McNeil
Healthcare, LLC

February 5, 2010

Ms. Margarita Santiago
Compliance Officer
U. S. Food and Drug Administration
466 Fernández Juncos Ave.
San Juan, PR 00901-3223

Subject: FDA Inspection: October 22, 2009 – January 8, 2010

Ms. Santiago:

During October 22, 2009 to January 8, 2010, a general GMP inspection was conducted at the McNeil Healthcare, LLC, Las Piedras facility. At the end of the inspection, January 8, 2010, a Form FDA-483 was issued with seven (7) observations. Attached are the observations and the corresponding response.

McNeil acknowledges the concerns raised by the FDA in the Form 483. McNeil is taking this issue very seriously and has already started to implement corrective and preventive actions. We are confident that the corrective and preventive actions detailed in this response address the FDA's concerns and will improve our Quality, Production and Laboratory Control Systems.

The Quality System components of this corrective action plan, which are detailed in this response, will be implemented systemically throughout McNeil.

We trust that the actions described in this response convey our commitment to address the inspection observations in a comprehensive manner. In order to ensure timely completion of all committed corrective actions, McNeil will be implementing a (b) (4) Senior Management Review to oversee progress against these actions. This review will ensure appropriate resources and priorities are in place. The review will include all impacted groups associated with these actions and will be led by the Vice President Quality Assurance OTC and the Vice President North America Supply Chain.

We thank Mr. José R. López and Ms. Raquel González for their professionalism during the inspection.

Attached please find detailed responses to the Form 483 observations from the inspection conducted in our facility.

Should you have any other questions, please contact me at (215) 273-8726.

Sincerely,

Robert Miller
VP QA GLOBAL OTC

Saribel Estrada
Quality Site Leader

Desk copy: Ms. Maridalia Torres, Mr. José R. López and Ms. Raquel González

OBSERVATION 1

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning bacteriological contamination and significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically,

On 2008, your firm received a heightened number of uncharacteristic musty odor consumer complaints for Tylenol Arthritis Relief Caplets (TAR) lots 08BMC013 (approximately 27 complaints) and 08BMC020 (approximately 49 complaints). However, no formal investigation was conducted even though your firm received over eight (8) complaints associated to gastrointestinal adverse events reports. Although organoleptic examination confirmed the presence of the odor in September 2008, your firm concluded that based on macroscopic and microscopic examination the odor does not originate from the presence of microorganisms in the product or container closure. Your quality unit failed to conduct additional testing to evaluate the possibility of chemical contamination or other change or deterioration in the distributed drug product. No field alert was generated in 2008 for the distributed drug product.

Afterward, your firm received atypical trends of uncharacteristic odor complaints and associated adverse event reports for lots 09BMC034, 09CNC036, and 09CMC040 since April, June, and August 2009 respectively, but the trend was not discovered until 08/03/2009. A Contract Operations Quality Management (COQM) Investigation Report (b) (4) was generated on 09/17/2009. A field alert was not initiated until 09/18/09 and a recall was initiated on 12/04/09 during the current inspection.

Response 1:

McNeil Consumer Healthcare acknowledges that the processes that were in effect during this investigation did not allow for timely reporting of this issue. The NDA Field Alert procedure, SOP (b) (4) at the time, did not specifically include complaint trending as a trigger for filing a NDA Field Alert. While that NDA Field Alert SOP required that McNeil notify FDA via a Field Alert within 3 days of awareness of various other triggers, complaint trending was not one of those triggers. As a result, McNeil has modified the reporting requirements of the NDA Field Alert SOP (b) (4) to now require that McNeil will file a Field Alert Report within 3 days of awareness of a complaint trend where potential bacteriological contamination and significant chemical, physical, or other change or deterioration in a distributed product cannot be ruled out. In addition, the (b) (4) procedure, SOP (b) (4) has also been modified to require escalation of complaint trends to management. The modifications to these procedures will ensure that NDA Field Alert reports get submitted to FDA within three working days of receipt of information concerning bacteriological

contamination and significant chemical, physical, or other change or deterioration in a distributed drug (see corrective actions #6 and #7 below).

2008

On August 13, 2008 and August 15, 2008, during consumer complaint trending analysis, an atypical number of complaints for uncharacteristic odor for two specific lots (08BMC013, and 08BMC020) of TYLENOL® Arthritis Pain Caplets (TAR) packaged in EZ Open 100-count bottles was identified. As per procedure, (b) (4) (b) (4) this trend observation was escalated to supervisory staff within 24 hours, however, (b) (4) occurred on 09/02/08 because the SOP did not require a more rapid escalation related to these types of events.

Based on this timing gap, SOP (b) (4) has been updated to include escalation to ensure that NDA Field Alert requirements are met (see corrective action #7 below).

The outcome of this first Notification to Management meeting was to immediately cease distribution of these two lots (08BMC013, 08BMC020) showing the atypical uncharacteristic odor trend and to initiate a cross-functional investigation

The specific components of the 2008 investigation included the following:

1. Microbiological testing of complaint and retain samples from these two lots.
2. The creation of an (b) (4) to better understand the magnitude and frequency of the atypical odor when evaluating returned patient complaint samples. The (b) (4) was composed of (b) (4) from (b) (4) and (b) (4)
3. A review of impacted lot batch records, including all in-process and release data, at the site of the tablet manufacturer (McNeil in Las Piedras) and at the (b) (4)
4. A review of all other TAR-100 count batches to determine if the atypical uncharacteristic odor complaints were widespread.

Based on the nature of specific complaint verbatims mentioning "mold" or "moldy", microbiological testing was performed on the QC retains and returned complaint field samples. The specific testing included (b) (4) and (b) (4) All microbiology results were negative for mold and fungi, indicating that the cause of the uncharacteristic odor was not due to the presence of microbiological organisms.

In addition, the (b) (4) that was convened to evaluate the issue concluded that the odor in the returned complaint sample was (b) (4) and (b) (4)

A review of the Las Piedras manufacturing batch records and the (b) (4) records for both lots did not identify a root cause for the uncharacteristic odor.

A review of the complaint profile determined that the presence of the specific uncharacteristic odor was isolated to these two lots of TAR-100 EZ Open. The level of adverse event reports seen for uncharacteristic odor was not atypical for these two lots when compared to the baseline rate for TAR.

After 10/08 the level of uncharacteristic odor complaints significantly decreased (three complaints each in 11/08 and 12/08 for these two lots). There were only 7 additional complaints for these 2 lots during first quarter of 2009 and the complaint trend returned to baseline.

