McNeil
Consumer Healthcare

Peter Luther
Président

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CONFIDENTIAL
February 5, 2010

Margarita Santiago
Food and Drug Administration
San Juan District Office
466 Fernandez Juncos Ave.
San Juan, PR 00901-3223

Subject: Response to the Warning Letter dated January 15, 2010

Dear Ms. Santiago:

On behalf of McNeil Consumer Healthcare, Division of McNEIL-PPC, Inc. ("McNeil"), please find our written response to the Warning Letter issued to us on January 15, 2010 (the "Warning Letter"). This document provides a summary of the corrective actions to the issues raised in the Warning Letter. The second document is the more detailed response to the FDA Form-483 ("483") issued January 8, 2010. Therefore, in considering this response to the Warning Letter, the FDA should also consider and reference the more detailed 483 response document.

McNeil and Johnson & Johnson management are taking this issue very seriously and are committed to ensuring that McNeil implements all necessary corrective and preventive actions to improve the McNeil quality systems.

McNeil shares FDA's primary concern of ensuring the safety and efficacy of our products and understands the important obligation we have to the consumers that use them. Given this obligation, our quality systems are of utmost importance to us and we appreciate the feedback and input received from the FDA in the Warning Letter. We have already begun implementing the corrective actions detailed in this response.

McNeil Investigation

McNeil acknowledges the concerns raised by the FDA in the 483 and the Warning Letter with respect to the thoroughness and timeliness of various aspects of this investigation. The corrective actions detailed below directly and indirectly address FDA's concerns and will improve the thoroughness and timeliness of our investigations in the future.

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As an initial matter, it's important to review the scope of the investigation that led McNeil to the source of the contamination, the primary root cause of the 2, 4, 6-tribromoanisole ("TBA"), and the decision to recall various McNeil products. Reviewing this investigation has been critical to our development of an effective corrective action plan. The components of this corrective action plan, which are highlighted below, and detailed in the 483 submission, are being implemented systemically throughout McNeil.

In McNeil's experience, many of the challenges raised by this particular investigation were unique. Only after we engaged (b) (4) an external forensic laboratory, that has unique testing capabilities, did we determine that TBA was a likely source of the uncharacteristic odor. After McNeil confirmed the source of the odor, we were able to launch a comprehensive investigation focused specifically on how TBA could have entered the McNeil supply chain.

While (b) (4) has the appropriate analytical equipment and methodologies capable of detecting trace amounts of TBA in parts per trillion ("ppt") levels, the nature of this testing was, and continues to be, limited to only 8 samples per day. We continue to evaluate other laboratories capable of conducting this testing; however, very few laboratories have been able to meet our ppt sensitivity requirements and no laboratories, as of the date of this letter, have been able to validate at these levels. In parallel, we are pursuing in-house development of this testing capability.

Our next challenge was to determine how TBA could have entered the supply chain. This stage of the investigation led us to review multiple potential sources of contamination, including, but not limited to caps/liners, bottles/resins, pallets, manufacturing/packaging lines, bulk product, and ingredients. We also conducted extensive literature searches and worked with toxicology experts to help us better understand the chemical and how to evaluate its potential toxicity. From this, we learned that there was no toxicity data available for TBA. Relevant Health Hazard Evaluations ("HHEs") were developed and provided to FDA. The scope of the investigation widened significantly before it narrowed. Each time our knowledge increased, we expanded our search for affected or potentially affected products.

Based on this comprehensive forensic 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 2, 4, 6-tribromophenol ("TBP"). From the literature, we know TBP can lead to the formation of TBA under certain environmental and handling conditions. 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 and decided on January 14, 2010 to initiate the very broad recall of any potentially impacted products.

Our investigation continues and we will be providing an update to you at our February 11, 2010 meeting.

In the Warning Letter, FDA identified the following 3 specific violations that were observed during the inspection:

1. *Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed. In addition, you failed to extend the investigation to other batches of the*

same product and other products that might have been associated with the discrepancy as required by 21 C.F.R. Section 211.192.

2. *Failure of your Quality Control Unit to ensure a thorough investigation in accordance with 21 C.F.R. Section 211.192 with conclusions and follow up accomplished as required by 21 C.F.R. Section 211.198. As described above, the timing and depth of your investigative efforts regarding uncharacteristic odor complaints were insufficient to meet good manufacturing practice. Your firm's management, including the Quality Control Unit, was not proactive in response to consumer complaints. In addition, during the 2008 examination of complaint samples, your firm's analysts noted that the tablets, once removed from the bottle, did not have an unusual odor but the bottle retained a strong odor. Nonetheless, you did not pursue chemical testing at that time.*

   Your firm's quality management should have ensured the start of chemical testing far earlier. Failure to do so prolonged identification and resolution of the problem, resulting in contained consumer exposure. Quality problems must be thoroughly investigated, root cause determined, and appropriate corrective and preventative actions implemented as quickly as possible to limit exposure of the public to substandard drugs.

3. *Failure to submit NDA-Field Alert Reports (FARs) within three (3) working days of receipt of information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug products as required by 21 C.F.R. Section 314.81(b)(1)(ii).*

   Your firm received numerous uncharacteristic odor complaints during the period of April 2008 through September 2008 for your product Tylenol Arthritis Relief caplets. Nevertheless, you failed to submit a FAR within three working days to inform the Agency of the nature of the problem and the steps that you were taking to address it. You did not submit the FAR until September 18, 2009, after again noting an adverse, continuing trend of numerous complaints over the course of a several month period.

McNeil is implementing a corrective action plan, described below, and in more detail in the 483 response, which we believe addresses each of these 3 items in a comprehensive way. We have the appropriate knowledge, resources and direction to execute these enhancements and improvements. As the President of McNeil, I understand that I and McNeil's Management Board have final oversight responsibilities to ensure that the commitments described in our responses are addressed and given priority attention by our organization.

