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SUMMARY

A routine cGMP inspection of this pharmaceutical and medical device manufacturer was conducted as per New Jersey District FY '08 workplan, FACTS assignment 929422, op. id. 362914. Pharmaceutical coverage was provided as per CP7356.002, Drug Manufacturing Inspections and medical device coverage was provided as per CP7382.845, Inspection of Medical Device Manufacturers.

The previous inspection of 10/25/06 et. al. included cGMP, pre-approval, and field alert coverage. The inspection was classified VAI with deviations regarding a lack of thorough investigations. Approval was recommended for the site as an alternate manufacturer of the bulk solution for NDA [redacted] (b) (4)

The current inspection revealed that this former Pfizer manufacturing site is still owned by Pfizer; however the Pfizer consumer healthcare business was acquired by McNeil PPC, Inc. (a Johnson and Johnson company) on 12/21/06. [(b) (4)] McNeil PPC, Inc. leases the manufacturing site from Pfizer and continues to manufacture consumer and prescription pharmaceuticals and one medical device. The majority of the firm's products have been transferred to new locations with the exception of the Visine formulations, [(b) (4)] [(b) (4)] The site also continues to manufacture the one medical device, Visine for Contacts on the same equipment and filling line as all other Visine formulations. During the inspection the last batch of [(b) (4)] Tablets was also packaged at the site. Deviations were noted in that the complaint handling system did not assure that all complaints including the possible failure of a medical device or pharmaceutical product to meet any of its specifications were evaluated or investigated by the Quality Unit. The firm's current procedures and practices including "autoclosure" of complaints do not assure that all quality data from all sources is evaluated by the Quality Unit in making product quality decisions. Deficiencies were noted in written procedures for complaint handling and investigations (Quality Assurance Reports). [(b) (4)] assay data failed to meet the concurrent process validation acceptance criteria for [(b) (4)] bulk solution used in [(b) (4)] during a concurrent process validation of the bulk solution. The lot was released 5/28/08, despite the unknown cause of the low assay bulk solution results. No samples were collected and there were no refusals during the inspection. An FDA 483, Inspectional Observations was issued to Roy J. Pera, Director of Operations, Site Leader. Robert Foster, Director Quality Operations stated the firm would respond in writing to New Jersey District Office within 30 days.

ADMINISTRATIVE DATA

Inspected firm:	McNeil PPC Inc.
Location:	100 Jefferson Rd Parsippany, NJ 07054
Phone:	973-887-2100
FAX:	
Mailing address:	100 Jefferson Rd Parsippany, NJ 07054
Dates of inspection:	7/7/2008, 7/8/2008, 7/14/2008, 7/15/2008, 7/16/2008, 7/21/2008, 7/22/2008, 7/23/2008, 7/31/2008
Days in the facility:	9
Participants:	Erin D. McCaffery, Investigator Robert G. Ruff, Investigator

On 7/7/08, I, Investigator Erin D. McCaffery presented credentials and issued an FDA 482, Notice of Inspection **(Att)** to Nathan Anderson, Compliance Validation Manager. Mr. Anderson stated that he was authorized to accept the Notice. I stated the purpose of the visit as a routine cGMP inspection.

On 7/14/08, credentials were presented and a second FDA 482, Notice of Inspection **(Att)** was issued to Robert J. Foster, Director Quality Operations to add Investigator Robert G. Ruff to the inspection. Mr. Foster stated that he was authorized to accept the Notice. I, Investigator McCaffery explained that Investigator Ruff would be providing medical device coverage during the inspection.

On 7/31/08, Discussions with Management were held and an FDA 483, Inspectional Observations **(Att)** was issued to Roy J. Pera, Director of Operations, Site Leader. A list of attendees at the exit meeting is provided as **Exh. 1.** Robert Foster, Director Quality Operations stated that the firm would respond in writing to New Jersey District within 30 days.

Dates of inspection:
Investigator McCaffery: 7/7-8, 14-16, 21-23, 31/08
Investigator Ruff: 7/14-16, 21-23, 31/08

Explanation of the FDA 483 observations 1-4 were written by Investigator Ruff. Observations 5-6 were written by Investigator McCaffery.

HISTORY

Roy Pera, Director of Operations, Site Leader explained that McNeil PPC, Inc. is the parent company for the McNeil Consumer Healthcare and Johnson and Johnson Healthcare Products Divisions. The Parsippany, NJ site was owned and operated by Pfizer, Inc. until the acquisition of the Pfizer Consumer Healthcare business on 12/21/06. The facility, (b) (4) square feet) is currently owned by Pfizer, but (b) (4) square feet are leased by McNeil PPC, Inc. The remaining (b) (4) square feet are used by Pfizer as a distribution center for pharmaceutical and animal health products. Following the acquisition by McNeil PPC, Inc., (a Johnson and Johnson company), the site was given a two year extension for manufacturing. It is scheduled to close 12/19/08 and most products have already been transferred from the site to their new manufacturing locations. Transitional supply agreements and quality agreements were developed to assure continued supply of products on the market. A summary of the completed and scheduled product transfers was provided as **Exh. 2.** According to Mr. Pera, Director of Operations, Site Leader, the Visine formulations will be the last remaining products at the facility. They will continue manufacturing until late September 2008 or early October 2008 to build inventory for the transition in manufacturing sites. The gross annual revenue for 2007 was estimated at (b) (4) with Visine accounting for (b) (4) All Visine formulations currently manufactured by the site are being transferred to the Beerse, Belgium manufacturing facility which is owned by Johnson and Johnson. The site operates on a (b) (4) shift for the Visine operation according to Nathan Anderson,

Compliance Validation Manager; however he stated that weekend shifts vary based on staffing and demand. There are (b) (4) There are currently (b) (4) employees on site. A summary of the products within each of the consumer healthcare divisions was provided as **Exh. 3.** A list of the last dates of manufacture for each product at the site was provided as **Exh. 4.** A specific Visine batch production summary since 11/20/06 was provided as **Exh. 5.** A facility diagram is provided as **Exh. 6** and a specific process description and aseptic filling diagram are provided for the Visine line as **Exhs. 7, 8.**

INTERSTATE COMMERCE

Robert Foster, Quality Director estimated that approximately (b) (4) % of the firm's pharmaceutical and medical device products move in interstate commerce. He explained that the firm's distribution centers are all located outside the state of New Jersey.

JURISDICTION

Review of activities since the last inspection of 10/25/06 et. al. revealed that the firm manufactures prescription and over-the-counter pharmaceuticals and one medical device product. The site is scheduled for closure in 12/19/08 but continues to manufacture multiple Visine formulations, including the medical device, Visine for Contacts. They also continue to manufacture (b) (4) (b) (4)) and completed the last packaging operations for Unisom Tablets during the inspection.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Comprehensive lists of employees interviewed are provided as **Exh. 9.** Organizational charts for the site and the reporting structure to upper management are included as **Exhs. 10, 11.**

The following firm personnel provided the majority of the information, documentation and copies upon request during the inspection:

Roy J. Pera, Director of Operations, Site Leader is the most responsible person at the site. He formerly worked for Pfizer and was previously employed at the site as well as several other Pfizer facilities. Mr. Pera replaced (b) (6) of Pfizer and is responsible for facilitating the site closure including product transfers and decommissioning activities. Mr. (b) (6) became the site leader for Pfizer in Brooklyn, NY and Mr. Pera returned to the facility as site leader for McNeil PPC. Mr. Pera provided information regarding organizational changes, reporting structure for both production and quality, timeframes for site closure, scheduled and completed product transfers and discussed the changes. He was present periodically during the inspection and discussed policy changes since the acquisition of the Pfizer consumer healthcare business by McNeil PPC, Inc. (a Johnson and Johnson company). Mr. Pera reports to Paul Lefebvre, Vice President North American Supply Chain.