Based on the findings from this investigation, it was concluded that the complaints were limited to these two specific lots of TAR-100 EZ Open; that they were (b) (4) and (b) (4) in nature; that they were not due to the presence of microbiological organisms; and that they were not indicative of a product contamination issue.

2009

During third quarter 2009, McNeil implemented (b) (4) complaint reviews. This review process, involving senior leadership from (b) (4) and (b) (4) identified another atypical trend for second quarter 2009 for TAR-100 EZ Open. In preparation for the (b) (4) held in August 2009 it was determined that two lots of TAR manufactured in 2009 showed a trend in uncharacteristic odor complaints (09BMC034 and 09CMC036). As part of the complaint management process improvements, the (b) (4) complaint trend review process will now identify these trends earlier (see corrective action #3 below).

Per the (b) (4) procedure, SOP (b) (4) (b) (4) was conducted on August 3, 2009. At that meeting, the following next steps were defined:

1. Immediately cease distribution of these two lots (09BMC034 and 09CMC036) and further evaluate this atypical uncharacteristic odor trend. Stop distribution notices were issued for the first two lots (09BMC034 and 09CMC036) on 08/03/09 and then subsequently a third lot (09CMC040) on 09/06/09 when similar complaints were received.

2. Review impacted lot batch records and all in-process and release results generated at McNeil Las Piedras and at (b) (4)

3. Conduct analytical and microbiological testing of retains and returned complaint samples.

4. Investigate other non-traditional technologies to better understand the cause of the uncharacteristic odor.

5. Expand the investigation to include the two previous lots of TAR from 2008 due to the similarity of these complaints to those previously identified in August 2008.

As part of the investigation, (b) (4) a review of the (b) (4) and (b) (4) batch records for these lots from Las Piedras and (b) (4) respectively, was conducted. In addition, a review of the (b) (4) and procedures, product complaint history, complaint/retain samples and environmental data was conducted. There was no evidence that any of these sites/areas contributed to the atypical odor. At this time, it was discovered that the five product lots (two 2008 product lots and three 2009 product lots) of TAR-100 count, which generated the majority of "musty/moldy" complaints, exclusively, shared two common shipments of bottles from (b) (4) to (b) (4)

Based on these new complaints and the similarities to those seen in 2008, McNeil expanded the investigation and pursued assistance from an external expert that could support us in the identification of the source of the odor. Based on this, we identified (b) (4) an external forensic laboratory with unique testing capabilities to assist us in this investigatory process. This forensic laboratory is highly specialized and uses non-traditional, highly sensitive analytical equipment and methodologies. On 08/31/09, samples were sent to (b) (4) to determine if the odor could be attributed to a specific chemical. On 09/11/09, (b) (4) identified 2,4,6 tribromoanisole ("TBA") as the likely cause of the uncharacteristic odor.

Thus, for the first time, McNeil was able to identify the presence of TBA in the complaint sample of a marketed product lot. The level of TBA seen in the returned complaint samples tested has ranged from (b) (4) As a result, McNeil initiated a Field Alert on 09/18/09. Since the time of this first Field Alert, there have been additional follow-up Field Alerts issued on 10/04/09, 10/13/09 and 11/03/09.

On 11/06/09, McNeil voluntarily recalled the five lots of TAR-100 EZ Open (08BMC013, 08BMC020, 09BMC034, 09CMC036, and 09CMC040) associated with this investigation. While the majority of the product complaints were associated with these 5 TAR-100 EZ Open lots (greater than 96%), when McNeil looked across all products, we did identify other "moldy/musty" odor product complaints. McNeil conducted additional testing and based on the results of this testing of other lots of returned complaints at the forensic laboratory, as well as the fact that we could not rule out that other TAR-100 EZ Open lots did not contain TBA, McNeil conducted an additional voluntary recall on 12/18/09, which included all lots of TYLENOL® Arthritis Pain packaged in the 100-count EZ Open Cap. A total of 59 lots were recalled.

McNeil recognizes the important role of appropriate complaint handling procedures in ensuring that trends are detected early and investigated thoroughly. We also acknowledge that opportunities exist to improve the Quality Systems involved with complaint trending, management oversight, investigations and reporting of significant

complaint trends via the Field Alert Report process. As a result, the following corrective actions have been implemented:

1. *Changes to complaint handling procedures:*
   McNeil will continue to investigate all complaints associated with our products. In addition, changes to the complaint handling procedures were made to include the following:

   (b) (4) have been developed, based on the severity or frequency, for trends above baseline levels for all products. This approach in trending will enhance our ability to identify and recognize trends for product families, product lots, and across product lines. This trending will enable the early identification of issues requiring an expanded investigation, management notification and prioritization of action. This trending will be done on a (b) (4) and (b) (4) by the McNeil quality organization.

   These changes to the complaint handling procedures are reflected in SOP 02-QA-CMP-001 "Requirements for Complaint Handling" attached to this response. Refer to Attachment I.

2. *Change to* (b) (4)
   We will expand our (b) (4) where we currently review complaints, to include a more extensive review of (b) (4) (b) (4) across all McNeil product lines, and will formally include (b) (4) representatives in addition to (b) (4) and (b) (4) This expanded process will be in place in April 30, 2010.

   These changes to the (b) (4) are reflected in SOP (b) (4) "Requirements for Complaint Handling" attached to this response. Refer to Attachment I.

3. *Changes to the site specific complaint review process:*
   The (b) (4) complaint trending review process has been expanded at McNeil's Las Piedras site and (b) (4) to include senior (b) (4) and (b) (4) management at the manufacturing sites and from the (b) (4) and will drive greater transparency and visibility to emerging complaint trends.

   In addition, complaint updates will be included at the (b) (4) McNeil Management Board meetings in order to drive greater visibility to complaint trends earlier at a senior level in the organization to ensure that they are given appropriate prioritization, attention, and action by the organization. Potential

trends will be determined based on the new trend alert limits established (see corrective action #1 above).

These changes to the complaint handling procedures are reflected in SOP (b) (b) (4) "Las Piedras Complaints Receipt and Investigation", and SOP (b) (b) (4) 'Handling Complaint Investigations for Third Party Contractors". Refer to Attachments II and III.

