SUMMARY(MAF)

Routine inspection of this Over the Counter (OTC) drug manufacturer was part of the FY09 workplans. This firm continues to contract manufacture OTC drugs, medical devices and cosmetic products. They also distribute these same products under their brand name "TRIAD". Compliance Program 7356.002 was used as guidance for this inspection. The Quality, Laboratory, Facilities and Equipment, Production and Materials systems were covered.

The previous inspection of this firm was conducted 8/2-3/06 at the Pewaukee, WI location which is no longer used. That inspection did not result in the issuance of a FD 483, two verbal observations were discussed with management. The previous inspection of this firm at their Mukwonago, WI location which is no longer used, was conducted on 11/7-9/2006 and was classified VAI. The firm was issued a one item FD 483 for failure to adequately address potential contamination in Raw Material used to manufacture OTC drug product. Management promised to correct observations.

This inspection resulted in the issuance of a 21 item FD 483. These observations were regarding cGMP deficiencies with respect to the manufacture of OTC drug products. The observations include: the responsibilities of the QC unit are not in writing and fully followed, GMP training is not conducted with sufficient frequency, investigations of a failure of a batch did not extend to other batches of the same type of product, reprocessing was performed without the approval of the QC unit, rejected in-process materials are not identified and controlled to prevent their use in manufacturing, drug products failing to meet specifications are not rejected, deviations from written specifications are not justified, lack of supplier qualification, procedures describing the warehousing of drug products are not followed and other observations as discussed in this report. Management did not propose corrective action, but stated a written response will be sent to the Minneapolis District Office.

Two documentary samples were collected, DOC380715 Hemorrhoid suppositories with Phenylephrine and DOC380716 Glycerin suppositories for infants and adults. These samples were collected to document interstate movement of the finished product and cGMP deficiencies. The affidavit attached to the collection reports was read, agreed to and signed by Mr. Eric C. Haertle, Chief Operating Officer.

ADMINISTRATIVE DATA

Inspected firm:	H & P Industries, Inc. dba Triad Group
Location:	700 West North Shore Drive Hartland, WI 53029
Phone:	262-538-2900
Mailing address:	700 West North Shore Drive Hartland, WI 53029

Dates of inspection:	7/15/2009, 7/16/2009, 7/17/2009
Days in the facility:	3
Participants:	Marie A Fadden, Consumer Safety Officer Joel D. Hustedt, Consumer Safety Officer Sandra A. Hughes, Consumer Safety Officer

HISTORY(MAF)

This firm had previously utilized two manufacturing sites and two warehouses. Approximately one year ago all operations were consolidated into the current facility. This facility was custom built for this firm and consists of square feet. The facility is controlled access with employees using access cards to enter the facility. The access cards are programmed to allow the employees access to specific areas depending upon their position. There are approximately full time employees working . shift produces about % of the products with the shifts producing the remaining product.

This firm manufactures several different types of products including creams, ointments, suppositories, liquids, wipes, swabs, sachets, tubes and pads. The products are manufactured under contract for companies with brands such as (b) (4) their own brand TRIAD and many other brands. A list of the products manufactured and the last date of sale is attached as **Exhibit #MAF01**. The products are distributed throughout the United States as well as being exported to different countries. Promotional materials for the TRIAD brand products are included as **Exhibit #MAF02**.

INTERSTATE COMMERCE(MAF)

Two documentary samples were collected to document the interstate movement of the Hemorrhoid suppositories with Phenylephrine (DOC380715) and Glycerin suppositories for infants and adults (DOC380716). These samples are attached to this report.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED(MAF)

Upon arrival at the firm we were greeted by Messrs. Mike McIntosh, Engineering Manager and John Waterman, Regulatory Manager and Ms. Claudia Jackson, Quality Assurance Manager, Complaints. They stated that the firm continues to be owned and operated by three siblings, Mr. David Haertle, President and CEO, Mr. Eric C. Haertle, COO and Ms. Donna Petroff, CFO. These are the three officers of the corporation (b) (4) . Messrs. David and Eric Haertle oversee all areas of the country, Ms. Petroff is generally more responsible for the finance group. Mr. David Haertle (b) (6) was not present during our inspection. The FD 482 Notice of Inspection and credentials were presented to Mr. Eric C. Haertle, COO. Note the FD 482 did not include "Inc." in the firm's name. This was inadvertently left out,

the name as it appears in this report is correct. An organizational chart showing the reporting structure is attached as **Exhibit #MAF03**.

Ms. Jackson and Messrs. McIntosh and Waterman were present throughout this inspection. Questions were also answered by the following:

Jacquelynn Karau, Laboratory Manager
Validation Engineer
Quality Control

FIRM'S TRAINING PROGRAM (JDH)

I reviewed the firm's form Work Instruction entitled "Training Guidelines" (WI-TRN-0007), effective date 6/03/09 **Exhibit# JDH01**. This document outlines the overall responsibilities of the Human Resources Manager, Department Managers, Senior Management, IT Department, and employees in the execution of training activities. Section 3.9.1 of this document states that
"

." Current Good Manufacturing Practices (cGMP) training is included on the firm's New Employee *Non-Management* Training Form (TRN-0007-3) and the New Employee *Management* Training Form (TRN-0007-4). These forms are included as part of **Exhibit# JDH01.**

I discussed the firm's cGMP training with Claudia Jackson. Ms. Jackson said that the firm has a working policy of providing cGMP training every 12 to 18 months. There is no written policy regarding the frequency of cGMP training at the firm. Ms. Jackson provided an outline showing the organization of the firm's cGMP training program **Exhibit# JDH02.** The program is divided into five levels. The level of training employees are provided is dependent on their particular job function. Each training level builds upon the previous levels, for example, level III training includes all level I and level II information. Multiple choice tests are administered to assess understanding of the trainings. The trainings are provided as PowerPoint presentations. Ms. Jackson provided examples of the presentations for Level 2 Training **Exhibit# JDH03** and Level 3 Training **Exhibit# JDH04**.

Ms. Jackson explained that new employees are provided cGMP training in groups. Ms. Jackson contacts Human Resources to let them know which employees need cGMP training based on information obtained from the firm's document control system. It was noted that there are several new employees in Quality Assurance and Quality Control. Seven out of the new employees in these areas received cGMP training 30 – 120 days after starting, refer to the list of Quality Assurance and Quality Control new hires within the past two years attached as **Exhibit #MAF11**.

I requested the training records for three employees. One of these employees was a Quality Inspector (level III) and two were Machine Operators (level II). An example of the cGMP Training – Level 3 Examination for an employee is included as **Exhibit# JDH05.** This examination was dated 7/11/08 which was over 12 months from the dates of the current inspection. A copy of this employee's (initials Personal Training Record Summary, demonstrating the training on, and understanding of various job functions is included as **Exhibit# JDH06.** A two-sided document with a QC Department Memorandum dated 6/9/2008 and a General Training Record (Spec No.:01-027) from this employee's file is included as **Exhibit# JDH07**. The memorandum, which was directed to QC Staff, describes the responsibility and authority of QC to request immediate corrective actions if production lines are found to be producing materials that are out of specification. Further, the memo states that if QCs have difficulty receiving cooperation from machine operators or other personnel; they shall immediately report such incidents to the Production Team Leader.

MANUFACTURING OPERATIONS

The firm consolidated its manufacturing operations approximately two years ago at the current facility located in Hartland, Wisconsin. A general floor plan is included as **Exhibit# JDH08.** The firm previously maintained two production facilities; one located in Pewaukee, WI and another in Mukwonago, WI. The firm's manufacturing operations are divided by category and are identified by colors:

Swabs = (b) (4)
Small pads = (b) (4)
Large wipes = (b) (4)
Bottles = (b) (4)
Cream/Ointment/Suppositories = (b) (4)

This company manufactures several different types of products on several different lines including: Glycerin suppositories in the Glycerin suppository room (labeled "Suppository Blending" on the facility diagram), Hemorrhoid Suppositories with Phenylephrine and other suppositories which are blended in their own blending area and filled on one of suppository filling lines, Ointments and creams (labeled "Ointment Blending" on the facility diagram), these products are filled on a tube filling line, lubricant jelly's and other lotion products (labeled "Lube Jelly & Lotion Blending" on the facility diagram), filled on either the tube or bottle filling line, Iodine and alcohol based antiseptic products packaged in sachets, separate liquid and flammable blending areas, wipes and pads filling lines, powder blending and packaging, and swab packaging. During our tour of the facility we observed the warehouse, raw material and label storage, Glycerin suppository blending and molding area, Hemorrhoid suppository blending and filling area, the ointment blending area, and raw material weigh area. (b) (5) .

