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December 4, 2008

Ms. Joanne M. Givens
District Director
Detroit District
Food and Drug Administration
300 River Place
Suite 5900
Detroit, Michigan 48207

Orig: DCB
cc: DIB
cc: DD
ljk 12/5/08

Dear Ms. Givens,

This letter and the accompanying attachments serve as Perrigo's response to the FDA's November 7, 2008 483 that was issued following its recent inspection of Perrigo's facility in Allegan, Michigan.

To assist with your review, our response follows the same sequence of observations that appeared in the FDA 483. Each observation is listed separately, followed by our response to that observation. Where applicable, the response also includes completed or planned corrective actions to address specific observations and system enhancements. Because Perrigo had identified many of the listed observations prior to the inspection, corrective actions for these observations have been completed or are in the process of being completed.

Quality is Perrigo's top priority. Consistent with that priority, our Quality Unit has the responsibility for, and the authority to address, all quality-related issues at Perrigo. We believe that the Quality Unit has the right management, infrastructure and procedures in place to enable it to effectively approve or reject materials manufactured internally and externally.

Still, Perrigo remains committed to a continuous improvement approach to our quality systems and processes. Indeed, we have invested significant efforts and resources on quality improvements, including quality unit oversight, investigation of deviations, external manufacturing oversight, stability and validation. By way of some examples:

- While our overall right-first-time performance is better than 99%, we remain focused on driving continuous quality improvement towards 100% right-first-time performance. To that end, we have dedicated additional resources that will enable us to enhance our focus on error prevention.

Ms. Joanne M. Givens

Page 2

December 4, 2008

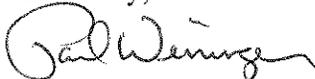
- We are developing and implementing global policies and standards to ensure sustainable compliance at all of our locations, including the oversight of external manufacturers.
- We have invested additional resources and organizational infrastructure in Quality, Technical Services and Procurement dedicated to external manufacturing oversight, with the goal of ensuring that our processes and procedures are robust throughout the life cycle of supplier management.
- We continue to implement improvements to the overall quality, depth and consistency of our investigations. We have enhanced our processes and metrics for monitoring the status of all open investigations, and our improved trending and monitoring processes have led to additional continuous improvement projects.

While we feel that significant and demonstrable improvements have been made with respect to our quality systems and processes, we recognize that opportunities exist for further improvement. Again, as part of our commitment to making those improvements, the corrective actions to the observations noted in the FDA 483 have been or are being addressed.

In closing, we assure you that Perrigo takes these observations seriously and is committed to working aggressively and promptly to address your concerns to your satisfaction. With that goal in mind, where ongoing projects or activities are referenced in our response to a particular observation, Perrigo will provide the District Office with periodic progress updates to keep you informed.

Of course, we welcome you to contact us at any time should you have any questions in regards to our response. In the meantime, we request that a copy of Perrigo's response, with all confidential product information redacted, be included in future freedom of information communications regarding the FDA's November 7, 2008 483 related to our facilities.

Sincerely,



Paul Weninger.

Enc.

Cc: Joseph C. Papa
John T. Hendrickson
Todd W. Kingma
Louis Yu

Perrigo Company
FDA 483 Observation Response
September 15 - November 7, 2008 Inspection

Observation 1

Drug product production and control records are not reviewed by the quality control unit to determine compliance with all established approved written procedures before a batch is released or distributed.

- A.) Two lots of Sleep Aid tablets (Doxylamine Succinate Tablets, 25 mg – ANDA (b) (4) lot numbers 8EE0802 and 8JE0699 were assigned an unapproved 36 month expiration date and released.
- B.) Multiple lots of Naproxen Sodium 220 mg tablets (10 lots) and caplets (25 lots) were assigned an unapproved 48 month expiration date and released. Examples include: 8GE0281 and 8GE0304.
- C.) Three lots of APAP 500mg Gelcaps were assigned an unapproved 48 month expiration date and released. Examples include: 8GE0488 and 8GE0745.