4. *New Quality Systems Management Review Process:*
   a. *Site Level:* A monthly quality indicators trending meeting and a (b) (4) (b) (4) process have been implemented at McNeil's Las Piedras site and at (b) (4) to monitor a series of key quality performance metrics (for example, complaint investigation closure time), emerging trends and corrective and preventive action plans. These processes ensure that site management reviews the suitability and effectiveness of the quality systems and resources. These review meetings will involve (b) (4) and (b) (4) leadership representatives and will provide appropriate site management leadership with important visibility to significant elements of the quality system. Critical items identified at the site level (b) (4) are escalated to senior leadership according to SOP (b) (4) (b) (4)

      The (b) (4) and (b) (4) will take place in February and April 2010, respectively. These new procedures (b) (4) "Las Piedras Track and Trending Quality Systems Review"; (b) (4) "Site Quality Systems Management Review"; (b) (4) (b) (4) are included in Attachments IV, V and VI.

   b. *Executive Level:* A (b) (4) Executive Board Quality System Review process will be implemented for the McNeil Management Board as well as relevant members of the quality organization and others as appropriate. This will include a review of all of our quality system elements with very specific management action plans established and tracked. This will provide senior management with the appropriate level of visibility and will ensure adequate support and prioritization of key issues.

      The first review will take place prior to April 30, 2010. The new procedure (b) (4) "Quality and Compliance Metrics Process") is included in Attachment VII.

5. (b) (4)
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This change to investigation procedures will be reflected in SOP (b) (4) "Deviation Investigation Policy" attached to this response. Refer to Attachment VIII.

6. *Change in Field Alert Reporting Requirements for Complaint Trends:* To help ensure more timely notification to FDA of NDA-Field Alert reports, the McNeil FDA Field Alert procedure has been revised to require the issuance of a Field Alert once a confirmed complaint trend where bacteriological contamination or significant chemical, physical, or other change or deterioration in a distributed drug product cannot be ruled out. This Field Alert will be issued within 3 business days of McNeil becoming aware of a complaint trend. In addition to timely communications, this interpretation of Section 314.81(b)(1)(i) and (ii), as codified in Title 21 of the Code of Federal Regulations, will likely result in more frequent communications with FDA.

   These changes to the Field Alert Reporting Requirements for Complaint Trends are reflected in SOP (b) (4) attached to this response. Refer to Attachment IX.

7. *Changes to the* (b) (4) The (b) (4) (b) (4) procedure, SOP (b) (4) has been enhanced and will result in the timely escalation of issues, including complaint trends, to management. The modifications to these procedures will ensure that NDA Field Alert reports get submitted to FDA within three working days of receipt of information concerning bacteriological contamination and significant chemical, physical, or other change or deterioration in a distributed drug. Refer to Attachment X.

OBSERVATION 2

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

Specifically,

A. *Since April 2009, your firm has received an increasing trend of uncharacteristic smell consumer complaints for Tylenol Arthritis Caplets (TAR). According to investigation* (b) (4) *initiated on 09/17/09, the trend was discovered on 08/03/09. Interim reports for investigation* (b) (4) *approved on 10/28/09 and 12/11/09 concluded that the most probable root cause for the uncharacteristic odor complaints is the proximity of chemically treated wood from pallets and empty bottles transported from the bottle manufacturer to the product* (b) (4). *However, since the date of the discovery, your firm did not extend the assessment of the event to the other products that received packaging components from the same supplier, such as Rolaids, which received over ten (10) musty-moldy odor consumer complaints. Your firm neither extended the assessment to other product that received similar complaints such as Tylenol Extra Strength (ESK), which received over thirty-nine (39) musty-moldy odor consumer complaints including three (3) adverse event reports. Even though the investigation has not identified a root cause for the event, your Quality Unit did not conduct an evaluation of other possible sources of contamination at your site, external contractors, and suppliers.*

Response 2A:

The nature of this investigation was such that it was very dynamic and extremely fluid. In the midst of this investigation, on almost a daily basis, we were learning something new about the source of this uncharacteristic odor, 2,4,6 tribromoanisole ("TBA"), the root cause of the TBA and how TBA could have entered into the supply chain. Each time our knowledge increased, we expanded our search for affected or potentially affected products.

While the investigation began on 8/3/09, the (b) (4) (b) was not initiated until 09/17/09 (see response 3a for corrective action). This investigation was based on the uncharacteristic odor complaint trends that were seen with the TAR-100 count EZ Open product. As part of this on-going investigation, a forensic laboratory (b) (4) determined that the chemical responsible for the uncharacteristic odor was TBA. The level of TBA seen in complaint samples has been at parts per trillion (ppt) levels which helps explain why the chemical was not detected during routine assay testing of the complaint samples conducted as part of the investigation.

From the literature, we learned that TBA is a breakdown product of 2,4,6-tribromophenol ("TBP") under certain environmental and handling conditions. TBA is formed from the degradation of TBP which is known to be used as a fungicide/preservative in wood sourced from a small number of countries. To date, TBP has not been found in any product samples tested. In addition, other related chemical compounds such as 2,4,6-trichlorophenol ("TCP") and 2,4,6-tricholoanisole ("TCA") have not been found either.

The identification of TBA as the source of the uncharacteristic odor enabled us to focus our search more specifically on "musty/moldy" complaints.

The investigation initially focused on the TAR-100 product due to the atypical number of complaints on this size as compared to other sizes of TAR. At this stage of the investigation, we reviewed multiple potential sources of contamination, including, (b) (4) (b) (4)

In October 2009, it was believed that the cause of the atypical complaint trend was associated with an isolated (b) (4) event at (b) (4) based on the following evidence:

- Over 96% of all complaints received from (b) (4) products were associated with TAR-100 EZ Open.
- Of these atypical complaints received from (b) (4) products that were associated with TAR-100 EZ Open, the overwhelming majority were from five specific lots of TAR-100 EZ Open.
- The 5 lots of TAR-100 EZ Open product, which generated the majority of "musty/moldy" complaints, exclusively, shared two common shipments of bottles from (b) (4) to (b) (4)
- Only TAR-100 EZ CAP uses this bottle/cap configuration at (b) (4)
- This bottle/cap configuration was used for another McNeil product from a different (b) (4) and that product did not show an atypical level of uncharacteristic odor attributed to "musty/moldy" complaints.

On November 6, 2009, McNeil also became aware of an emerging complaint trend associated with 2 lots of Extra Strength TYLENOL® Tablets (ESK) 325-count. A trend investigation (b) (4) was initiated on 11/11/09. This trend was identified when we reviewed all verbatims from the entire McNeil complaint database for all products from 1/07-11/06/09 using the specific term "musty/moldy" rather than uncharacteristic odor, taste, smell or appearance. Based on the fact that ESK-325 did not share common packaging components and suppliers with the TAR products, our investigation shifted into a different direction.