While on the tour of the facility we observed the raw material receiving, raw material staging and raw material reject areas. Raw materials, containers and labels are staged outside of the manufacturing and packaging suites that will be using them. The storage of OTC drug labels in this area for a time period of up to two days was noted on the FD 483 as observation #21. During the two days they are stored in this area, the labels are out in the open and not under strict control.

It was also noted that finished product that is on hold or rejected for various reasons are kept in this area next to staged product. The finished products we observed were not all clearly identified as to their current status. The procedure "General Rejection Procedure" #WI-QC-0094 effective 5/6/09, attached as **Exhibit #MAF04**, covers reject storage areas. Section 3.2.7.3 references "

." The rejected storage area is not designated as such with signage or spatial separation or some other means. Management was able to provide documentation as to the status of the product, however the status of the product is not always clear to the operators working in that area. This was cited on the FD 483 as observation #9.

Water System(JDH)

The firm utilizes a purified water system which was designed and is remotely monitored by The system contains (b) (4) . A system schematic is included as **Exhibit# JDH09.** The pipes from the water processing area to the production area are . The water is heated for some types of product and for sanitizing to °F.

Qualification/Validation(JDH)

On 07/15/2009, I requested documents related to the qualification of equipment used in the manufacture of suppositories at the firm following the move to the Hartland facility. Mr. provided copies of the firm's Installation/Operational Qualification Protocol for the Glycerin Suppository Molding Press Machine **Exhibit# JDH10** and the Installation/Operational Qualification Protocol for the (b) (4) Scale Automatic Weighing Machine (S/N: for the glycerin suppository line **Exhibit# JDH11.** These IQ/OQ protocols have not been approved or implemented since this equipment was moved to the Hartland facility, refer to FD 483 observation #14. This equipment is used in the manufacture of adult and infant glycerin suppositories. The manufacture and packaging of adult glycerin suppositories was observed during the inspection.

Mr (b) (6) also provided a copy of the Validation Master Plan, issue date 06/24/2009, that was recently completed **Exhibit# JDH12**. At the time of the current inspection, Mr. said he has been employed at the firm for approximately (b) (6) . Mr. said he plans to update the firm's Validation Master Plan and address any outstanding IQ/OQ studies for production equipment that have not been completed since the move to the Hartland facility. Mr. provided a copy of a spreadsheet showing the equipment for which IQ/OQ has been completed **Exhibit# JDH13**. Mr. (b) (6) explained that all equipment with "Hartland" identified in the "Facility" column has an approved IQ/OQ. Equipment with either "Mukwonago" or "Cheaney" in

the "Facility" column does not have a completed IQ/OQ at the Hartland facility. Mr. said this spreadsheet does not encompass all of the equipment or processes in the firm nor does it encompass all pending IQ/OQ studies at the firm.

Mr. also provided copies of the Installation Qualification document **Exhibit# JDH14** and the Operational Qualification document **Exhibit# JDH15** for the Machine used in the production of starch and cocoa butter hemorrhoidal suppositories. The IQ/OQ for this equipment was completed and approved in June of 2008.

This firm was not able to provide any process validation for the OTC drug products currently manufactured, refer to FD 483 observation #19. This firm has manufactured OTC drug products for several years. . Refer to the Master Validation Plan attached as **Exhibit# JDH12** for more information.

Production(MAF)

The first production area that we observed was the suppository blending area. This area contains mixing tanks (50 and 51). Tank 50 is used for . We observed Starch Hemorrhoid suppositories, #9G115B in tank 51. The product was being filled on the (b) (4) suppository filling line which is (b) (4) the operator takes an amount out of the mixing vessel using a plastic five gallon pail and carries it to the hopper on the filling line. There is no record of the plastic bucket being cleaned between uses. The use of the five gallon bucket in direct product contact with no cleaning documentation was listed on the FD 483 as observation #10a. In addition, we observed a metal spatula used by the operator to scrape the side of the mixing vessel resting on the metal steps that the operator uses to reach into the mixing vessel. The scraper had product residue on it and it had obviously been used in the product. This was listed on the FD 483 as observation #11a. When questioned about the spatula, the operator stated that she would clean it and brought it to the sink.

In this same area we observed that tank #50 had a green "Ready for Use" sign hanging on it. The sign is in a clip with several other signs of different colors. When I looked into the mixing vessel product was present in it and being mixed. I asked what was in the mixing vessel and was told that (b) (4) phase of production for the next product was starting. I asked to see the batch record. The operator left the area to retrieve the batch record for hemorrhoidal Suppository with Phenylepherine, lot #9G123B. The batch record as it was shown to me is attached as **Exhibit #MAF05**. Several sections of the batch record had not yet been completed including (b) (4) section titled "Equipment" had not been completed. This section also includes recording cleaning and batch information in the "Tank Cleaning and Sanitization Log". The "Tank Cleaning and Sanitization Log" for tanks 50 and 51 were observed, the last entry in both logs was dated 7/2/09, the last page from both logs is attached as **Exhibit #MAF06**. Note that the

logs are not identified as to which is tank 50 or 51, however both logbooks are missing entries because there was product in both tanks on 7/15/09. Management also stated that the suppository line is used per week indicating that the equipment had been used many times since 7/2/09 with no entry in the "Tank Cleaning and Sanitization Log". This was cited on the FD 483 as observation numbers 12a, 12b and 18a.

The second production area that we observed is the creams. and ointments mixing area. This area has mixing vessels, one was observed to be out of service. Tank #40 was observed to have a "Ready for Use" sign attached to it. The product Hemorrhoid Cream, lot #9G109B was observed mixing in it. The "Tank Cleaning and Sanitization Log" for tank #40 did not have any entries after 6/29/09, first and last page attached as **Exhibit #MAF07**. Tank #41 was observed to have lot #9G110B mixing in it. The "Tank Cleaning and Sanitization Log" for tank #41 had the following entry "7/15/09 Hem Oint Batch No 9G109B #...", first and last page of log is attached as **Exhibit #MAF08**. This was cited on the FD 483 as observation numbers 12c, 12d, 12e and 18b.

When I asked the operator about the "Ready for Use" signs on the tanks he stated that they had just been put up recently. The signs referenced a work instruction (aka procedure) #WI-PM-0090 that has an effective date of 7/14/08. The operator's unfamiliarity with the signs and how to use them indicated to me that cGMP training is not current nor is training in the procedures current. More discussion on cGMP training is in the cGMP Training section of this report. In addition, insufficient cGMP training frequency was cited on the FD 483 as observation #2.

Infant and Adult Glycerin Suppository Manufacturing(JDH)

On the morning of 07/16/2009, I observed the manufacture and packaging of glycerin suppositories. Later that day, Investigator Fadden also observed the production process. Batch# 9G128B, formula # 04-144 was in process when I first entered the production area. The production area consists of (b) (4)

(b) (4) . Molds that were filled at the time of the inspection were not sufficiently cleaned and were observed to have product from previous batches remaining in the molds when filled with new suppository solution refer to the photograph attached as **Exhibit# JDH16**. A production employee said that molds are cleaned (b) (4) using hot water degrees F) and are then wiped down with isopropyl alcohol.

Following filling, the molds are wheeled near large metal fans which according to management, are used to facilitate cooling of the suppository solution in the molds. When I first entered the

production area, the fans were in use, but were not used to cool product at the time. The fans were turned off shortly thereafter. These fans had accumulations of dust and debris on them, refer to the photograph attached as **Exhibit# JDH17.** This was noted on the FD 843 as observation #11b.