Response:

Perrigo acknowledges the three expiry date issues noted in Observation 1 and confirms that it has taken the appropriate corrective actions to address these issues as discussed below.

Prior to the release of product, the Quality Unit reviews drug product production and control records at each stage of manufacturing and packaging to ensure compliance with applicable SOPs, including a review of expiry dating applied to product labels and cartons compared to the expiry on the packaging order.

With respect to the three examples noted in the observation, they are all related to each other. The initial incident was caused by an isolated human error related to the execution of a change control to expiry dating for a new package size of Sleep Aid tablets, lot 8EE0802. Execution errors in the corrective action and rework from this incident resulted in the additional expiry issues referred to in the observation.

As reviewed with the investigators, Perrigo's investigation included a detailed review of the applicable stability studies for the three products. Based on the results of those studies, a Field Alert was filed and a recall initiated relative to the Sleep Aid product; however, no action was taken relative to the Naproxen or APAP products as the stability data supported their respective shelf life.

Perrigo has taken the following corrective actions to address the expiry issues raised in Observation 1:

- The Production Date (date of manufacture) and Shelf Life have been added to the Goods Issue List, which is printed after issuing materials to a packaging order. This will provide for an independent review and verification of the accuracy of expiry dating by the Quality Unit. SOPs related to this data and its verification have been updated. This includes SOP (b) (4) (b) (4) (b) (4) SOP (b) (4) (b) (4) (b) (4) and (b) (4) (b) (4) (b) (4). These changes were effective November 6, 2008.
- An SOP was created to clarify and further define the responsibilities of the QC Stability department during the review of packaging configuration changes. This SOP - SOP (b) (4) (b) (4) which governs the review of configuration change, became effective August 28, 2008. Among other things, this SOP requires that, (b) (4) (b) (4)
- SOP (b) (4) rev (b) (4) (b) (4) was changed effective on October 28, 2008. This change requires the (b) (4) (b) (4)
- Another corrective and preventative action was initiated with an SOP revision that required Quality Assurance review and assessment of previously released materials when changes are made to expiry dating in the material master. That SOP revision, SOP (b) (4) rev (b) (4) Procedure for Establishing, Reducing or Extending Product Shelf Life, was effective October 23, 2008.
- New (b) (4) month studies were initiated for both the Naproxen (8GE0181, 8GE0282, 8GE0364, 8GE0632) and APAP (8HE0078, 8GE0488) product batches involved with this incident.
- Finally, as noted above, Field Alerts were filed with the Detroit District Office and recalls initiated relative to the applicable batches of the Sleep Aid tablet product.

Observation 2

Written records of investigations into the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

- A.) The following lots of natural Senna Laxative tablets, manufactured by (b) (4) (b) (4) failed stability assay and remain on the market:

- 1.) Investigation of deviation (b) (4) dated 10/29/2007 reported an OOS 3 month stability result of lot 7B0991. This investigation remained open and unresolved. The decision to recall was made 9/23/2008 by (b) (4). This lot's expiration date is March 2009.
 - 2.) Investigation of deviations (b) (4) dated 6/12/2008 reported OOS at 9 month stability results for lot 7G0903. This investigation remains open and unresolved. This lot's expiration date is July 2009.
 - 3.) Investigation of deviation (b) (4) dated 8/23/2007 reported an OOS 9 month stability result for lot 6GE0670. The investigation into this issue remained open and unresolved. This lot expired 4/2008.
- B.) Investigation (b) (4) dated 12/21/2007 reported failing release assay result obtained 10/31/2007 for natural Senna Laxative tablet, annual 2007 confirmation batch, lot 7E1788 manufactured by contract supplier (b) (4). (b) (4) remains open and unresolved. Lot 7E1788 is maintained in an on hold status and has not been rejected. Subsequently received lots were not tested prior to release/distribution. Examples 7K2158, 8A2470 and 8C1587.
- C.) Investigation of deviation (b) (4) dated 3/28/2008 reported and OOS 18 month stability result for Chlorpheniramine Maleate tablet lot 6F1641 manufactured by contract supplier JB Laboratories. This investigation remained open and unresolved. This lot's expiration date is April 2010.
- D.) Investigation of deviation (b) (4) dated 7/31/2008 reported an OOS 24 month stability result for 81mg Enteric Coated Aspirin tablet lot 6EE0500 manufactured by contract supplier (b) (4). This investigation remained open and unresolved. This lot expired in March 2008.