Robert Miller, Ph.D., Vice President Global Quality Assurance, OTC, McNeil Consumer Healthcare, was present on 7/31/08 at the FDA 483 exit meeting. Dr. Miller reports to Richard D'Sousza, Chief Technology Officer.

Teresa Gorecki, Vice President, North America Quality Assurance, Johnson and Johnson Consumer and Personal Products, was present on 7/31/08 at the FDA 483 exit meeting. Ms. Gorecki reports to Santosh Jiwrajka, Global Vice President Quality Assurance.

Robert Foster, Director Quality Operations was present throughout the inspection. He discussed numerous Quality Assurance Reports (QARS), complaints, SOPs, and history of business. He discussed efforts to sustain compliance despite the pending site shutdown. He described the transfer and decommission for products such as BenGay, Desitin, Cortizone, Plax, and Zyrtec Syrup. He also discussed the ongoing transfer of the Visine formulations to another Johnson and Johnson facility in Beerse, Belgium. Mr. Foster reports to Robert Miller, Ph.D., Vice President, Global Quality Assurance OTC.

Christopher Coughlin, Manufacturing Director was formerly the Quality Director for the site, but became the Manufacturing Director in the spring of 2006. He provided information during a walkthrough of the limited areas that are still manufacturing to include the aseptic filling line for Visine, the packaging line for Unisom Sleep Gels and Tablets, and the liquid manufacturing and filling area for (b) (4) He also discussed the transfer of many of the firm's previously manufactured products and the decommissioning of the equipment and facilities. Mr. Coughlin reports to Mr. Pera and was present at the exit meeting.

Colin McArthur, Packaging Director provided information during some of the facility tours. He provided information and diagrams of the Visine filling line to include details of the equipment and design of the class 100 area. Mr. McArthur reports to Roy Pera, Director Operations, Site Leader.

(b) (6) **Manufacturing Manager** provided information during the walkthrough of the existing and decommissioned manufacturing facilities. He discussed several batch rejections and provided information regarding the completion of manufacturing operations at the site. Mr. (b) (6) reports to Christopher Coughlin, Manufacturing Director.

(b) (6) **Quality Assurance Manager, Receiving and Inspection** provided information during a walkthrough of the shipping/receiving and inspection area. He described the process of incoming materials and the status assigned to the materials. He also discussed the manufacturing transfer of the (b) (4) bulk solution from the (b) (4) facility to the McNeil manufacturing site. Mr. (b) (6) reports to Robert Foster, Director Quality Operations.

(b) (6) **Aseptic and Packaging Manager** provided information during walkthroughs of the facility including the aseptic Visine production area. Mr. (b) (6) reports to Colin McArthur, Packaging and Aseptic Processing Director.

(b) (6) **Compliance Validation Manager** has been at the site since 4/05 and in his current position since 5/06. Mr. (b) (6) received the initial FDA 482, Notice of Inspection and facilitated the inspection. He provided information and documentation throughout the inspection. He is responsible for compliance, validation and the microbiology laboratory. He provided information regarding specific Quality Assurance Reports (QARS) especially related to Visine manufacturing and the aseptic manufacturing area. Mr. (b) (6) also assisted in obtaining information regarding the corporate complaint handling system including the call center, quality complaints, and adverse event reporting. He reports to Robert Foster, Quality Director.

(b) (6) **Senior Validation Specialist, Quality Operations** acted as the scribe during the inspection and also provided information on (b) (4) validation. She was present throughout the inspection and provided copies upon request. She reports to (b) (6) Compliance Validation Manager.

(b) (6) **Quality Assurance Manager, Laboratories and Compliance** facilitated the laboratory walkthroughs and provided information regarding laboratory investigations, procedures, methods, and practices. He also discussed the data acquisition and review process. Mr. (b) (6) reports to Robert Foster, Quality Director.

(b) (6) **Microbiological Analyst** was present during the walkthrough of the microbiology laboratory. She answered questions about sterility testing and current laboratory practices. We observed Ms. (b) (6) conducting sterility testing on 7/16/08. Ms. (b) (6) reports to (b) (6) (b) (6) Quality Assurance Team Leader/Supervisor.

(b) (6) **Quality Assurance Team Leader/Supervisor** was present during a walkthrough of packaging/labeling operations and discussed the re-inspection process for products which are automatically removed from the line in-process. She provided detailed information regarding several investigations that occurred since the last inspection. Ms. (b) (6) reports to (b) (6) Quality Assurance Manager, Receiving and Inspection.

(b) (6) **Aseptic and Packaging Manager** was present during the walkthroughs of the (b) (4) bottle filling operation, Visine packaging/labeling operation, and the aseptic manufacturing area. He provided information and documentation regarding procedures for line clearance, re-inspection of product removed in-process, contamination control for antibiotic products, and discussed current aseptic practices. We discussed the need for additional personnel controls regarding the (b) (4) filling area to prevent potential contamination issues. Mr. (b) (6) reports to Colin McArthur, Packaging and Aseptic Processing Director.

(b) (6), **Associate Director, Integrated Safety Operations, Benefit Risk Management** is located at the firm's Morris Plains, NJ facility. She was present on 7/15/08 to review applicable procedures regarding quality investigations associated with adverse event reports. She reports to Ellen Carroll, Director, Benefit Risk Management.

FIRM'S TRAINING PROGRAM

Review of training files on SOPs, corporate policies, and methods was limited to investigative follow-ups or inspectional findings that required initial or re-training. General training procedures are in place and there were documented records of employees in attendance for training activities.

MANUFACTURING/DESIGN OPERATIONS

The only remaining manufacturing operations at the site are the aseptic filling line for Visine formulations, including the medical device, Visine for Contacts; liquid filling/packaging operations for (b) (4) (b) (4); and a packaging line for Unisom Tablets. All other manufacturing lines for products such as Ben Gay, Cortizone, Desitin, Plax and Zyrtec Syrup were sold or transferred to other Johnson and Johnson or contract facilities. The sole aseptic filling line used for Visine formulations remains unchanged since the prior inspection; however a need for increased capacity was identified in 2006. As a result, to reduce changeover time, Visine products were filled into unlabeled bottles known as brite stock and placed in shippers for labeling in other areas at a later time. Mr. Pera stated that it significantly increased their capacity. Procedural controls for brite stock were reviewed and observed in practice. No deviations were noted. A description and schematic of the aseptic filling line for Visine products was provided as **Exhs. 7, 8** by Colin McArthur, Packaging Director.

Coverage of the Quality and Production systems revealed that the firm manufactures approximately (b) (4) batches of Visine formulations per year. A summary of the number of Visine batches of other products manufactured since the last inspection were provided as **Exhs. 5, 4.** We discussed the reporting of deviations/investigations. They include Quality Assurance Reports (QARS) which must be completed in 7 days for non-product impact and 30 days for potential product impact. QARS capture manufacturing, engineering, and quality deviations. The laboratory uses three types of reports to capture issues. They include "Data Not Reported" in cases of a system suitability or set-up failures; Analytical Laboratory Investigations (ALIs) for out-of-specification or out-of-trend results which can then become Quality Assurance Reports (QARS) if confirmed. Two other types of deviations are captured as Quality Incident Sheets for issues such as minor packaging problems (which can also be escalated as needed to a QAR); and the change control system for planned deviations. Review of investigations revealed that there have been no media fill failures since the last inspection. Robert Foster, Director Quality Operations, stated that he was not aware of any media fill failures since 2001. According to (b) (6) Compliance Validation Manager, media fills are conducted (b) (4) times per year to qualify (b) (4) people including operators, mechanics, samplers, cleaners, quality inspectors and management. He also described the routine personnel and environmental monitoring activities conducted for the aseptic Visine line.