When sufficiently cooled, the molds are placed in the glycerin suppository molding press machine blade made of
The blade on the press machine was worn and chipped, refer to the photograph of the blade attached as **Exhibit# JDH18**.
storage area, photograph attached as **Exhibit# JDH19.** The bins are located in a corner of the room near the entrance and are held until . There were

Some of the bins of material were covered with plastic, while others were uncovered or had holes in the bags. may be left in this area for several weeks as

, batch record for this formula attached as **Exhibit #MAF14**. There is no microbiological testing performed on this product prior to re-processing, refer to FD 483 observation #20b. It was later determined by Investigator Fadden that the reprocessing of testing, but without the approval of the QC unit, refer to FD 483 observation #4.

Investigator Fadden questioned some of the production employees on how they handle material. One employee was visibly confused regarding the proper disposition of and was seen holding the (b) (4) against his shirt and handling a portable metal staircase with his gloved hand and subsequently touching (b) (4) with the same gloved hand. Production employees normally would place (b) (4) . Following this observation, the (b) (4) were placed in white plastic carts, refer to the photograph attached as **Exhibit# JDH20.** This was listed on the FD 483 as observation #20a.

(b) (4) . Several of the rods were observed to be chipped, cracked, or missing, refer to the photograph attached as **Exhibit# JDH21**. This was listed on the FD 483 as observation #10. There is no visual inspection procedure for blade or (b) (4) ejector rods. Mr. McIntosh said the blades are changed based on functionality and are considered a wear item. There is no system in place to prevent or identify plastic fragments from the (b) (4) blade or the (b) (4) rods in the finished suppositories or for reprocessing.

At one point during production, it appeared that the plate with the ejector rods was not in alignment with the mold. I observed a production employee repeatedly engaging the ejector plate via its push-button controls, which caused the (b) (4) rods of the plate to repeatedly impact the mold.

but few suppositories were ejected. This continued until Mr. McIntosh instructed the employee to stop.

When I first entered the production area and observed the press machine, production had just begun for the day and the press machine had not yet been used. A production employee said that the press machine is cleaned after each batch, however, I observed accumulations of glycerin on the rods. Cleaning of the equipment commenced following this observation. There is no specific written procedure for cleaning and sanitizing of the glycerin suppository press machine. Mr. McIntosh said that cleaning of equipment is covered under Work Instruction WI-PM-0056, Cleaning and Sanitizing Batching Equipment, Tanks and Totes, effective 4/6/09 **Exhibit# JDH22**.

The glycerin suppository production area is part of the Team's work area. The firm's Team Daily/Weekly Housekeeping Checklist, Form No. FM-MTL-0015, was completed and posted in the main room. The Quality Inspector for the room said she is responsible for completing the document and covering the main yellow room as well as the glycerin production area. An example of the Team Daily/Weekly Housekeeping Checklist is included as **Exhibit# JDH23**.

The suppositories are ejected from the molds into a plastic ejector bin. This bin contained clear tape and what appeared to be heavy paper or cardboard, photograph of the bin with tape and heavy paper or cardboard attached as **Exhibit# JDH24.** Refer to FD 483 observation #10. From the ejector bin, the suppositories are dumped through a plastic hopper filler that contained protruding screws, scratches, and crevices between the plastic components, photograph attached as **Exhibit# JDH 25.** Refer to FD 483 observation #10. The suppositories are stored in plastic tubs until packaging on the (b) (4) Scale Automatic Weighing Machine.

In a corner of the room stacked behind some plastic bins, I observed lbs. of glycerin from batch 9C150B that had a (b) (4) QA acceptance placard with a date of 4/6/09. Mr. Waterman said that this product was rejected based on (b) (4) refer to FD 483 observation #5.

A photograph showing the overall layout of the glycerin suppository production area is included as **Exhibit# JDH26**. A CD-R containing the photos taken by Investigator Hustedt is included as **Exhibit# JDH27**.

Products labeled as sterile (MAF)

This firm distributes alcohol prep pads, lubricating jelly in sachets, bottles and tubes that are labeled as sterile. These products are medical devices. Other products that undergo sterilization include oral relief swabsticks and makeup remover. The alcohol prep pads, lubricating jelly sachets, bottles and tubes are manufactured on a regular basis. The product is manufactured and packaged using the

same equipment that is used for non-sterile processes. The firm does not use aseptic processes for the manufacture of these products. The products are packaged into their final packaging configuration, cased and shipped to sterilization. I asked to see the documentation showing that the product is actually sterile upon return from The firm was unable to provide documentation that the lubricating jelly in the 4 oz bottles and 2 oz and 4 oz tubes is in fact sterile. In 2009 batches of lubricating jelly in the tubes and bottles packaging configuration have been distributed. These products are distributed under several brand names including: TRIAD, . Labels for the 4 oz lubricating jelly products are attached as **Exhibit #MAF09**.

This firm does perform sterility testing on the products. This is done by in 2009 has been completed so far, no growth was detected in those samples. In 2008 samples were sent in . No growth was detected in those samples. I explained that the presence of a few samples in a batch that pass sterility testing does not indicate that the entire batch of product is sterile.

During this inspection, the firm was not able to produce any documentation that the bottles and tubes of lubricating jelly are in fact sterile. This is an area that should be covered in depth during the next inspection.

Quality System – (SAH)

A review of the firm's deviation log since the last inspection revealed numerous deviations related to the Phenylephrine HCl Assay tested in the release of Hemorrhoidal Suppositories. A summary of the deviations reviewed are located in Table 1.

Table 1

Date	Deviation End Date	Deviation Number	Batch/Lot	Deviated specification for % Phenylepherine (original)	Cases Affected	OOS Number
09/09/08	open	P0908.003	8H234B/8H234			OOS-08-132
10/08/08	10/14/08	P1008.001	8K100B/8K100			
10/08/08	10/15/08	P1008.002	8K151B/8K151*			
10/15/08	open	P1008.007	8K101B/8K101			OOS-08-134
11/24/08	11/26/08	P1108.021	8L162B/8L200			OOS-08-144
12/06/08	12/06/08	P1208.004	8M101B/8M101			OOS-08-146
12/18/08	na	P1208.009	8M161B/8M161			OOS-08-151
12/30/09	01/02/09	H0109.003	8M204B/8M204*			OOS-09-002
02/02/08	02/02/09	H0109.020	8M186B/8M186			OOS-09-004
02/04/08	02/04/09	H0209.003	8M186B/8M186			OOS-09-011

Date	Deviation End Date	Deviation Number	Batch/Lot	Deviated specification for % Phenylepherine (original)	Cases Affected	OOS Number
03/05/09	03/05/09	H0309.008	6B44/0206129P*			OOS-09-015
04/17/09	04/17/09	H0509.002	7D04/030794			OOS-09-041
04/17/09	04/17/09	H0509.005	6D12/04061P		s	OOS-09-044

*Hemorrhoidal cream

Several issues were noted in the deviations reviewed.