Response:

Perrigo has the systems and controls in place, governed by SOP (b) (4) to timely perform, document and close investigations. This SOP also drives the identification of root cause and appropriate corrective and preventative actions.

The investigations noted in Observation 2 were still open, and drafts of the deviation investigations were shared with the investigator, during the site inspection. The formal conclusion and follow-up were part of the completed investigation and are discussed below.

A & B. The Senna Laxative investigations centered on the test methods employed by Perrigo and the external manufacturer, (b) (4) and the discrepancies between their respective test results. That external

manufacturer, (b) (4) developed the formulation and sold the product to other customers, such that it had considerable experience with the formulation, manufacture and testing of this product. Throughout the course of this investigation, (b) (4) maintained its confidence in the test results that it generated for all batches of its formula.

Nevertheless, Perrigo actively investigated the discrepancy between the various test methods. Its activities included a thorough investigation of the analytical method, analytical technique, analytical equipment, formulation, raw material purity, batch yield and process variances. Perrigo also tested the product at multiple laboratories and conducted multiple site visits to (b) (4) facility. Despite Perrigo's extensive investigation into this matter, Perrigo could not explain the discrepancy between its and (b) (4) (b) (4) test results.

Pursuant to the contract between Perrigo and (b) (4) a qualified independent contract laboratory was retained to address and resolve the differences between the two parties' test results using approved USP methods. Based upon results generated by the third party laboratory, (b) (4) (b) (4) initiated a manufacturer's recall to Perrigo for distributed lots still within expiry with test results outside of the (b) (4). Given the uncertainty involved with the test method and the number of lots involved in this action, Perrigo extended the recall to all lots still within expiry as a precautionary measure.

Although this action effectively closes the investigation from Perrigo's perspective, (b) (4) has continued its investigation into method discrepancies, and it is actively engaged with the USP in regards to potential issues with the test method and the USP reference standard which could potentially cause unintended high bias in test results. (b) (4) continues to stand by its test methods and test results.

- C. During the site inspection, a draft of the deviation investigation of (b) (4) was shared with the investigator. The investigation was in draft form pending receipt of the final investigation from the contract manufacturer, (b) (4). Once (b) (4) completed its investigation and reported the results to Perrigo, Perrigo's investigation was finalized, and the Quality Unit Review Team (QURT) met to discuss the investigation and determine the batch disposition and potential market implications. The QURT document was finalized on September 26, 2008. The conclusion contained within this document indicates that product is stable over the shelf life of the product (b) (4) (b) (4)

(b) (4)
(b) (4)

Additionally, process improvements were implemented after the manufacture of batch 6F1641 as a result of the

2007 annual product review. Based on this conclusion, the recommendation was to take no market action for this or any other batches and that the formula should continue to be monitored through the APR process.

A final copy of the investigation, including the QURT document, was provided to the investigator on October 1, 2008.