MANUFACTURING CODES

An example of the manufacturing codes used was provided as follows:

Visine AR lot# VB08060= Visine Brite Stock (VB) + 2008 (08) + 60th lot of the year (060)
A finished packaged lot number is also assigned once the brite stock is labeled for commercial distribution. The VB gets replaced with a numerical code to represent the finished product.

COMPLAINTS

The complaint handling system was reviewed for both medical devices and pharmaceuticals. Deficiencies were documented as FDA 483, Inspectional Observations 1 and 5. Promised corrective actions were provided by Robert Foster, Director Quality during the inspection and more extensive corrective actions to include corporate changes in complaint handling were promised to be documented in the firm's written response to the FDA 483. Current procedures and practices do not assure that all complaints which potentially require review and investigation by the site are forwarded due to current complaint trending practices and "autoclose" procedures for incoming complaints. We discussed assessment of risk and the need to evaluate all sources of quality data in order to make decisions about products. We also noted that similar complaint trending issues and the failure to address repetitive complaints in a timely manner by the site was previously discussed during the 8/29/05 et. al. inspection.

RECALL PROCEDURES

Recall procedures were reviewed and discussed during the current inspection. Mr. Foster notified us that the only recall since the last inspection was for Vistaril® Suspension which the firm contract manufactured for Pfizer. A field alert was filed 12/13/06 due to a 6-month stability failure for low out of specification assay results for hydroxyzine pamoate. Investigation revealed that although vigorous shaking was required prior to use of the product, a decision was made to recall the product to assure that sub and or superpotent doses were not used by patients. According to Mr. Foster, all lots on the market were recalled **(Exh. 12).**

DISCUSSIONS WITH MANAGEMENT

On 7/31/08, prior to the issuance of the FDA 483, Inspectional Observations at the exit meeting, Investigator Ruff and I presented abbreviated discussions with management summarizing discussions held during the inspection for items of concern which were not documented as FDA 483 observations.

I, Investigator McCaffery discussed the following:

- During a review of Quality Assurance Reports (QARS), I noted that investigations did not always focus on scientifically determining root cause, but instead focused on trying to prove that the product was acceptable for release. An example was provided as QAR 07-00320, in which white particles were observed during an in-process particulate matter test during the sterile filling of Visine A/C 0.5 oz. bottles, lot# VB07106 on 12/7/07. Prior to completion of the investigation, a decision was made to remove all tubing and other disposable parts ("wear parts") from the filling line which were speculated as a potential root cause. Although the white particles were collected during the investigation, they were not analyzed. The investigation report concluded, "(b) (4) (b) (4) (b) (4)." **(Exh. 13).**

  On 1/14/08 a second particulate matter in-process test failure was documented in QAR 08-00011 for the filling of Visine A/C 0.5 oz. bottles, lot# VB08006 **(Exh. 14).** The second investigation also described particles (foreign matter) which were observed during the testing. The second investigation included testing of the particulate matter and a thorough visual inspection of the line. The investigation revealed a set-up issue in which the filled capped bottles were scraping the (b) (4) rail upon exiting the class 100 area, generating particles. The white particles were adhering to the exterior of the Visine bottles and would drop off the bottle during testing and interfere with the filtration testing, causing the failures. As a result of the second event, the root cause was determined and corrective actions were made; however the failure to adequately investigate the first findings resulted in a second event and extensive investigation. During the inspection, Mr. Foster stated that he did not recall the reason that the particles were not analyzed and that he understood the need to objectively and scientifically try to determine root cause when investigating.

- During a walkthrough on 7/14/08, following the completion of the filling operation for an (b) (4) an employee was observed leaving the gowning area and re-entering the main facility wearing a uniform that contained (b) (4) on the leg of his white uniform. The facility design and the existing procedures do not prevent the employee from leaving the gowning area to enter the main facility. The current procedures (SOP 3067, version 4.0 and SOP 2312, version 7.0) only require the removal of a soiled external lab coat and require that, "(b) (4)." **(Exhs. 15, 16)** By design, the employee is currently required to leave the controlled area which has numerous allergy placards and gowning controls in place in order to remove a soiled uniform. Another employee noted that they were going to break (in the lunchroom) and then going to another

line for labeling of Visine brite stock. We discussed that although the facility was closing, design controls should be evaluated to reduce risk to products and employees. Mr. Pera and Mr. Foster both stated that they understood the issues regarding the design and procedural controls necessary for the [(b) (4)] product.

- We observed examples of partial lot releases of Visine products when action limits were exceeded for environmental and personnel monitoring and investigations could not determine the cause of the atypical results. We discussed the need to fully investigate the results which exceeded action limits and cautioned that releasing portions of sterile batches in which monitoring results are atypical should not be a routine practice. Although rejection of a shift of product may be deemed a "conservative approach" for a product in which action limits are exceeded, there are still questions as to why the results are outside the normal operating conditions and whether repetitive occurrences of exceeding action limits may be indicative of other issues that require corrective actions. Examples were discussed during the inspection such as QAR 08-00055 for Visine LR, lot# VB08023 **(Exh. 17)** and QAR 08-00084 for Visine for Contacts, lot# VB08043 **(Exh. 18).**

Investigator Ruff discussed the following:

- During discussions of complaint handling, I observed that procedures for determining when a complaint trend exceeded a "threshold", (thus triggering a complaint investigation), were not established. I explained that the firm relies on the trending of complaints and the monitoring of these trends to ensure investigations are initiated when threshold limits are exceeded. However, I explained that there appears to be no objective mechanism for the establishment of these "thresholds". According to Mr. [(b) (4)], this observation was cited in an internal quality system audit and corrective actions were being investigated. Mr. [(b) (4)] voluntarily provided **Exh. 19** to support this contention. I explained that **Exh. 19** did not appear to specifically call out my concern. Mr. [(b) (4)] stated that my concern was clear and that it would be addressed.

- During my review of QAR 07-0020 relating to confirmed instances of grease on caps used for Visine for Contacts lot VB07079 (identified prior to distribution), I asked if any other lots of Visine for Contacts had been manufactured using the contaminated lot of caps. Upon investigation, Mr. [(b) (4)] stated that Visine for Contacts lot VB07056 was also manufactured using the problematic lot of components (caps). Mr. [(b) (4)] stated that this lot was rejected. I explained that during an investigation, the firm must identify and appropriately control all product that may have been affected by a problematic component. I explained that I would have expected this activity to have been documented in the QAR. Mr. [(b) (4)] and Mr. Foster explained that, in fact, it is the firm's practice to identify and control all potentially nonconforming product during an investigation and document that activity. Neither gentleman could explain why this activity was not documented in QAR 07-0020.

- During my review of the control of rejected products, I observed that when inventory control personnel make an inventory data entry error, there is no formal mechanism to ensure the error is rectified. These errors may not be recognized until a physical inventory is performed. I explained that the firm should formally establish a mechanism for the reconciliation of inventory errors so that the electronic inventory accurately reflects the physical inventory.