1. The firm lists the Phenylephrine HCl on their labeling for Hemorrhoidal Suppositories at 0.25%, see **Exhibit #SAH01**. The final monograph for Phenylephrine Hydrochloride suppositories at 0.25% for Hemorrhoidal Suppositories. The deviations in Table 1 changed the specification for the percent Phenylephrine HCl from a range of to accepting product with a percent Phenylephrine HCl range from . During this time, the label claim for Phenylephrine HCl did not change. This was cited on the FD 483 as observation #6.
2. The deviation SOP 01-019 - Internal and External Deviations, effective 01/31/07, states in section 4.3, "(b) (4) [redacted]", see **Exhibit #SAH02**. OOS reports were not initiated for two of the deviations reviewed (P1008.001, P1008.002) even though (b) (4) cases of product were accepted outside of the specification. This was cited on the FD 483 as observation 7a.
3. OOS-08-132 issued 9/9/08 in response to deviation P0908.003 listed a possible root cause for the low assay for Phenylephrine HCl as "(b) (4) [redacted]" see **Exhibit #SAH03**. Twelve (12) similar deviations were written to accept product which did not meet the percent Phenylephrine HCl specification in the following 8 month time period. During this time no investigation or CAPA was initiated to determine a corrective action.
4. Nine out of eleven OOS reports reviewed above did not have the required Director of QA/QC/RA and Technical Services signature required per SOP WI-LAB-0040 – Laboratory Out Of Specification (OOS) Investigations (effective date 6/17/09), see **Exhibit #SAH04**. When this oversight was brought to the attention of Ms. Karau she stated that those reports should have been signed, but she was not at this company at that time. Mr. Waterman also stated that this position was vacant during that time period. Although many of the duties of this position were being done by committee, this signing of OOS reports was not delegated. This was cited on the FD 483 as observation #7b.

I reviewed the Master Batch Formula and Mixing Instruction for batch 8M186B, see **Exhibit #SAH05**. Ms. Karau stated during the running of this batch the firm decided to test for the percent

Phenylephrine HCl assay (see **Exhibit #SAH06** - OOS-09-004 for results from the f cases). Ms. Karau stated . A deviation was written, see **Exhibit #SAH06** – H0109.020, to accept product within

Another deviation (H0209.003) and out of specification form (OOS-09-011) needed to be filled out to accept product within for the Phenylephrine specification, see **Exhibit #SAH07**. A final out of specification form, OOS-09-009, was initiated at had Phenylephrine results of , see **Exhibit #SAH08**. No deviations were listed in the batch record to pull additional samples for testing of the Phenylephrine assay

. The yield page (page 10 of 13) was never completed for this batch although the batch was tagged acceptable on Jan 6, 2009.

I reviewed the lot history file for batch 8M186B, see **Exhibit #SAH09a** for Lot Approval Report packet. Several issues were noted concerning this documentation:

1. Page 1 - FM-WI-ADM-009-1 Lot Approval Report is incomplete.
   a. marked NA for deviation numbers when deviations are part of the history file.
   b. (b) (4) " is not verified by the QC department.
   c. (b) (4) " is not verified by the QC department.
   d. The form is missing the Release Date and Signature (Day of Lot Closure).
2. Page 2 – (b) (4) for the labeling/packaging material is not calculated. Machine Used, Signature and Date is not filled in.
3. Page 5 – (b) (4) " is not completed.
4. Page 6b – It was noted that the last line in the Warning box of the back photocopy of the carton contained a wrinkle in the text. I asked to review the Receiving paperwork for the (b) (4) Hemorrhoidal Suppositories carton (item Control No. 23689, see **Exhibit #SAH10** to see if this was observed upon receipt. I noticed the following discrepancies to the SOP WI-QC-0002 – Incoming Inspection for Cartons, effective date 06/23/06, see **Exhibit SAH11**.
   a. According to section 3.2.4 of SOP WI-QC-0002, "(b) (4) " On page 2 of the receiving paperwork, the only documentation of inspection is a "Y" under the Pallet 1 column.
   b. Section 3.3.6 states to (b) (4) . Currently only a "Y" is recorded on the specification sheet. This was brought to the attention of Mr. Waterman.

5. Page 7 – A Nonconformance Report is documented for the destruction of case due to failed lab tests. The percent Phenylephrine HCl results for case listed on OOS-09-004 as passing, refer to **Exhibit #SAH06**. Ms. Karau could not explain what lab tests failed for case #5 or why it was destroyed.
6. According to SOP WI-QC-0214 – Quality Control Finished Goods Release – Effective 06/05/08, section 3.3.4 "

" see **Exhibit #SAH12**. None of the Finished Goods Acceptance Forms. contained in the History File have *"Lab Release/Final QC Release"* initialed and dated.
7. The Lot History File contains the Master Batch Formula and Mixing Instruction for the **Exhibit #SAH09b**, as failing Phenylephrine Assay at This sheet fails to reference the deviation H0109.020, refer to **Exhibit #SAH06**, which expanded the specification to The product failed the finished product specification and the expanded specification under deviation H0109.020. Page 2 of this packet, was never reviewed which violated SOP WI-LAB-0139 – Documentation Procedure and Use of Laboratory Notebooks, effective 04/03/09, which states in section 3.3.6 all calculations shall be documented and reviewed, see **Exhibit #SAH13**.
8. The Lot History File contains the Master Batch Formula and Mixing Instruction for the (b) (4) see **Exhibit #SAH09d**, as failing Phenylephrine Assay at (b) (4) and does not reference the OOS-09-009, refer to **Exhibit #SAH08**, which shows the results from cases (b) (4) . This contradicts OOS-09-011, attached as **Exhibit #SAH07**, which states the OOS results Phenylephrine will not be rejected but accepted with deviation H0209.003. However, deviation H0209.003 only changes the specification to (b) (4) A Nonconformance Report for cases (b) (4) was not found. Page 2 of **Exhibit #SAH09d**, was never reviewed which violated SOP WI-LAB-0139 – Documentation Procedure and Use of Laboratory Notebooks, effective 04/03/09, which states in section 3.3.6 all calculations shall be documented and reviewed, see **Exhibit #SAH13**.
9. Picking Slips with documentation of the shipper are attached for Hemorrhoidal Suppositories with Phenylephrine, lot 8M186, for product shipped 02/04/2009, see **Exhibit #SAH14**. According to the picking slips, cases were shipped. **Exhibit SAH09e** of the Lot History File contains the Master Batch Formula and Mixing instruction for (b) (4) Page 1 of this document shows the microbial results being received on February 9, 2009. According to Mr. McIntosh, currently this firm does not have an SOP on releasing a partial shipment of a lot.

After reviewing the OOS logs going back to 8/1/07, I pulled OOS-08-087, see **Exhibit #SAH15**. Note that the last page of this exhibit has an * with a comment added by Mr. Waterman. This comment was added by Mr. Waterman after a copy of this document was requested. OOS-08-087

was picked because it also dealt with the percent Phenylephrine HCl levels in a Hemorrhoidal Ointment. Attached to this OOS was the Non-conformance Report P08041801, see **Exhibit #SAH15**. Much of the documentation associated with this NCR was incomplete. OOS-08-087 stated, "

." When asked to review the deviations associated with these lots (8D120, 8D145), Ms. Karau could not provide any documentation. The failure of the firm to further investigate other Phenylephrine containing products was noted on the FD 483 as observation #3.

Quality Control Laboratory (SAH)

I reviewed the release data associated with lot 8M186, see **Exhibit #SAH09f and 09g**. The results sheet state the percent Phenylephrine Assay was run per WI-LAB-0117 – HPLC Analysis – Phenylephrine HCl Content for Gel, Suppositories, Ointment, effective 5/28/08, see **Exhibit #SAH16**. Upon review of the raw data several discrepancies were noted from the method although no deviation was referenced.

(b) (4)

Ms. Karau acknowledged these changes were significant enough to affect the validation and was able to provide a deviation H0109.018, see **Exhibit #SAH17**. Ms. Karau stated that since this deviation was written January 30, 2009, these changes were executed every time WI-LAB-0117 was run. According to pg 2 of deviation H0109.019, "(b) (4)

9, this validation has yet to take place. When questioned, Ms. Karau stated(b) (4)

see **Exhibit #SAH18**. Although the(b) (4)

(b) (4)

. The firm's failure to establish and document the accuracy, sensitivity, specificity and reproducibility of test methods was cited on the FD 483 as observation #15.

Ms. Karau confirmed that QC data is not always reviewed prior to QC release of a batch.

I toured the Quality Control laboratory with Ms. Karau. It was noted that according to the labeling on one of HPLC system compared to the Usage log, was expired at time of use (WI-LAB-0092 mp, prepared 4/1/09, expired 6/1/09). Ms. Karau showed me the notebook which documents

Ms. Karau could not provide any documentation on the calibration of the HPLC currently being used to release the OTC products. This was cited on the FD 483 as observation #17.