- D. A draft of deviation investigation (b) (4) was reviewed during the site inspection. The investigation was initiated on July 31, 2008 as indicated; the activities associated with the investigation were completed on August 22, 2008. No specific root cause was identified for the (b) (4) release OOS. The lot had expired in March, 2008. The investigation concluded that the OOS was consistent with previous investigations and that the corrective actions had been outlined in the earlier investigations. The investigation was provided to the Quality Unit Review Team (QURT) for market impact assessment. The investigation and market impact assessment was in-process when the site inspection began. An additional piece of data that QURT requested was the testing of retains samples for this batch. The retain testing completed on September 26, 2008 of batch 6EE0500 met drug release specifications. Specifically the (b) (4) drug release results for six tablets were (b) (4). Deviation investigation (b) (4) is now complete. The conclusion contained within the QURT document indicates that the testing of the retain sample, combined with the health assessment is consistent with actions previously taken by Perrigo. The stability test point was after batch expiration, no market action is recommended for batch 6C1427, packaging batch 6EE0500. The corrective actions remain consistent with the previously communicated plan to market the 535AD formula in 120 and 180 count packaging sizes, with 18-month expiration dating; and the completed commitment to optimize the existing process (March 2008) and reformulation efforts at (b) (4).

Observation 3

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Investigations into two content uniformity failures and batch rejections experiences 4 months apart for APAP 160 mg Jr. Grape Chewable tablets were both inconclusive. A Project Plan Request was issued 6/18/2008. To date no activities have been initiated.

<u>Lot</u>	<u>Date</u>	<u>Assay Result</u>	<u>Specification</u>
7B0254	3/11/2007	Acetaminophen Content Uniformity =	(b) (4)
7F1074	7/01/2007	Acetaminophen Content Uniformity =	(b) (4)

Response:

Both batches noted in Observation 3 (7B0254 and 7F1074) were rejected after being reviewed and investigated through Perrigo's deviation investigation process. These batches were rejected for assay failure (average of ten content uniformity results) rather than failing content uniformity criteria. The project plan referenced in Observation 3 originated from the Annual Product Review assessment of process capability (Cpk). The low Cpk was driven primarily by the assay failures, and the project plan request was initiated to identify sources of variability leading to the low process capability.

The current internal release limit is (b) (4) for this product based on stability data, which is wider than the previous (b) (4) limit. Batch 7F1074 would have been acceptable when compared to the stability based internal release limits. A working team has been collaborating on a revision to SOP (b) (4) Internal Alert Limits, to apply a consistent approach for the establishment of internal alert and internal release limits. The revision to this SOP will incorporate data-driven internal alert limits and internal release limits based on the statistical capability of the process and on-going and completed stability studies, respectively. This SOP is routing for approval and is targeted to be effective by December 31, 2008.

The APAP 160mg Jr. (b) (4) tablet product is a (b) (4) product, with (b) (4) batches produced over the last 2 years. Due to the (b) (4) number of batches, a (b) (4) assay value can greatly affect the Cpk measurement. This is the case with product formul (b) (4). The assay value of (b) (4) affects the Cpk to the extent that, if it was removed, the Cpk would be well above the acceptable limit. The outlying value was investigated through the deviation process.

Based on the revision to SOP (b) (4) the open project concerning the APAP 160 mg Jr. (b) (4) tablets has been closed. This product is under consideration for discontinuation due to low product demand. Product monitoring and trending will continue as part of the (b) (4) product review cycle.

Observation 4

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Field Alert was not filed following a Quality Assurance error (deviation (b) (4)) which resulted in multiple lots of naproxen Sodium Caplets and naproxen Sodium Tablets being released labeled with expiration dates exceeding the 36 months filed in the application

(b) (4) by 12 months (48 months). Examples include: Lot (b) (4)

(b) (4)

Response:

Perrigo commits to filing an ANDA/ NDA – Field Alert Report in addition to reporting via the annual ANDA/ NDA report process for expiry dating errors. Perrigo has previously filed ANDA/NDA Field Alerts for dating errors that lacked sufficient stability studies to support the expiry date.

The intended dating for this product is 36 months. The Quality and Regulatory Affairs units reviewed the incident upon discovery. Real time stability studies had been completed, and those studies supported 48 month expiry period. These studies were part of previous Annual Report submissions to the FDA. The approved stability protocol filed in the ANDA indicates that extension of the expiry date is to be filed in the Annual Report according to 21 CFR 314.70(d)(5). The decision was made to proceed with the investigation, initiate additional stability studies with the product packaged with 48 month dating, and report the deviation along with the supporting stability data in the annual report. Root cause and corrective actions were identified as part of the deviation investigation and implemented as noted in the response in Observation 1.