- During my review of corrective and preventive actions, I observed that procedures used to control corrective and preventive actions generated from internal quality audit findings did not clearly describe the process for ensuring CAPA investigations are conducted consistently according to established procedures (i.e. WWSP027 Management of Nonconformance and CAPA).

- During my review of J&J Consumer Group Corporate Quality System procedures, I observed a procedure that does not reference current regulations (e.g. reference to 21 CFR Part 804, a regulation that no longer exists). In addition section 12.7 of the firm's QUALITY ASSURANCE COMPLAINT INVESTIGATION & CLOSURE FOR PCH AQUIRED PRODUCTS WITHIN THE BABY, BEAUTY, AND CHC GLOBAL BUSINESS UNITS, QSP-000324, Rev. 1 **(Exh. 20)** states "[redacted (b) (4)] (See Section 18.)" The complaint vigilance monitoring process is not described in Section 18. Section 18 specifies "RETENTION PERIODS". Section 3.1 of the **Exh. 20** references the use of BRM SOP 206 – Handling Product Complaints with Adverse Events. This is an inappropriate reference for Pfizer legacy products, such as Visine for Contacts. The appropriate procedure to handle these products is BRM (Consumer) Handling Product Complaints with Adverse Event Reports (US Process) Procedure BRMC-SOP-802, v.01 **(Exh. 21).** This procedure is not referenced in Exh. 20. I explained that operating units are expected to develop procedures reflecting these corporate "umbrella" procedures. I explained that if these corporate procedures are not accurate, the potential exists for the operating unit procedures to be inaccurate as well. I explained that the discussed corporate quality system procedures appeared sloppy and may not send an appropriate message to the operating units.

In addition the following documents were reviewed and discussed:

Quality System Requirements for Medical Devices, Procedure No. 2958, Ver. 3.0 **(Exh. 22)**
ANNUAL RECORDS REVIEW, Procedure No. 2378, Ver. 5.0 **(Exh. 23)**
QUALITY ASSURANCE GMP AUDIT REQUIREMENTS, QSP1037, Rev. 4 **(Exh. 24)**
Visine for Contacts Box Label (including package insert, **Exh. 25**)

On 7/31/08 an FDA 483, Objectionable Conditions was issued to Mr. Roy J. Pera, Director of Operations, Site Leader **(Att).** A list of employees present at the exit meeting is provided as **(Exh. 1).** In addition to site management, Robert Miller, Ph.D., Vice President Global Quality Assurance OTC, McNeil Consumer Healthcare from the Fort Washington, PA site and Teresa Gorecki, Vice President North America Quality Assurance, J&J Consumer and Personal Products Worldwide from the Skillman, NJ site were also present. Robert Foster, Quality Director stated that the firm would respond in writing to New Jersey District Office within thirty days.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

Medical Device Observations

OBSERVATION 1

Complaints involving the possible failure of a device to meet any of its specifications were not investigated where necessary.

Specifically, complaints maintained in the firm's electronic Product Quality Management System (PQMS) that meet Automatic System Closure ("AUTOCLOSE") criteria may never be investigated to determine whether the complaints are related to nonconformities in production or design processes. For example, the following Visine for Contacts adverse event complaints were "autoclosed" in the PQMS system without investigation:

Tracking No.	Lot/Control No.	Event Description
30000084439	0107101	"consumer (sic) used product and had allergic reaction had to go to ER, had burning and halo sight, even had hearing problem, has been told that a perservative (sic) in our product that can cause a (sic) allergic reaction by opthomologist (sic)"
30000084307	0106353	"cons. (sic) put 3-4 drops in her left eye and immediately had a burning sensation and blurred vision/flushed eye out with water and did not call HCP/sx's"
30000083712	0107262	"Consumer used product and developed a burning sensation in eyes."
30000103643	0107307	"was (sic) using product and the product got on his cheeks and he said his face became swollen and red and it burned. he (sic) still has the burning but it is getting better"

30000104112	**Not available**	**"The burning the drops caused was extremely painful. Visine for contacts would be a good choice with my new contacts. (sic) I was terribly wrong."**

Reference: 21 CFR 820.198(c)

Supporting Evidence and Relevance:

According to section 12 of the firm's QUALITY ASSURANCE COMPLAINT INVESTIGATION & CLOSURE FOR PCH ACQUIRED PRODUCTS WITHIN BABY, BEAUTY, AND CHC GLOBAL BUSINESS UNITS, QSP-000324, Rev. 1 **(Exh. 20)** '(b) (4)
(b) (4)

Note: Regarding the previous paragraph, according to Mr.(b) (4) there is no formal mechanism for trending complaints by the firm's Benefits Risk Management/Global Product Safety Group ("BRM/GPS") including the identification of thresholds when complaint trends would trigger investigations.

Mr. Anderson explained that, basically, the Automatic System Closure (a.k.a. "AUTOCLOSE", a.k.a. "System Closure") is an algorithm within the firm's electronic Product Quality Management System (PQMS) which, based on certain fields being populated, results in automatic closure of the complaint. If the "autoclosed" complaint also represents an Adverse Event (AE), it will be reviewed by the firm's Benefits Risk Management/Global Product Safety Group ("BRM/GPS") to determine whether the complaint represents an event requiring a regulatory submission (e.g. Medical Device Report) or further investigation. If the BRM/GPS concludes no further investigation is necessary, the complaint remains closed, the manufacturing site is not notified of the complaint, and no investigation is performed. A summary of the five complaints cited in the observation appears in the chart below.

Tracking No.	Lot/Control No.	Event Description
30000084439	0107101	"consumer (sic) used product and had allergic reaction had to go to ER, had burning and halo sight, even had hearing problem, has been told that a perservative (sic) in our product that can cause a (sic)

		allergic reaction by opthomologist (sic)"
30000084307	0106353	"cons. (sic) put 3-4 drops in her left eye and immediately had a burning sensation and blurred vision/flushed eye out with water and did not call HCP/sx's"
30000083712	0107262	"Consumer used product and developed a burning sensation in eyes."
30000103643	0107307	"was (sic) using product and the product got on his cheeks and he said his face became swollen and red and it burned . he (sic) still has the burning but it is getting better"
30000104112	Not available	"The burning the drops caused was extremely painful. Visine for contacts would be a good choice with my new contacts. (sic) I was terribly wrong."

According to Mr. (b) (4) none of the cited complaints were identified by the BRM/GPS group as requiring further investigation and remained "autoclosed" within the firm's PQMS system. Mr. Anderson stated that none of the cited complaints were investigated by the manufacturing site.

The event described in one complaint (30000084262, not cited in this observation) was recognized internally as requiring investigation during trending of monthly reports by the manufacturing site (not BRM/GPS). However, no root cause of this event was identified and there was no evidence in the investigation report (QAR 07-00287, **Exh. #26**) that product design was considered as a potential source of the event (refer to FDA 483 Observation #4 for additional discussions of this subject).

Additional documents collected during my discussions of FDA 483 Observation 1 appear as **Exh. 27.**

Discussion with Management:

I explained that I would have expected the cited complaints to have been investigated. I asked whether Mr. Foster and Mr. (b) (4) thought it would be beneficial to be aware of a complaint documenting that a consumer had to visit an Emergency Room for the symptoms described in the first cited complaint. Mr. (b) (4) stated that one patient going to the ER for the cited symptoms may not trigger an investigation because it may not represent a trend requiring investigation. Mr. Foster stated that this would be useful information and that further investigation was warranted in his opinion.