I reviewed WI-LAB-0123 - PM/OQ/PV for the HPLC, effective date 10/02/07, see **Exhibit #SAH19**. I reviewed the deviation P0508.001 associated with this document which states due to t, the HPLC would be used after (b) (4) Ms. Karau stated this was done prior to her working at the firm and that this practice would not be acceptable anymore.

(b) (4) . Although the lab has , it is currently not being used to release product. The laboratory (b) (4) balances although according to the analyst, balances are used regularly. Ms. Karau stated they currently don't use one of their analytical balances due to a (b) (4) This balance was currently tagged as in use and I mentioned it should be tagged out of service to ensure others don't use it until it is fixed. The firm's balances are calibrated internally every (b) (4) and have a (b) (4) verification. The last calibration took place on 04/30/09.

COMPLAINTS(MAF)

The complaint log from the last two years was reviewed. The procedure "Complaint Handling System" #P-QA-0003 effective 4/7/08 covers the handling of customer complaints. The procedure does not include the evaluating and reporting of adverse events to the FDA. I suggested that a procedure be drafted that includes evaluating and reporting complaints to the FDA as well as the reporting timeframe and where to send the reports. Ms. Jackson agreed to include adverse event reporting. The trending and analysis of the complaints for the calendar years 2008 and 2009 were also reviewed. Ms. Jackson is responsible for generating these reports. She trends the complaints by manufacturing line and by type of complaint within a product code. If trends change over time, she generates a CAPA to correct the issue. Nothing remarkable was noted in the complaints and/or the reports.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE(MAF)

A close out meeting was held with the following individuals from the firm: Messrs. Eric Haertle, McIntosh, Waterman, Ms. Jackson, Ms. Karau and Ms. A 21 item FD 483 was given to Mr. Eric C. Haertle with cGMP deficiencies listed. The firm did not have any corrective action to present but stated that a written response will be sent to the Minneapolis District Office with timeframes for corrective action and documentation of the action.

Observations listed on form FDA 483

Quality System

OBSERVATION 1

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

Reference: 21 CFR 211.22(d)

Discussion with Management:
There was quite a bit of discussion during the inspection regarding the firm's final release of product for distribution procedures. Currently the firm has a procedure SOP WI-QC-0214 – Quality Control Finished Goods Release – Effective 06/05/08 for the release of finished goods. This does not include a signature, rather initials and date are placed on the Finished Goods Acceptance Form that is attached to a pallet. There were several OOS investigation that were noted to have not been signed by the Director of QA/QC/RA and Technical Services. There are several OOS investigations related to Hemorrhoid Suppository with Phenylephrine, this did not extend to other products containing Phenylephrine such as the creams and ointments. I asked for the written procedure describing the responsibilities of the Quality Control department. I was provided the DRAFT procedure "Responsibilities of the Quality Department" #P-QA-0007, attached as **Exhibit #MAF10**. Currently there are (b)(4) employees in the Quality Control unit. They are present during shifts supporting production. I requested a list of new employees within the past two years for the Quality Control Unit and the Quality Assurance laboratory, list attached as **Exhibit #MAF11**. There were (b)(4) new employees in these areas during the past 2 years including the Laboratory Manager and the Quality Control Manager. Ms. Jackson is not on the list, but informed me that she has been at the company about 1 ½ years – she is Quality Assurance Manager, Complaints. There was no further comment regarding this observation at the close out.

OBSERVATION 2

GMP training is not conducted with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

Reference: 21 CFR 211.25(a)

Discussion with Management:

Currently there is no written policy regarding the frequency of cGMP training for current employees at the firm. Ms. Jackson stated verbally that cGMP training is provided every 12 -18 months. A timeframe for providing new hires with cGMP training is not specified. It was noted that there are several new employees in Quality Assurance and Quality Control. Seven out of the new employees in these areas received cGMP training 30 – 120 days after starting. During the close out management asked for clarification of this observation. I stated that it appeared from the other observations noted on the FD 483 that the employees were not trained in cGMP's often enough. Management did not have any further comments or questions regarding this observation.

OBSERVATION 3

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product.

Specifically, multiple Out of Specification investigations into Hemrrhoidal Suppositories with Phenylephrine were not extended to other products containing Phenylephrine i.e. Hemrrhoidal Cream and Ointment with Phenylephrine.

Reference: 21 CFR 211.192

Discussion with Management:

As noted in this report, the firm has had several OOS investigations related to the Hemorrhoidal suppositories with Phenylephrine. Those investigations have not extended to the Phenylephrine containing creams and ointments. During this inspection we discovered two OOS investigations related to Phenylephrine Hemorrhoid ointment OOS-08-087) and Hemorrhoid cream OOS-09-057 (b) (4)). There was no further investigation or CAPA initiated related to Phenylephrine containing products. The OOS investigations OOS-08-087 (**Exhibit #SAH15**) and OOS-09-057 (**Exhibit #MAF12**) did not have a conclusion, root cause or corrective action. Management had no response to this observation.

OBSERVATION 4

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

Specifically, the Infant and/or Adult Glycerine Suppositories, formula #04-154, are manufactured using
The quality control unit does not approve the reprocessing of the batches prior to production.

Reference: 21 CFR 211.115(b)

Discussion with Management:
During the manufacture of Glycerin suppositories, both the infant and the adult dosages,

At that point placed in plastic totes and stored in a corner of the Glycerin suppository blending room. On 7/16/09 we observed the following batches: # of 9F172B, # of 9F203B, # of 9G103B, # of 9F204B, an unknown weight of 9F149B and an unidentified batch. According to management had been sitting there for 3 – 4 weeks.

to manufacture a batch of either infant or adult Glycerin suppositories. (b) (4) Some of the product that had been sitting in the room for 3 – 4 weeks was not covered or the plastic covering was torn exposing the product. I asked if microbiological testing was performed on this product, Messrs. Waterman and McIntosh did not know the answer. (b) (4) . The finished product specifications are attached as **Exhibit #MAF13**. This batch is formula #04-154 and is titled "(b) (4) ", issued 8/23/05, master batch record attached as **Exhibit #MAF14**. Each batch of product is listed along with the weight of the batch on the first page of the batch record. I asked Ms. if there was any Quality Control approval prior to (b) (4) in the formula #04-154 batch, she said that she does not need to approve the (b) (4) .

During the close out meeting I explained to management that Quality Control should have final say as to (b) (4) . Management appeared to understand this requirement, but had no comment.

OBSERVATION 5

Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable.

Specifically, Glycerine Suppository lot #9C150B was observed in the Glycerine Suppository room with a "QA Accepted Material" tag on it. The material was in a corner of the room with items around it. The material was dispositioned on 7/16/09 after we observed it stored in the corner.

Reference: 21 CFR 211.110(d)

Discussion with Management:
While in the Glycerin suppository blending room on 7/16/09 Investigator Hustedt observed material in the corner of the room with plastic bins in front of it. Closer examination of the item revealed it was in process Glycerin blend. There was a total of lbs. of in process glycerin from lot #9C150B that had a green QA acceptance placard with a date of 4/6/09. Mr. Waterman said that this product was rejected based on . The rejected material did not have any indication on it as to its status. Mr. Waterman stated that the product was to be discarded, and it should have been identified as such. We were provided the batch record for lot #9C150B, attached as **Exhibit #MAF15**. Page 7 of the batch record shows the "QA Laboratory Batch Analysis", note that the (b) (4) ". It is not clear from this why this material was rejected. We asked Mr. Waterman why the material was rejected if the laboratory analysis stated that (b) (4) , he did not know why the material was ultimately rejected. The last page of this exhibit is the Notice of Destruction for lot #9C150B dated 7/16/09. Management did not have anything more to add during the close out meeting.

OBSERVATION 6

Drug products failing to meet established specifications are not rejected.