The key elements of the corrective action plan for the Warning Letter include:

- Enhancements to the Quality System
- Organizational Changes
- Senior Management Oversight

Enhancements to the Quality System

Based on our investigation, we recognize opportunities to enhance our Quality System. As a result, we have immediately implemented the following improvements:

- *Changes to complaint review process:* McNeil recognizes the importance of appropriate categorization of complaints in helping to facilitate accurate, timely, and actionable trending of complaints based on reported defect types. Based on this, 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.
  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) "Requirements for Complaint Handling" attached to the 483 response.
- *Changes to complaint handling procedures:* McNeil recognizes the important role of appropriate complaint handling procedures in ensuring that trends are detected early and investigated thoroughly. McNeil will continue to investigate all complaints associated with our products pursuant to SOP (b) (4) In addition, we have developed (b) (4) based on 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 continuous basis including monthly and quarterly reviews by the McNeil quality organization.

  These changes to the complaint handling procedures are reflected in SOP (b) (4) "Requirements for Complaint Handling" attached to the 483 response.

- *Change to Investigation Procedures:* We are amending the current investigation SOP to require that if an (b) (4) (b) (4) (b) (4) Such decisions will be documented and are intended to ensure the broadest investigatory approach. (b)(4)

  This change to investigation procedures will be reflected in SOP (b)(4) attached to the 483 response.

- *Change to Central Complaint Vigilance Quarterly Process:* We will expand our Central Complaint Vigilance Quarterly Process, where we currently review complaints, to include a more extensive review of adverse event trends across all McNeil product lines, and will formally include (b) (4) and (b) (4) This expanded process will be in place in April 2010.

  These changes to the Central Complaint Vigilance Quarterly Process are reflected in SOP (b) (b) (4) "Requirements for Complaint Handling" attached to the 483 response.

- *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 the 483 response.

Organizational Changes

McNeil has already begun implementing organizational changes that it believes will strengthen our focus on quality and compliance. Dr. Veronica Cruz has been appointed to the position of Vice President of Quality Assurance, OTC, effective February 15, 2010, and will be a member of the McNeil Management Board. Dr. Cruz has extensive experience in Quality within the API and pharmaceutical dosage manufacturing environment. She has supported manufacturing and distribution to global markets of OTC liquids and solids and spent much of her career in Puerto Rico, including previous experience in McNeil's Las Piedras site. She moves to this role from the position of Vice President, North America Quality Operations for Johnson & Johnson's Global Pharmaceutical Supply Group. Throughout her career, she has also developed and implemented various quality systems and processes resulting in significant improvement in the compliance level of the site quality systems.

As announced in the appointment of Dr. Cruz, she will now report directly to Sam Jiwrajka, who has been appointed to the role as head of Quality for the Johnson & Johnson Group of Consumer Companies. This move is part of changes already underway within the Johnson & Johnson Consumer organization which we believe will further strengthen our Quality operating model. Under this new model, McNeil will receive increased support from the Johnson & Johnson Consumer quality organization; however, the McNeil Management Board, consisting of executive leaders from various functions, will continue to be directly accountable for product quality and regulatory compliance of McNeil. This will allow these organizations to realize the benefits of Johnson & Johnson Consumer's scale and scope while continuing to preserve the benefits and accountabilities of our decentralized structure.

Senior Management Oversight

McNeil senior management is committed to more detailed and frequent oversight of our quality systems and quality-related issues with our products.

We are in the process of initiating enhanced Quarterly Executive Board Quality System reviews. These reviews will include the McNeil Management Board as well as relevant members of the McNeil quality organization, plus participants from Johnson & Johnson. While Executive quality reviews were initiated in 2009, we have identified opportunities to improve the depth and breadth of these reviews. Therefore, they will now 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.

In addition to the Quarterly Executive Board Quality System Reviews, we will be adding complaint updates to our monthly McNeil Management Board meeting. This will give the McNeil Management Board greater visibility to complaint trends earlier to ensure that they are given appropriate prioritization, attention, and action at a senior level in the organization.
These senior management quality review processes are reflected in SOP (b) (4) attached to the 483 response.

In addition to the Quality System enhancements outlined above, Dr. Cruz will lead a comprehensive assessment of the McNeil quality system in coordination with resources from Johnson & Johnson Quality & Compliance Worldwide. This assessment will be completed by the end of April 2010. Based on this assessment, Dr. Cruz will develop a plan that would continue to strengthen our focus on complaint vigilance, corrective and preventive actions ("CAPAs") and quality systems. We will share this plan with FDA to underscore our ongoing commitment to improving our quality system.

Remediation Plan related to Pallets

In addition to the corrective actions outlined above, 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:

- All existing McNeil components from the (b) (4) plant 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).

- 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 aforementioned component supplier, (b) (4)

- 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 third-party manufacturing sites. Monitoring of compliance with this pallet requirement will be conducted.

Conclusion

McNeil recognizes the seriousness of this situation and has identified this corrective action plan as our top priority. We are dedicated to providing the resources, time, effort and executive oversight to ensure that our quality systems meet all requirements and operate effectively and efficiently. We are confident that this corrective action plan provides the approach necessary to identify and implement systemic actions that will improve and enhance our quality processes and systems while addressing the concerns raised by the FDA in the Warning Letter and the 483.

We look forward to our February 11 meeting and the opportunity to engage with you more fully on our corrective actions and plans moving forward and on our on-going investigation. Please feel free to contact me by phone at (b) (4) if you have any questions or concerns.

Sincerely,

Peter Luther
President

cc: Maridalia Torres