Prior to the conclusion of the inspection, Mr. Foster stated that changes were being discussed to ensure "serious complaints" would be provided for investigation to the manufacturing site by BRM/GPS. "Serious complaint" is defined in section 5.0 of the firm's QUALITY ASSURANCE COMPLAINT INVESTIGATION & CLOSURE FOR PCH ACQUIRED PRODUCTS WITHIN BABY, BEAUTY, AND CHC GLOBAL BUSINESS UNITS, QSP-000324, Rev. 1 **(Exh. 20)** as

"[redacted (b) (4)] ." I explained that non-serious complaints (also defined in section 5.0 of **Exh. 20**, basically, anything not considered a "significant complaint") may also represent events requiring investigation.

OBSERVATION 2

The corrective and preventive action procedures addressing the investigation of the cause of nonconformities relating to product, processes, and the quality system were not complete.

Specifically, Quality Assurance Report (QAR) Procedure No. 2222, Version 4.0 used to investigate, review, and document deviations from product and process procedures, methods, specifications, etc., does not contain provisions to ensure product design activities are considered for investigation as a potential cause of product nonconformity where applicable.

Reference: 21 CFR 820.100(a)(2)

Supporting Evidence and Relevance:

Quality Assurance Report (QAR) Procedure No. 2222, Version 4.0 **(Exh. 28)** used to investigate, review, and document deviations from product and process procedures, methods, specifications, etc., does not contain provisions to ensure product design activities are considered for investigation as a potential cause of product nonconformity where applicable.

As discussed in Observation #4 below, the firm's Quality Assurance Report (QAR) 07-00287 **(Exh. 26)** documents "... an unusual number of complaints related to Adverse Events (AE) for Visine for Contacts Lot 0107101 ..." was identified during monthly trend analysis in November of 2007.

Although an investigation of manufacturing operations was performed in an attempt to identify the root cause of the events, the firm's Quality Assurance Report (QAR) Procedure No. 2222, Version 4.0 **(Exh. 28)** did not specify that product design activities also be considered for investigation as a potential cause of product nonconformity where applicable.

Additional documents collected during my discussions of FDA 483 Observation 2 appear as **Exh. 29.**

Discussion with Management:

Mr. (b) (4) agreed the cited procedure did not capture these requirements. Mr. (b) (4) believes the firm investigated design controls relating to these events, but did not adequately document these activities.

OBSERVATION 3

Not all data from quality data sources are analyzed to identify existing and potential causes of nonconforming product and other quality problems.

Specifically, adverse event complaint descriptions contained within monthly "ADVERSE EVENT REPORT FOR QUALITY CONTROL" reports used to communicate quality data regarding closed adverse event complaints (as determined by the J&J Benefits Risk Management/Global Product Safety Group) to manufacturing locations contain abbreviated adverse event descriptions. For example, the chart below contains descriptions of Visine for Contacts adverse event complaints "autoclosed" within the firm's electronic Product Quality Management System (PQMS) and descriptions of the same complaints contained within monthly quality reports provided by the Benefits Risk Management/Global Product Safety Group ("BRM/GPS"). The quality data contained within the PQMS event description was not captured for analysis by this manufacturing location's Corrective and Preventive Action system.

Local Ref. No.	PQMS Event Description	BRM/GPS Monthly Report Description
007550720A	"consumer (sic) used product and had allergic reaction had to go to ER, had burning and halo sight, even had hearing problem, has been told that a perservative (sic) in our product that can cause a (sic) allergic reaction by opthomologist (sic)"	"hypersensitivity"
007541148A	"Consumer used product and developed a burning sensation in eyes."	"eye irritation"
007761899A	"was (sic) using product and the product got on his cheeks and he said his face became swollen and red and it burned. he (sic) still has the burning but it is getting better"	"skin burning sensation" "swelling face" "erythema" "accidental exposure"

Reference: 21 CFR 820.100(a)(1)

Supporting Evidence and Relevance:

Exh. 30 is a summary of complaints representing all Visine for Contacts Adverse Event Reports received from 01/01/08 – 07/14/08. From this summary I selected six complaints to review complaint investigation activities (Tracking No.s 30000084307, 30000084439, 30000083712, 30000084262, 30000103643, and 30000104112). A hardcopy of each of these complaints appears as **Exhs. 31-36**, respectively.

Exhs. 37, 38 are monthly ADVERSE EVENT REPORT FOR QUALITY CONTROL reports representing Visine for Contact adverse event complaints reviewed by the firm's BRM/GPS group for the months of January and June of 2008, respectively. Mr. (b) (4) explained that these monthly reports are the only mechanism for the manufacturing location to become aware of adverse event complaints that the BRM/GPS group has not elevated for investigation.

A summary of the three complaints cited in the observation appears in the chart below. The chart provides the complaint event description as it appears in the electronic PQMS system v. what appears in the monthly ADVERSE EVENT REPORT FOR QUALITY CONTROL reports.

Local Ref. No.	PQMS Event Description	BRM/GPS Monthly Report Description
007550720A	"consumer (sic) used product and had allergic reaction had to go to ER, had burning and halo sight, even had hearing problem, has been told that a perservative (sic) in our product that can cause a (sic) allergic reaction by opthomologist (sic)"	"hypersensitivity"
007541148A	"Consumer used product and developed a burning sensation in eyes."	"eye irritation"
007761899A	"was (sic) using product and the product got on his cheeks and he said his face became swollen and red and it burned . he (sic) still has the burning but it is getting better"	"skin burning sensation" "swelling face" "erythema" "accidental exposure"

Discussion with Management:

I explained that the monthly ADVERSE EVENT REPORT FOR QUALITY CONTROL reports distill the PQMS system event description to sometimes as few as one word. I explained that there was quality data within the event descriptions contained in the PQMS system that was never communicated to the manufacturing location for analysis within its Corrective and Preventive action system.

I asked Mr. Foster and Mr. (b) (4) if they would react differently to an event description of "hypersensitivity" v. "consumer (sic) used product and had allergic reaction had to go to ER, had burning and halo sight, even had hearing problem, has been told that a perservative (sic) in our product that can cause a (sic) allergic reaction by opthomologist (sic)". Both gentlemen agreed the event description contained in the PQMS system contained valuable quality data and stated that they would react differently to these two event descriptions.

OBSERVATION 4

Adequate quality requirements that must be met by suppliers were not established.

Specifically, the Consumer/BRM Compliance Agreement for the Management of Drug Safety and Surveillance contains no specified requirements (including quality requirements) relating to expectations and deliverables associated with investigations of design control activities as a potential source of nonconforming product. For example, Quality Assurance Report (QAR) 07-00287 reports "... (b) (4) **" was identified during monthly trend analysis in November of 2007. The complaints involved red coloring near the eyes where the product came in contact with skin. QAR 07-00287 documents the investigation of these adverse events and concludes that "...** (b) (4) **" The conclusion of the GPS/BRM group investigation was "** (b) (4) **" There were no documented requirements (including quality requirements) provided to the GPS/BRM group with respect to expectations and deliverables associated with this investigation (e.g. review of design controls associated with the development of the original formulation).**

Reference: 21 CFR 820.50(a)

Supporting Evidence and Relevance:

According to page 2 of the firm's Quality Assurance Report (QAR) 07-00287 (**Exh. 26**) "... (b) (4) (b) (4) ..." was identified during monthly trend analysis in November of 2007.