Hemrrhoidal Suppository with Phenylepherine has a Phenylephrine specification of %, multiple batches of this product were released outside of the specification range as follows:

Lot number	finished product test results
8K100	(b) (4) %
8K151	(b) (4) %
8L200	(b) (4) %
8M101	(b) (4) %
8M166	(b) (4) %
8M186	(b) (4) %

8H234 %
8K101 %

Reference: 21 CFR 211.165(f)

Discussion with Management:

The firm lists the Phenylephrine HCl on their labeling for Hemorrhoidal Suppositories at 0.25%. The final monograph for Phenylephrine Hydrochloride suppositories specifies 0.25% for Hemorrhoidal Suppositories. Deviations for each of the batch records listed in this observation changed the specification for that specific batch for the percent Phenylephrine HCl from a range of to a range of . During this time, the label claim for Phenylephrine HCl did not change. This specification change accommodated both low and high Phenylephrine HCl assay results. Batches of product that fail to meet established specifications should be rejected. In addition, no investigation or corrective action has been determined to eliminate future OOS results for the Phenylephrine containing products. Management had no comment regarding this observation at the close out meeting.

OBSERVATION 7

Deviations from written specifications are not justified.

a) No Out of Specification investigation was documented for Out of Specification finished product assay for Hemrrhoidal Suppositories with Phenylephrine lots 8K100 and 8K151.

b) The procedure "Laboratory Out of Specification (OOS) Investigations" #WI-LAB-0040 effective 6/17/09 section 3.3.10 requires approval by Quality Unit Managers. Nine out of eleven OOS investigations did not have Director of QA/QC/RA and Technical Services signature. According to the Lab Manager this should have been signed.

Reference: 21 CFR 211.160(a)

Discussion with Management:

7a - The deviation SOP 01-019 - Internal and External Deviations, effective 01/31/07, states in section 4.3, "(b) (4) [redacted] ". OOS reports were not initiated for two of the deviations reviewed (P1008.001, P1008.002) even though (b) (4) cases of product were accepted outside of the established specification for this product.

7b - Nine out of eleven OOS reports reviewed did not have the required Director of QA/QC/RA and Technical Services signature required per SOP WI-LAB-0040 – Laboratory Out Of Specification (OOS) Investigations (effective date 6/17/09). Ms. Karau agreed that the documents should have been signed. She stated she was not at the company when the OOS reports were completed. During the close out meeting Messrs. McIntosh and Waterman both stated that this position was vacant during that time period. Although many of the duties of this position were being done by a committee, this signing of OOS reports was not delegated.

OBSERVATION 8

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Reference: 21 CFR 211.84(d)(2)

Discussion with Management:

No supplier qualification has been done to date. Currently the company has a list of acceptable vendors for each product, but no testing has been done to support the reliability of those vendors. A DRAFT procedure "Supplier Qualification and Management System" #WI-QA-0010 has been written, attached as **Exhibit #MAF16**. According to Ms. Jackson she is in the process of evaluating the raw materials used, current supplier's and the tests that will need to be done. This program is still being put together. This company has been manufacturing OTC drug products for many years with no supplier qualification program in place. There was no comment from management during the close out meeting.

OBSERVATION 9

Procedures describing the warehousing of drug products are not followed.

Specifically, the finished product reject storage area described in the procedure "General Rejection Procedure" #WI-QC-0094 effective 5/06/09 section 3.2.7.3 is not indicated by signs or other designation and is not spacially separated from acceptable material.

Reference: 21 CFR 211.142

Discussion with Management:

It was noted that finished product that is on hold or rejected for various reasons are kept in the area outside of the packaging suites next to staged product. The finished products we observed were not

all clearly identified as to their current status. The procedure "General Rejection Procedure" #WI-QC-0094 effective 5/6/09 covers reject storage areas. Section 3.2.7.3 references "

." The rejected storage area is not designated as such with signage or spatial separation or some other means. Management was able to provide documentation as to the status of the product, however the status of the product is not always clear to the operators working in that area. Management asked for clarification of this observation. I stated that if they use the staging area for rejected materials it should be clearly identified as reject and should have a way to separate the rejected materials from the staged materials. I said if they wanted to be even more proactive the rejected materials could be stored in a designated location in the warehouse area away from staged items.

Facilities and Equipment

OBSERVATION 10

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use and cleaning and maintenance.

a) The Starch Hemorrhoid Suppositories operators utilize a plastic five gallon bucket to transfer product from the mixing vessel to the suppository forming and packaging machine.

- the plastic bucket is not easily cleaned and sanitized and it is not documented
- the plastic bucket has not been evaluated for cross contamination with the product

b) the Infant and Adult Glycerin Suppository filling line is not appropriate for the manufacture of OTC drug products in that:

- the scraper used to remove material from the molds is a plastic like material, with noticable chips and scratches. It is not easily cleanable and is a direct product contact surface. It is not inspected periodically to ensure that it is safe for use.
- the pins used to force the suppositories out of the molds are . It is not easily cleanable and is a direct product contact surface. Several pins were observed to be missing. The pins are not inspected periodically to ensure that it is safe for use.
- the ejector bin in which the suppositories are placed to ensure they are cool is plastic with clear plastic tape holding a piece of what appeared to be heavy paper inside of it. This is not easily cleanable and is a direct product contact surface.
- the funnel hopper in which the suppositories flow is plastic with several scratches and is not easily cleanable. This is a direct product contact surface.

Reference: 21 CFR 211.63

Discussion with Management:

10a - We observed Starch Hemorrhoid suppositories, #9G115B in tank 51. The product was being filled on the suppository filling line which is located on the other side of the wall from the suppository blending suite.

the operator takes an amount out of the mixing vessel using a plastic five gallon pail and carries it to the hopper on the filling line. There is no record of the plastic bucket being cleaned between uses. There is no documentation as to the cleaning of this bucket. In addition, the bucket is plastic and there the company has no knowledge as to whether there is any interaction between the plastic and the OTC drug product. Management had no comment regarding this observation during the close out meeting.

10b - When sufficiently cooled, the molds are placed in the glycerin suppository molding press machine where blade made of . The blade on the press machine was worn and chipped. It did not appear to be a surface that can be completely cleaned. , a plate with rods presses down on the mold to remove the suppositories which drop into an ejector bin. Several of the rods were observed to be chipped, cracked, or missing. There is no visual inspection procedure for the blade or the ejector rods. Mr. McIntosh said the blades are changed based on functionality and are considered a wear item. There is no system in place to prevent or identify plastic fragments from the blade or the rods in the finished suppositories(b) (4) . At one point during production, it appeared that the plate with the(b) (4) ejector rods was not in alignment with the mold. Investigator Hustedt observed a production employee repeatedly engaging the ejector plate via its push-button controls, which caused the(b) (4) rods of the plate to repeatedly impact the mold, but few suppositories were ejected. This continued until Mr. McIntosh instructed the employee to stop. The suppositories are ejected from the molds into a plastic ejector bin. This bin contained clear tape and what appeared to be heavy paper or cardboard. From the ejector bin, the suppositories are dumped through a plastic hopper filler that contained protruding screws, scratches, and crevices between the plastic components. Management did not have any comments regarding this observation.

OBSERVATION 11

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

a) in the suppository mixing room the spatula, with product residue on it, that is used to scrape in process product off the sides of the wall of tank 51 was observed during the manufacture of lot #9G115B to be sitting on the portable metal steps that the operator steps on to access the tank.

b) the fans used in the Infant and Adult Glycerine Suppository room to cool the suppository molds were observed on 7/16/09 to have accumulations of debris.

Reference: 21 CFR 211.67(a)

Discussion with Management:

11a – In the Hemorrhoid suppository blending suite we observed a metal spatula used by the operator to scrape the side of the mixing vessel resting on the metal steps that the operator uses to reach into the mixing vessel. The scraper had product residue on it and had obviously been used in the product. When questioned about the spatula, the operator stated that she would clean it and brought it to the sink. Management indicated that the operator should not have placed the spatula on the steps. No comment was made regarding this observation at the close out meeting.