McNeil Consumer Healthcare received additional evidence in December 2009 for an atypical moldy/musty complaint trend for Rolaids® and initiated an investigation (b) (4) on 12/11/09. As we investigated Rolaids®, our investigation shifted again and expanded even further into another direction because of the lack of commonalities between Rolaids®, TAR and ESK. Specifically, Rolaids® did not share common formulas or formulation ingredients with TAR or ESK; or common packaging components with ESK; or common packaging site with TAR.

Throughout the course of the investigation, we traced TBA from certain bottles to wood pallets, and then, more specifically, to wood used to build the pallets that was sourced from (b) (4) and treated with TBP. Once we confirmed via analytical testing that these wood pallets were treated with TBP and were likely the primary cause of the TBA, we expanded our review to include other sites that had received these pallets.

We now know based on our investigation that the following conditions must be present before TBA can form:

- Presence of 2,4,6-tribromophenol ("TBP")
- Environmental conditions (temperature and humidity)
- Exposure time

The investigation has progressed considering these factors. We will update FDA on the progress of the investigation during the upcoming February 11, 2010 meeting.

The following corrective actions are being implemented:

1. *Changes to complaint review process:* McNeil recognizes that accurate categorization of complaints is critical to early complaint trend detection and remediation. Complaint categories facilitate accurate, timely, and actionable trending of complaints based on reported defect types. In order to further enhance our existing complaint handling/investigation processes and categorization the following corrective actions are being implemented:
   a. McNeil has reassessed all complaint categories with specific focus on categories that may require subjective interpretation. These categories have been redefined or combined to increase consistency in complaint defect coding and to ensure accuracy in trending. Accurate complaint categories will increase our ability to identify signals and trends faster, and to take action more effectively. All affected employees have been trained in these new complaint category definitions. The implementation of the new complaint categories will occur in February 2010.

   b. Concurrent to the development of the new categorization, the existing procedural requirements for quality investigators to evaluate and correct complaint categorization during daily file review have been reinforced through training. This training was completed in January 2010.

Relevant changes to the complaint review process are reflected in SOP (b) (4) (b) (4) 'Requirements for Complaint Handling". Refer to Attachment I.

2. *Remediation plan related to pallets:*
McNeil has also developed a remediation plan specifically directed to TBA and wood pallets. Based on our determination that TBP-treated wood used to make pallets are the primary cause of the TBA contamination, a remediation plan was immediately developed which included the following:
   A. All existing McNeil components from (b) (4) shipped on wood pallets, where the pallets could not be confirmed to be TBP-free are in the process of being destroyed (along with the pallets themselves).

   B. McNeil packaging lines and warehouses are being cleaned at all sites per a protocol developed in consultation with an external TBA expert. A similar cleaning procedure was also used at the component supplier, (b) (4)

   C. McNeil has required of all in-coming material suppliers that any pending shipments or future shipments are to be on heat-treated, TBP/phenol-free pallets. An inspection process has been instituted to evaluate incoming materials to confirm that they are only shipped on heat-treated pallets. In addition, documentation from wood/pallet suppliers is required to confirm that the pallets are TBP/phenol-free. Materials on pallets not meeting these requirements are not accepted into any McNeil facility. This process is also being rolled out to our (b) (4) Monitoring of compliance with this pallet requirement will be conducted.

B. *Your firm did not take an action with the distributed finished product, Motrin IB Caplet 24 count bottle, lot SDA149 which was manufactured using granulation lot SDA0001017 that was involved in the manufacture of two (2) recalled lots, SHC003 and SHC004 (Motrin IB Caplet, 8 caplet vial).*

On 11/20/08 your laboratory detected a failure in the stability dissolution results (stages 1-3 (S1/S2/S3)) of the three (3) months time point stability samples of lot SHC003. Investigation # (b) (4) *initiated on 11/20/08 included additional testing of retain compression samples of associated granulation batches. On 12/16/08 your laboratory obtained out of specification dissolution result for retain samples of the bulk compression lot SDA0000807 used in the manufacture of finished product lot SHC004. The investigation #* (b) (4) *revealed an extended downtime of* (b) (4) *and* (b) (4) *due to electrical failure and for* (b) (4) *due to a broken bag situation during the manufacturing drying process of granulation lot SDA0001017. This granulation lot was used for the manufacture of finished product lots SHC003, SHC004, and*

SDA149. Investigation # (b) (4) did not find a root cause for the dissolution failures.

On 03/10/09, your technical services department generated the Development Report No. (b) (4) to simulate the extended downtimes during the granulation drying and coating processes and to document the impact on the dissolution of Motrin IB Caplet. The development study concluded that the extended downtimes in granulation and coating have no impact on Motrin IB Caplet Dissolution. However, the actual conditions such as electrical failures, temperature and sensor problems, computer and instrument problems that may affect the process critical parameters during extended downtimes were not considered during the study.

Your Quality Unit documented an amendment to investigation (b) (4) through investigation (b) (4) initiated on 09/18/09 to include additional assessment and testing findings. On 09/22/09, an atypical value of 57% (minimum limit 55%) with a dissolution range of 57%-103% and an average of 96% were obtained in stage 3 for additional testing of compression bulk lot SDA0000808, which was manufactured using the granulation lot SDA0001017 (subsequently used for packaging lot SDA149). Even though the investigation did not identify a root cause for the atypical behavior of lots SHC003, SHC004 and SDA149, corrective actions were isolated to lots SHC003 and SHC004 and not to the distributed drug product lot SDA149. There is no assurance that the causes affecting these lots whether or not they are associated to a failure or discrepancy have been identified and corrected.

RESPONSE 2B

McNeil Consumer Healthcare's decision for not initiating field action on lot SDA149 was based on the investigation conclusions which indicated that the shared granulation was not the cause of the dissolution OOS results. McNeil did commit to monitor the dissolution of the lot through shelf-life with additional time points with the bulk compression lot retain samples. The lot has met specifications through multiple retain testing up to (b) (4)

However, after additional evaluation, McNeil has decided to recall batch SDA149 as a precautionary action.

We would like to further describe the events related to this investigation. An OOS dissolution result was obtained for Motrin® IB Caplets stability lot SHC003 (packaged in 8-count vials) on 11/20/08. The results did not meet specification at the (b) (4) (b) (4) A comprehensive root cause investigation was initiated on 11/20/08 under Quality Notifications (b) (4) and (b) (4) The situation was communicated to the FDA San Juan-District Office via phone within 3

working days on 11/25/08 date followed by a written NDA Field Alert on 11/26/08. The second lot, SHC004, was included in a NDA Field Alert on 12/18/08 after OOS results were obtained. Both lots were recalled.