Observation 5

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

- A.) SOP (b) (4) entitled "(b) (4) (b) (4)" calls for investigation of any failed/OOS confirmation batches. It further calls for QA to determine "(b) (4) (b) (4) (b) (4)". This did not occur for the batches of Natural Senna Laxative Tablets received following the 10/30/07 OOS results obtained for batch 7E1788. The investigation remained as "Draft" as of the start of this inspection.
- B.) SOP (b) (4) (b) (4) (b) (4) was not followed with regard to compiling quality data on a quarterly basis for all external manufacturers. The following contract manufactured data were not compiled.
- 1.) For (b) (4) evaluations for (b) (4) 2007 and (b) (4) of 2008 were all dated 9/23/08. (b) (4) manufactures the following drug products for Perrigo: Natural Senna Laxative Tablets; 81 mg enteric coated aspirin (Yellow and Peach); and 325 mg enteric coated aspirin.
 - 2.) For JB Laboratories quarterly evaluations for 4th quarter 2007 and 2nd quarter 2008 were both dated 9/22/08. JB Labs manufactures the

following drug products for Perrigo: Alertness Aid, Chlorpheniramine Maleate Tablet, and APAP 500 mg Caplets.

- 3.) For (b) (4) evaluations for (b) (4) 2008 both were dated 09/26/2008. (b) (4) manufactures Loratadine D 10 mg and Loratadine 10mg QD tablets for Perrigo.
- 4.) In addition this SOP was not followed in that implementing corrective actions and improvements as necessary was not done. (b) (4) vendor quality evaluations show 18 and 100 advisories, respectively for the past (b) (4) the majority concerning the condition of incoming shipping cartons of Omeprazole products. There was no written plan to ameliorate the problem.

Response:

Perrigo acknowledges the timing gaps highlighted relative to the specific (b) (4) reports. Corrective actions have been initiated as outlined below.

Perrigo has dedicated incremental resources focused on the oversight of external manufacturers and materials. Specifically, QA, Technical Operations and Procurement personnel are responsible for externally procured raw materials, primary / secondary packaging materials, intermediate materials, bulk solid dose, primary packaged materials and finished goods. The same Quality systems that are in place for Perrigo's internally produced materials (i.e. (b) (4)

(b) (4)

(b) (4)

In addition, Perrigo has dedicated (b) (4) personnel that are (b) (4)

(b) (4) The responsibility of this QA staff is to provide direct oversight and support of our suppliers.

- A. *As discussed in the response to Observation 2, the investigation was focused on the Perrigo test method. Given (b) (4) expertise on the formulation and testing of Senna Laxative, Perrigo relied on the test results from (b) (4) (b) (4) to release the Senna product batches. Perrigo did not perform additional testing of new receipts as the Perrigo method was the primary focus of the investigation. As previously stated, (b) (4) continues to stand by its method and has been working with the USP to resolve discrepancies between the different test methods.*

As noted in Observation 2, batch 7E1788 remained on a hold status from the time that the deviation investigation was initiated. With the subsequent notification of a manufacturer's recall by (b) (4) and the completion of deviation (b) (4) the batch has been moved to a rejected status.

- B.1-3. *Perrigo acknowledges the timing gaps highlighted relative to the specific (b) (4) reports. The details of these observations and the need to complete*

th (b) (4) reviews on a timely basis were reviewed with all members of the external quality assurance team. In each of these cases, the Perrigo quality employee responsible for these accounts was working closely with each of these external manufacturers on product deviations and/or process capability improvements. As part of our continuous improvement efforts in the area of external manufacturing quality management, enhancements to the supplier scorecard process were initiated prior to the inspection. The objective of these enhancements was to provide the supplier more frequent feedback to enhance the supplier's ability to improve their performance

B.4. The root cause of the damage is attributed to air freight material handling. The damaged product was rejected by Perrigo at receipt. (b) (4) is addressing this issue with their freight carrier. Supplier advisory documentation was initiated based on the physical condition of the shipments and communicated to (b) (4). In addition to this action, the damage was documented on the material Bill of Lading. This is the formal documentation that the freight carrier of this material requires for notification of damage.