11b – There are approximately tall metal fans used to blow cool air directly onto the hot Glycerin to accelerate the cooling process of the suppository molds. The fans were observed to have accumulated dirt and debris on them. Investigator Hustedt observed the fans on and blowing around product when he was in the Glycerin suppository blending suite. Management had no comment regarding this observation during the close out meeting.

OBSERVATION 12

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

Specifically, during a tour of the facility on 7/15/09 the following deviations from the procedure "Cleaning and Sanitizing Batching Equipment, Tanks and Totes" #WI-PM-0056 effective 4/06/09 were observed:

a) mixing tank #50 had a "ready for use" sign affixed to it, the "in use" tag was not completed, the tank was observed to have product in it. According to management the next suppository batch had been started, lot #9G123B was in the melting phase of production.

b) the "Tote or Tank Activity Record" for tanks 50 and 51 did not have any entries for the use of those tanks after 7/2/09.

c) mixing tank #40 was observed to have a "ready for use" sign affixed to it, the "in use" tag was not completed. We were informed by the operator that Hemorrhoid Cream, lot #9G109B was in the mixing tank.

d) the "Tote or Tank Activity Record" for tank #41 was observed with the entry "7/15/09 Hem Oint 9F109B" - as mentioned above that product was observed in tank #40.

e) the "Tote or Tank Activity Record" for Tank #40 did not have any entries after 6/29/09.

Reference: 21 CFR 211.67(b)

Discussion with Management:

In the suppository blending suite we observed that tank #50 had a "Ready for Use" sign hanging on it. When we looked into the mixing vessel we observed product being mixed. I asked what was in the mixing vessel and was told tha(b) (4) phase of production for the next product

was starting. I asked to see the batch record. The operator left the area to retrieve the batch record for hemorrhoidal Suppository with Phenylepherine, lot #9G123B. Several sections of the batch record had not yet been completed including
the section titled "Equipment" had not been completed. This section also includes recording cleaning and batch information in the "Tank Cleaning and Sanitization Log". The "Tank Cleaning and Sanitization Log" for tanks 50 and 51 were observed, the last entry in both logs was dated 7/2/09. Note that the logs are not identified as to which is tank 50 or 51, however both logbooks are missing entries because there was product in both tanks on 7/15/09. Management also stated that the suppository line is used per week indicating that the equipment had been used many times since 7/2/09 with no entry in the "Tank Cleaning and Sanitization Log". In the creams and ointments mixing area we observed Tank #40 with a "Ready for Use" sign attached to it. The product Hemorrhoid Cream, lot #9G109B was observed mixing in it. The "Tank Cleaning and Sanitization Log" for tank #40 did not have any entries after 6/29/09. Tank #41 was observed to have Theraflex, lot #9G110B mixing in it. The "Tank Cleaning and Sanitization Log" for tank #41 had the following entry "7/15/09 Hem Oint Batch No 9G109B 2000#...". Management did not have any comments regarding this observation.

OBSERVATION 13

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used and description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance.

Specifically, the procedure "Cleaning and Sanitizing Batching Equipment, Tanks and Totes #WI-PM-0056 effective 4/06/09 does not include instructions specific to differently designed pieces of equipment i.e. Infant and Adult Glycerine suppository filling line (b) (4) suppository filling line, alcohol prep pad filling line, bottle filling line and tube filling line.

Reference: 21 CFR 211.67 b)

Discussion with Management:
Currently this firm has one procedure that covers the cleaning and sanitizing of all different kinds of equipment, tanks and totes. This facility utilizes numerous pieces of equipment for mixing, filling and packaging operations. I explained at the close out meeting that the more complex types of equipment should have procedures specific to the type of equipment. The procedures should explain if the equipment needs to be cleaned in place or taken apart and cleaned. In addition, specific information about hard to clean areas of the equipment should be included. I also said that photographs of the equipment help the operators, but aren't necessary. Management said they understand the observation.

OBSERVATION 14

Records of the inspections of automatic, mechanical or electronic equipment, including computers or related systems are not maintained.

Specifically, the Infant and Adult Glycerin Suppository Molding Press Machine and the Scale Automatic Weighing Machine (used for packaging the Glycerin Suppositories) have no records of qualification.

Reference: 21 CFR 211.68(a)

Discussion with Management:

We were provided copies of the firm's Installation/Operational Qualification Protocol for the Glycerin Suppository Molding Press Machine and the Installation/Operational Qualification Protocol for the Scale Automatic Weighing Machine (S/N: for the glycerin suppository line. These IQ/OQ protocols have not been approved or implemented since this equipment was moved to the Hartland facility. This equipment has been used in the manufacture of adult and infant glycerin suppositories at this location for over one year. Management had no comment regarding this observation at the close out meeting.

Laboratory

OBSERVATION 15

The number of containers to be sampled is not based upon appropriate criteria.

Specifically, the procedure "Sampling, Testing, Approval and Release of Incoming Chemical Materials #WI-QC-0203 effective 7/14/08 does not specify the number of containers within a lot of raw material to sample.

Reference: 21 CFR 211.84(b)

Discussion with Management:

The procedure "Sampling, Testing, Approval and Release of Incoming Chemical Materials" #WI-QC-0203 effective 7/14/08 is attached as **Exhibit #MAF17**. The procedure specifies that each manufacturer's lot/batch is sampled separately but does not say how many samples to take of each lot/batch. Ms. Karau stated that the procedure should be more specific as to how many containers within the lot should be sampled. During the close out meeting, Ms. Karau asked for clarification as to the number of containers to sample with in a lot/batch. I explained that it should be statistically based.

OBSERVATION 16

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.

a) As the method "HPLC Analysis - Phenylephrine HCl Content for Gel, Suppositories, Ointment #WI-LAB-0117 effective 5/28/08 is currently being run, it has not been validated.

b) The method HPLC Analysis - Phenylephrine HCl and Pramoxine HCl Content #WI-LAB-0120 effective 6/15/07 has not been validated.

Reference: 21 CFR 211.165(e)

Discussion with Management:

The percent Phenylephrine Assay was run per WI-LAB-0117 – "HPLC Analysis – Phenylephrine HCl Content for Gel, Suppositories, Ointment" effective 5/28/08 on several test results that we observed. Upon review of the raw data several discrepancies were noted from the method although no deviation was referenced.

(b) (4)

Ms. Karau acknowledged these changes were significant enough to affect the validation and was able to provide a deviation H0109.018(b) (4)

(b) (4)

this validation has yet to take place. When questioned, Ms. Karau stated . On the last day of the inspection, a list of QA Laboratory Method Validation Matrix was offered. Ms. Karau stated this list shows what methods are active, validated and the validation priority. Although (b) (4)

When asked, Ms. Karau stated they are(b) (4)

(b) (4)

, attached as **Exhibit #MAF18** has not been validated either. No further comments were made regarding this observation during the close out meeting.

OBSERVATION 17

The use of instruments not meeting established specifications was observed.

Specifically, the HPLC was used for assay of several OTC finished products prior to the PM/OQ/PV being completed.

Reference: 21 CFR 211.160(b)(4)

Discussion with Management:
Ms. Karau could not provide any documentation on the calibration of the HPLC currently being used to release the OTC products. Investigator Hughes reviewed WI-LAB-0123 - PM/OQ/PV for the HPLC, effective date 10/02/07. Investigator Hughes reviewed the deviation P0508.001 associated with this document which states the HPLC would be used after the PM was done (5/6/08) but before the OQ was completed (6/19/08). Ms. Karau stated this was done prior to her working at the firm and that this practice would not be acceptable anymore. No further comments were made regarding this observation at the close out meeting.

Production

OBSERVATION 18

All major equipment used during the production of a batch of drug product is not properly identified at all times to indicate contents.

a) tank #50 was observed with a "Ready for Use" tag on it. The tank contained the product Hemorrhoidal Suppository with Phenylepherine, lot #9G123B.

b) mixing tank #40 was observed to have a "ready for use" sign affixed to it. We were informed by the operator that Hemorrhoid Cream, lot #9G109B was in the mixing tank.