As part of the investigation, dissolution testing on retain samples of the three bulk compression lots that shared the same granulation as lot SHC003 was conducted. Retain sample testing of two of these bulk compression lots (SDA0000806 and SDA0000807) did not meet specifications. The packaged lots (SHC003 and SHC004) which used these bulk compression lots were recalled. Testing of the retain samples from the third bulk compression lot (SDA0000808) met specifications. Subsequently, additional testing of bulk compression lot SDA0000808 and packaging lot SDA149 (24-count bottle) at (b) (4) showed dissolution results that met specifications. Lot SDA149 used several bulk compression lots including SDA0000808.

During the OOS investigation it was noted that all in-process and release test results as well as critical process parameters met specifications, however there were (b) (4) (b) (4) and (b) (4) (b) (4)

All Motrin® IB granulation lots processed from 2006 to 2008 that had extended granulation downtimes were reviewed. Three lots exhibiting downtimes considered as worst case granulation drying process conditions were selected for additional testing. These were selected considering the length of downtime and the step in the drying process when the downtime occurred. Retain samples were tested for dissolution and found to meet specifications.

In order to determine if the downtime seen during the granulation and coating is responsible for the OOS results, an experimental study was conducted. An experimental batch was designed to mimic the length of the downtime and the condition of the unit during the downtime, not the specific events which caused the downtime. The study did not reproduce the OOS results seen.

Based on the investigation performed, the historical stability data results for both vials and bottles, and the experimental test to explore downtime effects on the dissolution, it was concluded that although the root cause for the atypical behaviour of these lots cannot be determined; the granulation or coating downtimes cannot be considered to be the cause of the dissolution OOS results for SHC003 and SHC004.

In the future, as referenced in the corrective action commitment for observation #1, we are amending the current investigation SOP to require that if an on-going investigation has not confirmed an assignable root cause after (b) (4) (b) (4)

OBSERVATION 3

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

Specifically,

A. *On September 2008, your firm initiated a* (b) (4) *according to procedure* (b) (4) *to notify uncharacteristic musty smell/odor complaints observed since May 2008 for Tylenol Arthritis Caplets (TAR). Nevertheless, your Quality Unit failed to complete the form according to procedure requirements and include a summary of the investigation steps taken, results obtained, corrective and preventive actions taken, conclusions, and site quality recommendation regarding the proposed disposition of the product. The Notification to Management form was not routed to the Quality Site Leader or QA designee for approval.*

No other record such as an event investigation or (b) (4) *Investigation Report (CIR) was generated as required in procedure* (b) (4) *"Contractor Investigation Procedure" to document the conclusions of the investigation until 09/17/09, one year later.*

Response 3A:

We acknowledge that there were opportunities to improve the documentation process regarding (b) (4) at the time of the 2008 event. As a result, the (b) (4) procedure, SOP (b) (4) has been modified to further enhance the documentation process. In the future, this modified procedure will ensure that management gets notified in a timely manner and that documentation is appropriately captured.

In order to ensure improvements in investigation, documentation and the notification process, the following enhancements have been made to SOP (b) (4) (b) (4) These changes apply to the sites and (b) (4)

1. The Quality Site Leader or designee is responsible for ensuring a site level investigation has been opened for the event and referenced appropriately. A local deviation or product quality complaint investigation number is required for a (b) (4) meeting to be convened.

2. Complaint trends must be escalated.

3. The (b) (4) will be considered closed once there is approval from the Quality Site Leader or designee on the investigation conclusion and next steps associated with the event via a signed form. SOP (b) (4) is included in Attachment X.

B. *Procedures describing the handling of written and oral consumer complaints related to drug product are deficiently written and followed.*

- *Complaint procedures (b) (4) "Requirements for Complaint Handling" and (b) (4) "Handling Complaint Investigations for Third Party Contractors" were not followed to monitor complaint data for the identification of possible trends. For example, trends for numerous atypical complaints of uncharacteristic musty smell/odor for Tylenol Arthritis Relief Caplets (over 200 complaints) and Tylenol Extra Strength (over 39 complaints) were not detected nor investigated in a reasonable time period. For example, your firm received multiple uncharacteristic smell consumer complaints reports since May 2008, but the trend was not detected until August 2008. The criteria for the identification, notification, and documentation of trends have not been clearly defined in the procedures.*

Response

The information, actions and improvements surrounding the uncharacteristic smell complaint trend events and investigation for TYLENOL® Arthritis Pain Relief caplets and Extra Strength TYLENOL® Caplets are fully described in our response to observations 1 and 2A.

Specifically, the following corrective actions are being implemented to improve the identification, documentation and trending of consumer complaints:

- Changes to the complaint trending to enable early identification of issues through trend alert limits at the site or (b) (4) level.
- An expansion of the monthly complaint review at the site and (b) (4) to determine if an emerging complaint trend exists.
- Changes to the (b) (4) procedures to require escalation of confirmed complaint trends.
- Changes to the (b) (4) process for a more extensive review of trends.

- *Procedure (b) (4) "Requirements for Complaints Handling", defines a "confirmed complaint" as one which cannot exclude the manufacturing or packaging process as a potential source of the complaint issue. However, even though your firm received one-hundred and twenty-three (123) mix-up related complaints, from which you received over fifty (50) consumer complaint samples for evaluation, none of them have been confirmed. Your Quality Unit considered all complaints as isolated occurrences of unknown origin. Most of the complaint investigations conclude that there is insufficient evidence to absolutely determine that the reported condition occurred at McNeil, even though your firm has reported over twelve (12) mix-up event investigations. In addition, at least seventeen (17) event investigations, four (4) In-Process Assessment Forms (minor events) and four (4) manufacturing "clearance incidences" (detected during verification) have been reported, all of them associated to cleaning deviations.*

Response:

McNeil Quality Assurance Unit investigates all consumer product complaints as per SOPs (b) (4) "Requirements for Complaints Handling". As per procedure, a confirmed complaint is determined when the investigation cannot exclude the manufacturing or packaging process as a potential source of the complaint issue.

The FDA inspection period covered from 08/08 until 12/09, where a total of 123 mix-up complaints were reported. These mix-up complaints were not confirmed for the following reasons:

- After review of all 123 complaints, there is no trend for any single lot. We identified one occurrence where we have 2 complaints for the same potential mixed product "contributor". In this case, the reported mixed product "contributor" was not packaged prior to or after the impacted lot.

- Review of all relevant records revealed no atypical situation during the manufacturing and packaging processes. Major cleaning activities and line clearance were appropriately performed.

- Retain sample evaluation was performed on all lots involved with mix-up up product complaints. In all cases, the mix-up product complaint was not confirmed in the samples.