Exh. 39 is a summary of complaints received against Visine for Contacts Lot 0107101 at the time of the cited investigation (as of 11/5/07). The chart below summarizes several of the Adverse Event (AE) complaints contained within **Exh. 30.**

Tracking No.	Event Description
30000066019	"Consumer used product and some ran down her cheeks. Made a red streak across her face and it started to burn and swell up."
30000066740	"used (sic) product and when the fluid came in contact with skin red streaks and burning was on side of face"
30000075441	"The drops that ran out of my eyes turned the skin on my face extremely red and burned"
30000077355	"Skin around eyes was painful an dburning (sic) red after use of product"

According to **page 8 of Exh. 26** ("CONCLUSION") ".. (b) (4) (b) (4) (b) (4) ."

According to Mr. (b) (4) the GPS/BRM group was tasked with investigating whether the design of the product (e.g. formulation constituents) or the design controls used to develop the product (e.g. characterization of the user population, design validation, etc.) may have contributed to the events. According to Mr. (b) (4) these activities were discussed with Charles P. Wajszczuk, M.D., Senior Director, Medical Safety Officer, J&J Consumer & Personal Products, Skillman, New Jersey on November 8, 2007. According to Mr. (b) (4) these discussions were not documented.

On April 21, 2008, Mr. (b) (4) received an e-mail from Dr. Wajszczuk (**Exh. 26, p. 10**) concluding "(b) (4) (b) (4)" I observed no evidence in the Quality Assurance Report (QAR) 07-00287 (**Exh. 26**) that the design of the product or design controls used to develop the product were ever investigated by GPS/BRM as a potential root cause of the events.

I asked to review the requirements (including quality requirements) provided by the firm to the GPS/BRM governing this investigation. Mr. (b) (4) provided a Quality Agreement entitled "Consumer/BRM Compliance Agreement for the Management of Drug Safety and Surveillance", QA-000193, Rev. 2 (**Exh. 40**). **Exh. 40** contains no documented requirements (including quality requirements) with respect to expectations and deliverables associated with investigations of design or design controls as potential sources of nonconforming product or other quality problems (e.g. review of design controls associated with the development of the original formulation).

Additional documents collected during my discussions of FDA 483 Observation appear as **Exh. 41.**

Discussion with Management:

Mr. [redacted] (b) (6) agreed the agreement did not capture these requirements. Mr. [redacted] (b) (4) believes the firm investigated design controls relating to these events, but did not adequately document these activities.

Pharmaceutical Observations
Quality System

OBSERVATION 5

Written procedures describing the handling of complaints do not include provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and a determination as to the need for an investigation of any unexplained discrepancy.

Specifically,

All product complaints maintained in the firm's electronic Product Quality Management System (PQMS) that meet Automatic System Closure ("AUTOCLOSE") criteria may not be evaluated or investigated by the Quality Unit to determine whether the complaints are related to product quality or require investigation into unexplained discrepancies. For example:

a. Complaint 30000101432, dated 5/28/08, for Visine (unnamed formulation), described burning of the eyes and a smell of chlorine following use. The complaint was not forwarded to the Quality Unit at the manufacturing site for investigation and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit.

b. Complaint 30000104929, dated 6/26/08, for Visine Tears described the loss of eyesight following use for three consecutive days. The complaint was not forwarded to the Quality Unit at the manufacturing site for investigation and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit.

c. Complaint 30000105985, dated 7/7/08, for Visine A.C., described the complainant's eyes as red, hot, and swelling shut following use. The complainant questioned whether there was

something wrong with the lot and stated three other family members experienced burning following use of the product. The complaint was not forwarded to the Quality Unit at the manufacturing site and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit.

Reference: 21 CFR 211.198(a)

Supporting Evidence and Relevance:

As observed by Investigator Ruff in FDA 483 observation 1 for the medical device, Visine for Contacts, we also observed that all products, both medical device and pharmaceutical, are subject to the firm's QSP-000324, Rev. 1, section 12, QUALITY ASSURANCE COMPLAINT INVESTIGATION & CLOSURE FOR PCH ACQUIRED PRODUCTS WITHIN BABY, BEAUTY, AND CHC GLOBAL BUSINESS UNITS **(Exh. 20).** The procedure indicates that, (b) (4) [redacted]

Review of summaries of all complaints from 4/16/08 through 7/16/08 revealed there were 51 pages of complaints (each summarized in 1-3 lines) for the 3 month timeframe evaluated **(Exh. 42)**. Representative complaints were selected for review and revealed that some documented complaints of adverse events for pharmaceutical products, which may also have quality relevance were not reviewed, evaluated or investigated by the Quality Unit at the manufacturing site due to the "autoclose" procedure.

(b) (6) [redacted] Compliance and Validation Manager explained that if the call center did not determine that a quality evaluation was required by the manufacturing site for a potential adverse event report, a secondary review by a physician in the firm's Benefits Risk Management/Global Product Safety Group ("BRM/GPS") could also result in the complaint being forwarded to the manufacturing site's Quality Unit for further evaluation. If both the call center and the BRM/GPS physician determined that no further investigation was necessary, the complaint remained "autoclosed." The manufacturing site was not notified of the complaint and no investigation was performed. I reviewed a number of the complaint reports with Mr. Foster. Three representative examples of product complaints for which Quality Unit review and investigation were not conducted are provided with brief case descriptions.

a. Complaint 30000101432, dated 5/28/08, for Visine (unnamed formulation) **(Exh. 43)**, described burning of the eyes and a smell of chlorine following use. The complaint was not forwarded to the Quality Unit at the manufacturing site for investigation and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit. The initial report from the call center notes, "consumer purchased visine and the seal was intacted and when friend put in his eye it burned and smelled like chlorine. Ref immediately to poison control. didnt fill out MI sceen/didn't have information" The formulation and lot number of the product were not obtained and the complaint was not forwarded for quality review or follow-up at the manufacturing site.

It was noted that a similar complaint, dated 6/17/08, approximately two weeks later was received as complaint 30000103750 for Visine Advanced Relief described "AE reported via CVS Risk Management Dept. Experienced severe reaction which caused his eyes to water excessively. Had a bleach smelling chemical. Letter from CVS includes: It appears that your product according to claimant had a bleach smelling chemical that caused him an alleged eye injury." **(Exh. 44)** The second page of the report includes the investigational findings from the manufacturing site. There was no indication why this complaint from CVS received quality follow-up at the manufacturing site and the other consumer complaint two weeks earlier did not. I discussed the inconsistency with Mr. Foster. He stated that they would address this issue as part of the system corrections for complaint handling.

b. Complaint 30000104929, dated 6/26/08, for Visine Tears described the loss of eyesight following use for three consecutive days **(Exh. 45).** The complaint was not forwarded to the Quality Unit at the manufacturing site for investigation and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit. The initial report notes, "consumers mother called in and said her daughter used the product 06/20, 06/21, 06/22 and her eyes were burning her the whole time but she kept treating the burning with the product and on the last day she lost her eyesight in her right eye. she went to the emergency room at 3 o'clock in the morning on 06/24. they ran tests and referred her to an eye doctor who said that her cornea had been severly burnt. almost as if by a chemical." **(Exh. 45 pp. 3-4).** The complaint had not been reviewed evaluated by the manufacturing site's Quality Unit and was automatically closed by the system. There was no investigation conducted. Mr. Foster agreed that the complaint should have been evaluated by the site and follow-up conducted. He stated that the promised system corrections would address this issue. He stated that as an immediate corrective action, the site would receive all serious adverse event reports to allow Quality personnel to determine if follow-up to the complaint was required. Investigator Ruff and I also discussed the potential for repetitive non-serious events to be indicators of quality issues. Mr. Foster agreed and stated that they would address the issue as part of their systemic corrective actions regarding complaint handling.