Reference: 21 CFR 211.105(a)

Discussion with Management:
See the discussion under observation number 12.

OBSERVATION 19

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically, this firm has not validated any of their manufacturing processes for OTC drug products. Examples of OTC drug products currently manufactured under contract and/or their own label include Infant Hemorrhoidal Suppositories, Adult Phenylepherine and other active ingredient Hemorrhoid Suppositories, Mouthrinse products, Antibacterial towelettes, Sterile Lubricating Jelly, Sterile Alcohol Wipes, Cold Sore Medication, Acne pads and Lice Kits.

Reference: 21 CFR 211.110(a)

Discussion with Management:
This firm was not able to provide any process validation for the OTC drug products currently manufactured. This firm has manufactured OTC drug products for several years.

. The Validation Master Plan is attached as **Exhibit #JDH12**. Management did not have any comments regarding this observation at the close out.

OBSERVATION 20

Procedures designed to prevent objectionable microorganisms in drug products not required to be sterile are not established.

a) operators were observed carrying the Infant and Adult Glycerin Suppository from the suppository mold machine over to the mixing vessel. The operators touched after touching the movable metal steps, the (b) (4) touched their clothes and were exposed to the air.

b) (b) (4) were observed in the Glycerin Suppository room. have been sitting there for up to four weeks. Some are covered by a thin plastic bag, some are not covered at all and some of the bags have holes in them.

Reference: 21 CFR 211.113(a)

Discussion with Management:
During production of the infant and adult Glycerin suppositories a horizontal blade made of (b) (4) from this step are placed in bins in the reprocessing storage area. The bins are located in a corner of the Glycerin suppository suite near the entrance and are held until there is enough material to create a new batch. There were glycerin (b) (4) batches in the storage area, one of which was not

identified with batch or lot information. Some of the bins of material were covered with plastic, while others were uncovered or had holes in the bags. may be left in this area for several weeks one batch – 9F204B – were identified with a production date of 6/25/09. There is no microbiological testing performed on this product prior to re-processing. During production one employee was visibly confused regarding the proper disposition of and was seen holding against his shirt and handling a portable metal staircase with his gloved hand and subsequently touching with the same gloved hand. Production employees normally would place . Following this observation, the were placed in white plastic carts. Management had no comment regarding this observation during the close out meeting.

OBSERVATION 21

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

Specifically, labels were observed unattended in the staging area. According to management this is standard procedure for all products and the labels can be left unattended in the area from 1 hour up to 2 days.

Reference: 21 CFR 211.125(a)

Discussion with Management:
Raw materials, containers and labels are staged outside of the manufacturing and packaging suites that will be using them. The OTC drug labels can be stored in this area for a time period of up to two days. During the two days they are stored in this area, the labels are out in the open and not under strict control. Management did not have any comments regarding this observation during the close out meeting.

There was no further discussion after the FD 483 was reviewed. The inspection was concluded.

REFUSALS

There were no refusals encountered during this inspection.

SAMPLES COLLECTED

Two documentary samples were collected DOC380715 – Hemorrhoid Suppositories with Phenylephrine and DOC380716 – Glycerin Suppositories for Infants and Adults. These DOC samples were collected to document cGMP deficiencies and interstate movement of the finished product.

EXHIBITS

MAF

1. A list of the products manufactured and the last date of sale
2. Promotional materials for the TRIAD brand products
3. organizational chart
4. "General Rejection Procedure" #WI-QC-0094 effective 5/6/09
5. batch record for hemorrhoidal Suppository with Phenylepherine, lot #9G123B
6. "Tank Cleaning and Sanitization Log" for tanks 50 and 51
7. "Tank Cleaning and Sanitization Log" for tank #40
8. "Tank Cleaning and Sanitization Log" for tank #41
9. Labels for the 4 oz lubricating jelly products
10. DRAFT procedure "Responsibilities of the Quality Department" #P-QA-0007
11. list of new employees within the past two years for the Quality Control Unit and the Quality Assurance laboratory
12. OOS Investigation OOS-09-057
13. finished product specifications for infant and adult Glycerin suppositories
14. "
    ", issued 8/23/05
15. batch record for Glycerin suppositories, lot #9C150B
16. DRAFT procedure "Supplier Qualification and Management System" #WI-QA-0010
17. "Sampling, Testing, Approval and Release of Incoming Chemical Materials" #WI-QC-0203 effective 7/14/08
18. "HPLC Analysis – Phenylephrine HCl and Pramoxine HCl Content" #WI-LAB-0120 effective 6/15/07

JDH

1. "Training Guidelines" (WI-TRN-0007), effective date 6/03/09
2. cGMP training program
3. Level 2 Training
4. Level 3 Training
5. example of the cGMP Training – Level 3 Examination
6. (b) (6) Personal Training Record Summary
7. QC Department Memorandum dated 6/9/2008 and a General Training Record (Spec No.:01-027) from (b) (6) training file
8. general floor plan
9. water system schematic
10. Installation/Operational Qualification Protocol for the Glycerin Suppository Molding Press Machine

11. Installation/Operational Qualification Protocol for the Scale Automatic Weighing Machine (S/N: for the glycerin suppository line
12. Validation Master Plan, issue date 06/24/2009
13. spreadsheet showing the equipment for which IQ/OQ has been completed
14. Installation Qualification for Machine
15. Operational Qualification for Machine
16. Photograph of the Glycerin suppository molds
17. Photograph of the fans used to cool the Glycerin suppository molds
18. Photograph of the blade on the Glycerin suppository press machine was worn and chipped
19. Photograph of the storage area for
20. Photograph of the cart used to store and before they are placed back into the blend tank
21. Photograph of the plate with rods that presses down on the Glycerin suppository mold to remove the suppositories which drop into an ejector bin
22. Work Instruction WI-PM-0056, Cleaning and Sanitizing Batching Equipment, Tanks and Totes, effective 4/6/09.
23. Team Daily/Weekly Housekeeping Checklist
24. Photograph of the plastic ejector bin
25. Photograph of the plastic hopper filler
26. photograph showing the overall layout of the glycerin suppository production area
27. CD-R containing the photos taken by Investigator Hustedt

SAH

1. Phenylephrine HCl Hemorrhoidal Suppository labeling
2. SOP 01-019 - Internal and External Deviations, effective 01/31/07
3. OOS-08-132 issued 9/9/08
4. SOP WI-LAB-0040 – Laboratory Out Of Specification (OOS) Investigations (effective date 6/17/09)
5. Master Batch Formula and Mixing Instruction for batch 8M186B
6. OOS-09-004 and deviation H0109.020
7. deviation H0209.003 and OOS-09-011
8. OOS-09-009

9a. Lot Approval Report packet for lot 8M186B

9b. Master Batch Formula and Mixing Instruction for the beginning sample for lot 8M186B

9d. Lot History File contains the Master Batch Formula and Mixing Instruction for the middle sample (case 535)

9e. Lot History File contains the Master Batch Formula and Mixing instruction for the End Sample (case 551) for lot 8M186B

9f. release data associated with lot 8M186

9g. release data associated with lot 8M186

10. Receiving paperwork for the (b) (4) Hemorrhoidal Suppositories carton (item (b) (4)), Control No. 23689
11. SOP WI-QC-0002 – Incoming Inspection for Cartons, effective date 06/23/06
12. SOP WI-QC-0214 – Quality Control Finished Goods Release – Effective 06/05/08
13. SOP WI-LAB-0139 – Documentation Procedure and Use of Laboratory Notebooks, effective 04/03/09
14. Picking Slips with documentation of the shipper are attached for (b) (4) Hemorrhoidal Suppositories with Phenylephrine, lot 8M186, for product shipped 02/04/2009
15. OOS-08-087
16. WI-LAB-0117 – HPLC Analysis – Phenylephrine HCl Content for Gel, Suppositories, Ointment, effective 5/28/08
17. deviation H0109.018
18. QA Laboratory Method Validation Matrix
19. WI-LAB-0123 - PM/OQ/PV for the (b) (4) HPLC, effective date 10/02/07

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