about six months before he/she handles actual samples. All the training samples are documented in an employee folder with the actual

chromatograms from the analysis. We reviewed three analysts' records from the QC labs. We asked if there were tests to find out how much a trainee had learned. Richard Fontana said that there are no formal tests. The trainer (team leader) asks questions and sees how they are performing the techniques. If he considers the answers inadequate, then more training takes place. Corrective actions from OOS results are in the employee's folder. We also looked at the records for two R & D employees.

Recall:

The firm explained that if there was a recall with a product that used the balance flow manufacturing process, all product would be recalled. Since each distribution batch can be related from commingling cores all product on the market would most likely be recalled, see exhibit #14. In addition, during an investigation to determine the cause of a problem, the firm could not trace back to the specific manufacturing batch or lot of drug substance.

Attachments:

1) Pre-approval assignment FACTS 83046
2) Assignment 980165
3) FDA-482
4) FDA-483

Exhibits:

1) Facilities overview
2) Oral dosage form equipment list
3) Liquid equipment list
4) IB suspension drops chronology
5) Imodium Liquid manufacturing directions comparison
6) NDA 19-487 page 34
7) Imodium AD Liquid Process Validation Report
8) Current Imodium batch record
9) NDA 19-487 manufacturing directions
10) Shipping records dated 1/7/2000
11) 483 close out sign up sheet
12) Products incorporating balance flow
13) SOP 20-MF-GP-07
14) Batch Flow Diagram
15) Actual balance flow
16) Process Validation ANDA 73-019
17) Firm's explanation of particle size failures
18) NDA and ANDA consolidation
19) In-processing testing
19a) ANDA 73-019 page 426

20) Summary Report
21) Batch record [redacted] b4
22) Batch record [redacted] b4
23) Change control/corrective action
24) Batch record [redacted] b4
24a) Outline for a Manufacturing Process Validation Protocol and Report
25) Hold times for Imodium AD corrective action.
26) Sugar Charging System Qualifications
27) SOP 20-MF-LM-43
28) Qualification Final Report Sugar Charging System
29) Calibration records
30) calibration records
31) SOP 20-MF-CB-40
32) Corrective action
33) SOP 20-MF-GC-11
34) SOP 20-MF-CB-71
35) Calibration records
36) Corrective action
37) Corrective action
38) Qualification re-issue
39) SOP 99-AW-DC-002
40) Distribution Network

MG - 1A to 1B, Melting Point results and notebook pg.70
MG – 2A to 2L, HPLC calibration logs
MG – 3A to 3B, [redacted] b4
MG – 3C to 3D, Checklist for HPLC detectors
MG – 4A to 4C, FTIR calibration SOP 99-QA-IPAP-020

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