- There were no mix-ups or line clearance investigations reported during the packaging of the 123 lots referenced. As per the requirements established in our procedures, a (b) (4) (b) (4) (b) (4)

(b) (4)

(b) (4)

In addition, in response to the mix-up event investigations and line clearance incidences referenced in the observation, there have been no complaints for mix-up received for any of the lots involved indicating that the identified events were appropriately resolved.

Based on the controls in place in the packaging lines and the investigations conducted, we concluded that the manufacturing and packaging processes can be excluded as potential sources for mix-up in these cases and therefore not confirmed. However, we have identified additional areas for improvement in this area. Please refer to our response to observation 5 additional details of on-going corrective and preventive action plans.

OBSERVATION 4

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

Specifically,

A. *Your firm did not investigate extended downtimes observed during the manufacturing process (granulation and coating) of Motrin to determine the impact of the event in the product even when critical parameters of the process may be impacted. Your procedure* (b) (4) (b) (4) *does not require the operator to notify the supervisor and generate an investigation for events that may impact the critical process parameters and the drug product. Investigation* (b) (4) *issued on 11/20/09, identified twenty-three (23) extended downtime events of Motrin granulation batches for year 2008 ranging from approximately* (b) (4) *For example,*

1) *On 04/16/08, during the Motrin IB granulation drying process of lot SDA0001017 (used in the manufacture of lot SDA149) and recalled lots SHC003 and SHC004), the manufacturing operator recorded in the batch record two electrical failures and a broken bag event for a total granulation downtime of* (b) (4) *Your firm did not initiate an event investigation at the time of occurrence to determine the impact of the* (b) (4) *process interruptions in the product. Afterward, on 11/20/08 your laboratory detected a failure in the stability dissolution results of the three (3) months time point stability samples of lot SHC003. Out of specification dissolution results were also obtained for lot SHC003 and atypical results for lot SDA149, which were impacted by this event.*

2) *On 04/06/08, during the Motrin IB* (b) (4) *process of lot SCA0002400, the manufacturing operator recorded a problem with the* (b) (4) (b) (4) *in the batch record resulting in a downtime of* (b) (4) *The operator notified the event to the mechanics and technicians which replaced the temperature recorder (RTD). However, there is insufficient information to determine if the* (b) (4) *exceeded the critical parameter limits of* (b) (4) *established in the batch record. The last* (b) (b) (4) *reading recorded in the batch record was* (b) (4) *Your firm did not investigate the event at the time of occurrence.*

Response 4A:

McNeil Healthcare, LLC, Las Piedras, documents all process downtimes or mechanical issues on the lot batch record. The following procedures provide instructions to manage these situations in the production areas:

- SOP (b) (4)
- SOP (b) (4) (b) (4) (b) (4)
- SOP (b) (4) (b) (4)
- SOP (b) (4) (b) (4)
- SOP (b) (4)

For events determined to have product impact, an investigation is initiated and documented following SOP (b) (4) "Documenting Investigations".

McNeil Healthcare, LLC, Las Piedras will enhance existing procedures to improve the impact assessment documentation and escalation. These will include the following:

1. Establishment of a downtime evaluation matrix and decision tree to determine product impact.

2. Specific instructions will be included to define escalation/notification process to both Operations and Quality Assurance management.

These enhancements will be implemented by February 28, 2010.

In response to the 2008 Motrin® IB lots showing extended downtimes referenced in the observation, all critical processing parameters were met and all in-process and release testing met specifications as documented in the lot records. As part of investigations (b) (4) and (b) (4), all Motrin® IB granulation lots processed from 2006 to 2009 that had (b) (4) were reviewed. Four lots exhibiting the (b) (4) during the granulation drying process conditions were selected for additional testing. These were selected considering the length of downtime and the step in the (b) (4) when the downtime occurred. Retain samples were tested for dissolution and found to meet specifications.

Specifically for examples 1 and 2 included in the observation,

Example #1: Based on the investigation performed, the historical stability data results for both vials and bottles, and the experimental test to explore downtime effects on the dissolution, it can be concluded that although the root cause for the atypical behaviour of these lots cannot be determined; the granulation or coating downtimes cannot be considered to be the cause of the dissolution OOS results for SHC003 and SHC004.

Example #2: Upon further review the downtime exhibited no negative impact to the physical properties of granulation SCA0002400 as documented in the batch record. It should be noted that the (b) (4) show that the (b) (4) process was stopped once the (b) (4) preventing exposure of the product to high temperatures. This condition lasted for (b) (4) and is part of the normal equipment recovery once a downtime has occurred.

As part of our corrective actions, occurrences like the ones above will be appropriately assessed and documented.

B. *Your firm failed to conduct a thorough investigation during the evaluation of the presence of unknown peaks observed during the Assay test for Motrin IB product in 2008. The presence of these unknown peaks continues to the present. The unknown peaks affected the results for the analysis of Total Chromatographic Impurities (TCI%). As per Methods # (b) (4) and (b) (4) the acceptance limit for TCI% is (b) (4) The root cause was attributed to laboratory contamination, specifically the use of disposable pipettes. The preventive actions taken were not effective in that your firm continues to encounter contamination incidents. The following are events related to the extraneous peaks:*

1) *The laboratory investigations (b) (4) (date initiated: 8/5/08), (b) (4) (date initiated: 10/30/08), (b) (4) (date initiated: 1/21/09), (b) (4) (date initiated: 5/29/09), and (b) (4) (date initiated: 9/25/09) were initiated because the out of specification of TCI% was observed (b) (4) (b) (4) for Motrin IB Caplet, lots #SHA0001798, SMA0001698, AAA0000394-IP, AEA0001306-F and (b) (4) The investigation concluded that the most probable root cause for the events was a laboratory external contamination during the vial filling, identified as acetaminophen.*

2) *The event # (b) (4) was initiated on November 11, 2008 because the out of specification of TCI% was observed (b) (4) for Motrin IB Tablet Lot # SMA0002592-IP. The root cause for this event was a laboratory external contamination during the vial filling, identified as acetaminophen. The most probable sources of contamination were the disposable transfer pipettes or HPLC vials.*

Response 4B:

We would like to clarify, that when considering year-to-year periods (January through December), a total of (b) (4) conducted were generated in 2008 and (b) (4) conducted in 2009 for Out of Specification (OOS) results in Total Chromatographic Impurities (TCI) test for Motrin® IB products. The information referenced in the observation includes event investigations from August 2008 to September 2009. A 57% reduction of incidences has been obtained when comparing 2009 to 2008 indicating that our corrective and preventative actions have been successful.