c. Complaint 30000105985, dated 7/7/08, for Visine A.C. **(Exh. 46)**, described the complainant's eyes as red, hot, and swelling shut following use. The complainant questioned whether there was something wrong with the lot and stated three other family members

experienced burning following use of the product. The complaint was not forwarded to the Quality Unit at the manufacturing site and was automatically closed in PQMS. The complaint was not reviewed or investigated by the Quality Unit. The initial report notes, "My husband used it last night and his eyes swelled almost shut. It also turned very red an hot. Could there be something wrong with this lot. Three people in my family used and said it burnt." **(Exh. 46 p. 4)** Mr. Foster and Mr. [redacted] (b) (6) confirmed that the complaint was not evaluated at the manufacturing site and was "autoclosed" as noted on the complaint report **(Exh. 46 p. 1).** Mr. Foster stated that he agreed that there should be Quality Unit review of such complaints. We discussed the complainant's question regarding the quality of the lot and discussed the call center and the reviewing physician's failure to identify it as a potential quality complaint requiring follow-up.

Discussion with Management:

During the inspection and at the exit meeting we discussed the need to evaluate all potential quality data in order to make decisions about product risk, necessary corrective actions, and potential product impact. We questioned the design of the complaint handling system which failed to provide some quality complaints to the manufacturing site for investigation. We discussed the initial evaluation of the complaints by the call center located in Pennsylvania to determine if quality, safety or both should evaluate the complaint. We discussed the use of the reviewing physician for reports of adverse events to make a secondary evaluation of the need for a quality investigation and the lack of review of such reports by the Quality Unit. Finally we addressed the process of "autoclose" by the computerized system for adverse event complaints. The "autoclose" process resulted in the failure of the Quality Unit to evaluate some product quality complaints. Following multiple discussions during the inspection, Mr. Foster provided a summary of the concerns raised during the inspection an action plan **(Exh. 47).** He agreed with our findings and stated that there were complaints that should have been further evaluated by their site. As an immediate corrective action, the firm committed to notification of QA of all "serious AE" reports, added quality input on decisions to perform quality investigations on adverse event reports and committed to investigations of all MDRs. He also stated that our concerns would be discussed with corporate quality personnel to determine if other sites had similar deficiencies. We discussed the need for systemic corrections despite the planned site closure due to the potential risk to products and customers. Investigator Ruff and I discussed our plan to recommend inspection of the other locations that were discussed during the inspection such as the call center and the BRM/GPS sites. Mr. Foster stated that they would provide additional information regarding corrective actions in the firm's written response to the FDA 483.

OBSERVATION 6

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, a concurrent process validation study was conducted for (b) (4) (b) (4) as per Process Validation Protocol (b) (4) 03, Revision 3, approved by the Quality Unit on 8/16/06. The second (b) (4) validation batch, (b) (4) manufactured 1/8/08, did not meet the validation protocol acceptance criteria for (b) (4) assay for the six batch complete samples obtained, (25.0, 25.0, 25.0, 25.0, 25.0, 25.1 mg/g; validation criteria (b) (4)). No root cause for the low (b) (4) results was determined in investigation 08-00031, dated 4/11/08. The batch was released to the finished product contract manufacturing site on 1/15/08. The (b) (4) (b) (4) were manufactured using the bulk solution which did not meet the validation protocol acceptance criteria and were released on 5/28/08.

Reference: 21 CFR 211.110(a)

Supporting Evidence and Relevance:

Review of QAR 08-00031, dated 4/11/08, **(Exh. 48)**, revealed that (b) (4) assay results for batch 04280-008 did not meet the validation protocol acceptance criteria for the bulk solution. The protocol, (b) (4) Rev. 0, dated 8/16/06 **(Exh. 49 p. 14)** identifies a bulk solution batch complete assay range of (b) (4) The investigation report noted that the following results were obtained:

Beginning of transfer:	25.0 mg/g
After (b) (4) bs:	25.0 mg/g
After lbs:	25.0 mg/g
After lbs:	25.0 mg/g
After lbs:	25.0 mg/g
End of transfer:	25.1 mg/g

The bulk solution is used for the further manufacturing of (b) (4) (b) (4) McNeil PPC, Inc. contract manufactures the bulk solution which is then shipped to a contract soft gelatin manufacturer for (b) (4) The protocol noted, "Process Validation will be conducted concurrently for (b) (4) in part due to the infrequency of production, (b) (4) lots per year. (b) (4) will be released for shipping to the encapsulating facility based on the

batch complete sampling results specified in the protocol **(Exh. 49 p. 6).** I, Investigator McCaffery requested any documentation from CDER to confirm agreement with conducting concurrent validation for the reasons stated. No documentation was provided.

(b) (6) Senior Validation Specialist, Quality Operations stated that the product and process were transferred from the (b) (4) facility. There was one unsuccessful full scale qualification batch originally manufactured which also had a low assay value **(Exh. 51 p. 14).** A root cause was determined as undissolved material was found in the vessel discharge piping and was determined to be based on design differences and the nitrogen purging process. Corrective actions were implemented and three successful full scale qualification batches were manufactured according to Ms. (b) (6) A concurrent process validation protocol was then written and approved 8/16/06 **(Exh. 49).** The first concurrent validation batch, (b) (4) was successfully manufactured as described in the Process Validation Report, (b) (4) **(Exh. 50 p. 6).** The second concurrent validation batch, (b) (4) was the subject of QAR 08-00031 **(Exh. 48).** Although the low assay results were investigated, the root cause could not be determined. I requested historical data from the technical transfer of the product and evaluation of the process differences. Limited information and data was available. The investigation report concluded **(Exh. 48 p. 12)**:

(b) (4)

We discussed the lack of process knowledge and understanding that resulted from the limited manufacturing experience, lack of historical data, and concurrent validation activities. I asked if the process was considered validated despite the failures. I also asked what the maximum validated fill volume was for the finished product. No answers were provided. They stated that (b) (4) contract soft gelatin encapsulator, (b) (4) indicated that the fill volume would be increased to compensate for the low assay of the bulk solution. I stated that I had numerous concerns regarding the concurrent validation activity, lack of process knowledge, and the failure to fully investigate the issue and obtain all historical data. Mr. Foster explained that they had requested some of the information but had not obtained it. Because they contract manufactured the product, they did not have access to all of the historical documentation. He stated that he understood the concerns and would try to get additional information.

The bulk solution batch which failed to meet the validation acceptance criteria was released in quarantine status by McNeil PPC, Inc. change control 08-009 to (b) (4) contract soft gelatin contract manufacturer, (b) (4) on 1/15/08 **(Exh. 52).** The product was filled into (b) (4) (b) (4) and was released by (b) (4) on 5/28/08 **(Exh. 53).**

During the inspection, additional information was obtained from (b) (4) An amendment was written to the process validation report, dated 7/23/08 **(Exh. 54)** which indicated that due to the differences in manufacturing between two sites, the normal process variation and acceptable batch QAALs may differ from the (b) (4) manufacturing site to the McNeil manufacturing site. They identified potential sources of variability during the inspection based on the additional data and information which was not previously provided by (b) (4) during the technical transfer. Ms. (b) (6) provided a summary of the batch results to support the new information that they had obtained **(Exh. 55)**. I discussed the need to document the process knowledge and understanding so that in the upcoming transfer to its new manufacturing site, the information would not be lost. Mr. Foster stated that he understood the concern and also the issues discussed regarding concurrent validation activities.