Analytical laboratory investigations are handled through the following procedures:

- (b) (4) "Laboratory Investigation and Retest Procedures"
- (b) (4) "Extraneous Peaks"

These procedures require that root cause and corrective and preventive actions are determined for analytical laboratory deviations. In addition, we perform quarterly trending for all root causes of laboratory investigations to define emerging trends and to track effectiveness of the actions taken.

As part of an ongoing corrective/preventive action program for Motrin® IB lab analysis, we have identified two specific areas of focus: (b) (4) (b) (4) (b) (4) and (b) (4) (b) (4) Corrective and preventive actions have been taken to address and reduce these occurrences. A review of the performance in 2008 and 2009 indicate the effectiveness of the corrective and preventive actions taken. These actions are detailed below:

1. Use of plastic disposable centrifuge tubes. Date completed: 02/08.

2. Use of a glassware washing machine. Date completed: 03/08

3. Require pre-rinsing of HDPE bottles and glass beads used for sample preparation. Date completed: 07/08.

4. Require segregation during washing operations. Date completed: 07/08.

5. Dedicate brushes and washing utensils by product with specific storage locations defined. Date completed: 08/08.

6. Dedicate a sample preparation area specific for Motrin® IB. Date completed: 08/08.

7. Segregate dedicated disposable droppers and HPLC vials for Motrin® IB with specific location. Date completed: 11/08.

8. Enhancements to the procedure for filling and handling of HPLC vials will be incorporated in SOP (b) (4) "Laboratory Practices" by 02/28/10.

Based on the improvements seen in these events, the corrective actions put into place have been effective. However, as part of site Quality Systems Management Review process defined in observation 1 we will continue to trend the causes of laboratory investigations to ensure appropriate corrective/preventive actions are implemented.

OBSERVATION 5

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,

The established procedures and controls for cleaning and maintenance may not be sufficient to prevent mix-ups and/or contamination during the manufacturing and packaging process as evidenced by the received mix-up consumer complaints, deviations, and incidents involving manufacturing and packaging operations. There is no assurance that operators and quality personnel follow the established procedures for the cleaning and verification of manufacturing and packaging areas and equipment. Since August 2008 your firm has reported twelve (12) mix-up events from which ten (10) are related to human error. For example,

A. *On 10/01/09, during the set up process of the packaging line No. (b) for ES TYLENOL PM GELTAB 24, the filler operator and the packaging area mechanic detected thirteen (13) TYLENOL PM RAPID RELEASE (b) (4) at the filler machine. Investigation QN# (b) (4) dated 10/01/09, concluded that the most probable cause for the cleaning failure was human error.*

B. *On 09/26/09, during the set up process of the packaging line No. (for ES Tylenol Caplet 150, the filler operator detected one (1) Tylenol PM Geltab (PMJ) at the filler machine. Investigation QN# (b) (4) dated 09/27/09, concluded that the most probable root cause was ineffective cleaning by the operators.*

C. *On 06/02/09, during the set up process of the packaging Line No. (b) for Motrin IB Caplet 100, the filler operator detected two (2) Tylenol PM Caplets (PMK) at the filler machine. Investigation QN # (b) (4) dated 06/02/09, found that the major cleaning performance and verification was inadequate since the packaging operators forgot to remove and install a (b) (4) prior to initiating the packaging process of Motrin IB Caplet.*

D. *On 05/29/09, the QA Manager of your (b) (4) site notified you that during the packaging process of Tylenol Arthritis (TAR) bulk transfer lot ADA212 (b) (4) the filler operator observed (b) round white tablet of Tylenol PM (PMK). Your investigation QN # (b) (4) dated 06/10/09, concluded that the most probable cause is that during the (b) (4) testing of TAR the manufacturing operator involuntarily mixed at least one core tablet of PMK with TAR during product handling.*

E. *On 04/16/09 during the rework activities of Children's Tylenol Meltaways 30 Grape lot ADA072 in packaging line No. (b) the packaging operator found a bottle*

containing Tylenol PM Geltab (PMJ) units at the Reject Station of the induction sealer. Investigation (b) (4) dated 04/18/09, concluded that the event is associated to an inadequate cleaning performance and verification.

F. On 09/27/08, during the packaging process of Motrin IB Caplet 300's in Line No. (b) the operator detected a white Tylenol (ESK325) caplet. Your investigation (b) (b) (4) dated 09/29/08, found as the most probable root cause the ineffective cleaning by the packaging operators and verification of QA technician.

G. ...

In addition, since August 2008 your firm has generated approximately seventeen (17) event investigations, four (4) In-Process Assessment Forms (minor events) and four (4) manufacturing "clearance incidences" (detected during verification) all of them associated to cleaning deviations.

Moreover, a total of one hundred and twenty-three (123) mix-up related consumer complaints have been received by your firm for the same period. Your Quality Unit classified all the referenced mix-up complaints as isolated occurrences based on the fact that no prior complaints were reported for the specific lot number investigated, and that no quality-related issue could be identified. (Refer to observation # 3 for additional deficiencies related to complaint management system).

There is no assurance that the preventive and corrective actions taken are adequate to prevent recurrence.

The potential for product mix-up at your facility is a recurrent observation.

Response 5

McNeil recognizes the importance of preventing product mix-up and assuring that adequate line clearance takes place at each of the manufacturing and packaging operations. As per McNeil Healthcare, LLC, Las Piedras requirements, a (b) (4) (b) (4) (b) (4) Additional cleanings are performed between each lot. Our procedures contain detailed instructions on how to adequately conduct line clearance exercises. All line clearances are verified by a second individual. In addition, there are specific training curriculums in place for all operators in this area. All operators are trained prior to executing these line clearance procedures.

Applicable procedures require that root cause, corrective and preventive actions are determined for all manufacturing and packaging events. As shared during the inspection, we monitor root cause of the events, take corrective and preventive actions and track effectiveness.

Since 2005, Las Piedras has been working on an improvement plan which resulted in a (b) (4) In addition, a (b) (4) has occurred during that same time period indicating the effectiveness of our corrective/preventative actions.

The 68% reduction in overall plant reportable events related to product mix-up includes the following:

- 88% event reduction achieved in the Coating/Printing area.
- 74% event reduction achieved in the Packaging area.
- 70% improvement has been achieved in mix-up events caused by human error.

We continue to work in the areas of Packaging and (b) (4) as well as other areas to further reduce the events that were identified by our quality system process. These initiatives are included below:

1. Enhance the cleaning instructions for line clearance execution effectiveness. Implementation date: 02/28/10
2. Modify key equipment areas to improve visibility, access and reduce potential areas were product could get trapped. Implementation date: 3/31/10
3. Replacement of tablet holders in (b) (4) machines to reduce potential of product falling from plates during processing. Implementation date: 06/30/10
4. A Site Master Plan is being developed to improve segregation and overall process flow. Completion date: 04/30/10.
5. Modify existing Packaging and (b) (4) procedures to require supervisory verification of final cleaning. Implementation date: 02/28/10

As part of the Quality Systems improvements summarized in observation 1, a Quality Systems Management Review process will be implemented at the site to oversee and monitor a series of key quality performance metrics and indicators including mix up and line clearance events as well as the corrective/preventive actions and effectiveness (see corrective action #4a in observation 1 above).

We re-evaluated the 12 events referenced in this observation and confirmed that appropriate investigations and actions were conducted. As stated previously, we will continue to focus on human error reduction. A 70% improvement in a 4 year period in mix-up events caused by human error demonstrates effectiveness of continued corrective action plans.

In response to this observation for mix-up related consumer complaints, we conclude that the manufacturing and packaging processes can be excluded as potential sources

for mix-up in these cases and therefore not confirmed. Please see our response to observation 3B for further details.

OBSERVATION 6

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

Specifically,

A. *Your firm established a limit of* (b) *for investigation of extraneous peaks on section* (b) *of the SOP* (b) (4) *Version* (b) *Effective date:* (b) (4) *Title: Extraneous Peaks. However, this limit was established without scientific data and rationale to support the established specifications.*

Response 6A:

McNeil Healthcare LLC, Las Piedras procedures require investigation of extraneous chromatographic peaks (EP) using a (b) threshold investigation limit. In addition, any atypical chromatographic peak observed that is not indicated in the reference chromatogram is investigated. Examples of investigations of chromatograms with peaks above the threshold limit of (b) as well as atypical chromatograms were reviewed with the Chemist Investigator during the audit. The following procedures were used:

- SOP (b) (4) "Extraneous Peaks"
- SOP (b) (4) "Laboratory Investigation and Retest Procedures"

The threshold limit of (b) (4) was established based on the previous procedure (b) (4) (b) (4) which was based on McNeil R&D recommendations of impurities for OTC products. This limit was considered adequate for McNeil Healthcare, LLC, Las Piedras products as we use well characterized APIs with extensive stability and toxicology information. In addition, the APIs used in the facility are known to be very stable.

In addition, we are implementing a recently developed procedure (b) (4) "Handling of Known/Unknown Impurities and Unidentified Chromatographic Peaks". This procedure establishes the threshold limits for reporting, identification and qualification of extraneous peaks based on the maximum daily dosage of the drug substance(s). The limits are aligned to those established in the FDA Guidance for Industry, Q3B(R2) Impurities in New Drug Products of July 2006 Revision 2 and ICH Guideline Impurities in New Drug Products Q3B(2) Step 4 version of June 2, 2006.

Local implementation of this procedure (SOP (b) (4) "Extraneous Peaks") will be completed by 02/28/10.

B. *No analytical method for stability test has been established to monitor the impurities and degradants in Tylenol Arthritis Caplets (TAR) product. Your firm*

currently monitors the impurities and degradants for other finished products containing the same active ingredient, acetaminophen.

Response 6B:

The product TYLENOL® Arthritis Pain Caplets (TAR) was registered with the Food and Drug Administration via the New Drug Application (NDA) numbered 19-872 approved on June 8, 1994. In this NDA, it was established that it is not necessary to monitor the TAR product for p-aminophenol (PAP), the only known degradant of acetaminophen, in a long term stability testing program. This decision was supported by stability data of four lots where no PAP was found in any of samples tested. We have recently verified that PAP is not formed by analyzing three lots of TAR which expired in 2009 using a stability indicating method.

Moving forward, we have developed and validated an analytical method (b) (4) which will be used to monitor PAP, the only known degradant for TAR. This method will used for all new TAR stability studies.

In addition, an assessment has been made of the entire McNeil Healthcare, LLC, Las Piedras product portfolio to ensure that stability indicating methods are being used. Appropriate method upgrades will be implemented by 12/31/10.

OBSERVATION 7

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Specifically,

A. *Laboratory records do not include the initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards. (b) (4) (Contract Laboratory) performed the test for the identification of the uncharacteristic odor of Tylenol Arthritis Caplets (TAR) related with investigation (b) (4) that was initiated on 09/17/09 by (b) (4) The chromatograms, spectra and records were not reviewed by a second person to assure that the records comply with the specifications. Additionally, your Quality Unit failed to review the data for errors. For example, some of the chromatograms showed the acquisition date as May 2003. However, the actual analysis was performed in September 2009. There is no assurance that the data provided is accurate and reliable.*

B. *Laboratory records related to the (b) (4) reports of 09/11/09, 09/25/09, 10/30/09 and 12/03/09 for uncharacteristic odor of Tylenol Arthritis Caplets, were not readily available during the inspection. Your Quality Unit failed to provide all spectra and raw data associated to the (b) (4) reports. The laboratory records do not include raw data to support the evidence of sample preparation, standards preparation and did not include a statement of the weight or measure of the samples used for each test.*

C. *The test method used by (b) (4) for the identification of the uncharacteristic odor for Tylenol Arthritis Caplets (investigation (b) (4) is not validated.*

Response 7A, 7B, & 7C:

The forensic laboratory (b) (4) was selected to perform the identification of the source responsible for the uncharacteristic odor in TYLENOL® Arthritis Pain Caplets because of its highly specialized, unique capabilities. The laboratory employs non-traditional methods which are able to detect TBA in the parts per trillion level utilizing gas chromatography (GC) coupled with mass spectrometry (MS) and to date no laboratory has been able to achieve validation at these ppt levels.

Given the highly specialized nature of the work required from (b) (4) and the need to generate testing results quickly, we decided to pursue the testing while

supplementing the existing quality systems in an effort to enhance cGMP compliance as detailed below. A written protocol is now used which defines the methodology to be used including the sample preparation and standard curve preparation. In an effort to expedite data review and to ensure timely transfer between the forensic laboratory and McNeil, we are reviewing and approving all chromatograms and results on an individual sample basis using McNeil personnel rather than waiting for a final report to be issued by the forensic laboratory.

In addition, at (b) (4) we have implemented the following enhancements.

- Added a second level review and approval by McNeil Quality for all data and chromatograms generated.
- Strengthened (b) (4) data archival process.
- Further defined the specific documentation requirements for routine analysis.
- TBA standard is used routinely to confirm calibration curve.
- Limit of detection and quantitation have been calculated using signal to noise ratio.
- Linearity studies have been conducted.
- Routine monitoring for the presence of TCA, TCP, TBA, TBP.