REFUSALS

There were no refusals encountered during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

Throughout the inspection, Investigator Ruff and I discussed our findings with site management on a daily basis (Mr. Foster and/or Mr. Pera). We had multiple discussions about the complaint handling system, the need for systemic corrections, procedural deficiencies and the outdated practice of using concurrent validation. Mr. Pera and Mr. Foster provided commitments for immediate corrective actions where possible and provided commitments for additional corrective actions to be documented in the firm's written response. They stated that they understood our concerns and promised timely corrections.

SAMPLES COLLECTED

No samples were collected during the inspection.

VOLUNTARY CORRECTIONS

During the inspection, two immediate corrective actions were initiated in response to our observations. The first corrective action was a change in procedure on the Visine packaging line. I, Investigator McCaffery observed multiple containers of various colors (green, red, yellow, clear, opaque) being used for material rejected during the Visine packaging process by the checkweighers and at other points on the line in which the vision systems or weighing systems remove product automatically. The bins were not clearly marked for their purpose. The process of reworking the rejected units was not described in the written procedures and there was no documentation of the reworked goods. During the inspection, some modifications were made to SOP 4671, version 6 to version 7 to include modifying step 4.09 to specify that yellow containers would be used to collect units blown off the line. The cartons would be re-opened and cartons discarded. The bottles would

be examined visually and if found acceptable, placed in a green bin for rework **(Exh. 56).** The other extraneous rework containers were removed from the line.

The second immediate corrective action was the "ACTION PLAN" **(Exh. 47)** provided by Mr. Foster to address the complaint handling system issues as discussed in FDA 483 observations 1 and 5. Mr. Foster also promised additional corporate corrective actions to be included in the firm's written response.

EXHIBITS COLLECTED

1. List of attendees at the 7/31/08 exit meeting, 1p.
2. Letter describing site closure and product transfer plans, dated 7/8/08, 3pp.
3. Business structure for consumer products, 1p.
4. Summary of batches manufactured since 11/20/06, 3pp.
5. Summary of Visine batches manufactured since 11/20/06, 1p.
6. Site blue print, 1p.
7. Visine operation process description, dated 7/21/08, 1p.
8. Visine filling line parts list and diagram, 2pp.
9. Daily summary of personnel interviewed, 8pp.
10. McNeil PPC, Inc. organizational charts, 11pp.
11. Corporate organizational structure, 2pp.
12. Vistaril® (hydroxyzine pamoate) recall information, 62pp.
13. QAR 07-00320, Visine AC 0.5 oz., lot# 661-1-314/VB07106, 88pp.
14. QAR 08-00011, Visine AC 0.5 oz., lot# 661-1-315/VB08006, 118pp.
15. SOP 3067, Version 6, Packaging Gowning Procedure, dated 11/16/07, 4pp.
16. SOP 2312, Version 7, Parsippany Production Dress Code, dated 12/20/07, 8pp.
17. QAR 08-00055, Visine LR, lot# 663-1-120/VB08023, 48pp.
18. QAR 08-00084, Visine Contacts, lot# 667-1-065/VB08043, 13pp.
19. Complaint Audit Report-redacted by firm, dated May 2008, 9pp.
20. QSP-000324, Quality Assurance Complaint Investigation & Closure for PCH Acquired Products within the Baby, Beauty, and CHC Global Business Units, 11pp.
21. BRMC-SOP-802-01, BRM (Consumer) Handling Product Complaints with Adverse Event Reports (US Process), dated 1/7/08, 8pp.
22. QSP1037, Quality Assurance GMP Audit Requirements, dated 11/21/06, 7pp.
23. SOP 2378, Version 5.0, Annual Records Review, dated 8/13/07, 5pp.
24. SOP 2958, Version 3.0, Quality System Requirements for Medical Devices, dated 1/18/08, 4pp.
25. Visine for Contacts, ½ fluid oz. carton, 1p.
26. QAR 07-00287, Visine for Contacts, 0.5oz., lot# 0107101/VB07028, 10pp.

27. Additional Visine for Contacts exhibits collected, 34pp.
28. SOP 2222, Version 4.0, Quality Assurance Report, dated 2/11/08, 10pp.
29. SOP 4524, Version 3.0, Administration of the (b) (4) Commitment Tracking System, dated 11/8/07, 40pp.
30. Visine for Contacts complaints summary from 1/1/08-7/14/08, 3pp.
31. Complaint 30000084307, Visine for Contacts, 2pp.
32. Complaint 30000084439, Visine for Contacts, 2pp.
33. Complaint 30000083712, Visine for Contacts, 2pp.
34. Complaint 30000084262, Visine for Contacts, 2pp.
35. Complaint 30000103643, Visine for Contacts, 2pp.
36. Complaint 30000104112, Visine for Contacts, 2pp.
37. Adverse event report for Visine for Contacts from 1/1/08-1/31/08, 1p.
38. Adverse event report for Visine for Contacts from 6/1/08-6/30/08, 9pp.
39. Visine for Contacts, 0.5oz., lot# 107101, 1p.
40. QA-000193, Consumer/BRM Compliance Agreement for the Management of Drug Safety and Surveillance, dated 7/18/08, 16pp.
41. Additional Visine for Contacts exhibits, 35pp.
42. Summary of Complaints from 4/16/08-7/16/08, 51pp.
43. Complaint 30000101432, Visine (formulation unnamed), 7pp.
44. Complaint 30000103750, Visine Advanced Relief, 7pp.
45. Complaint 30000104929, Visine Tears, 7pp.
46. Complaint 30000105985, Visine A.C., 10pp.
47. Action Plan, 1p.
48. QAR 08-00031, (b) (4) 2pp.
49. (b) (4) Rev. 0, Process Validation Protocol for (b) (4), Formula (b) (4) dated 8/06, 18pp.
50. (b) (4) Process Validation Report for (b) (4) Formula (b) (4) (b) (4) dated 4/08, 37pp.
51. (b) (4) Process Qualification Report for (b) (4), Formula (b) (4) (b) (4) Pound Batch, dated 7/05, 15pp.
52. Quality Change Control 08-009, (b) (4), 3pp.
53. Memo from (b) (6) regarding (b) (4) release dates for (b) (4) lot# 87P400A, dated 7/29/08, 1p.
54. PVAL-77-07-03.2a, Process Validation Report Amendment for (b) (4), Formula (b) (4) dated 7/08, 3pp.
55. (b) (4) Assay vs. Batch Yield graph, 1p.
56. SOP 4671, Version 7.0, Visine Secondary Packaging Checkweigher Operator, dated 7/10/08, 6pp.

ATTACHMENTS

- FDA 482, Notice of Inspection, dated 7/7/08, issued to [redacted] (b) (6), Compliance Validation Manager by Investigator McCaffery, 1p.
- FDA 482, Notice of Inspection dated 7/14/08, issued to Robert J. Foster, Director Quality Operations to add Investigator Robert G. Ruff to the inspection, 1p.
- FDA 483, Inspectional Observations, dated 7/31/08, issued to Roy J. Pera, Director of Operations, Site Leader, 5pp.

Erin D. McCaffery, Investigator

Robert G. Ruff, Investigator