Observation 6

The quality control unit lacks responsibility for approving or rejecting drug products manufactured under contract by another company.

Appropriate statistical controls were triggered and/or not used and product was released. For example;

A.) For Chlorpheniramine Maleate Tablets from JB Labs, lot 7I1978, released with a (b) (4) assay although your internal alert limit is (b) (4)

B.) For Chlorpheniramine Maleate from JB Labs, lot 6F1641, exp 4/2010, the OOS 18 month stability assay of (b) (4) was not predicted by "(b) (4) (b) (4)" from the release assay of (b) (4)

C.)

1. For Natural Senna Laxative Tablets from TCL, draft deviation investigation (b) (4) initiated 8/23/2007, represents the first of 4 deviation reports for stability or release testing that were Out of Specification for Total Sennosides or Uniformity of Dosage. The investigation describes a 6/6/08 decision whereby (b) (4) (b) (4) (b) (4). However, distribution of previously received lots including (b) (4) (b) (4) continued through 8/25/2008 or until gone.

2. Similarly, subsequent to the 1/18/08 issuance of a change control order to reduce the expiration date of peach colored 81 mg Aspirin Enteric Coated Tablets, following several stability failures, 32 lots were released with 24 month expiration dating periods assigned. For example:

300 Count 7KE0619 6/18/2009 24 months 2/12, 20/2008
 300 Count 7HE0550 5/11/2009 24 months 2/6/2008

D.) For yellow colored and for peach colored 81 mg Aspiring Enteric Coated tablets from (b) (4) the Quality Unit has not acted on the Acid Test stability failures, between 18 and 24 months, experienced consistently since 2005. Lots currently on the market with expiration dating periods assigned that have been longer than 18 months are:

500 Count	7FE0096	1/15/2009	24 months
500 Count	7LE0379	7/13/2009	24 months
500 Count	7LE0263	6/24/2009	24 months
500 Count	7HE0128	4/28/2009	24 months
500 Count	6FE0217	2/28/2009	36 months
500 Count	6EE0115	2/17/2009	36 months
300 Count	6FE0101	2/28/2009	36 months
300 Count	6EE0118	2/25/2009	36 months
180 Count	6EE0806	2/10/2009	36 months
180 Count	7JE0530	5/29/2009	24 months
300 Count	7KE0619	6/18/2009	24 months
300 Count	7JV0522	5/1/2009	24 months
300 Count	7HE0550	5/11/2009	24 months
180 Count	7LE0962	8/19/2009	24 months
180 Count	7KE0368	6/18/2009	24 months
180 Count	7LE0374	6/18/2009	24 months
180 Count	7HE0052	5/11/2009	24 months

Response:

The Perrigo Quality Unit has the full responsibility and authority to approve or reject drug products manufactured under contract by another company. This is further reinforced by (b) (4)
 (b) (4)

6A-B. *As discussed in our response to Observation 3, Perrigo is revising the procedure (SOP (b) (4) for establishment of (b) (4) (b) (4) to incorporate process capability, stability trend analysis and analytical method variability. This is targeted to be effective December 31, 2008. As discussed during the inspection, the internal alert limit has been established to initiate additional review of results that are between the product release specification and the internal alert limit. It was not established as an absolute limit to be used for product release. The incoming*

Certificate of Analysis for Perrigo batch 7J1978 reported a result of (b) (4) % from JB Laboratories. This result was outside the internal alert limits ((b) (4) (b) (4) %) Perrigo established for this product. This result triggered Perrigo's laboratory investigation process per SOP (b) (4) (b) (4) (b) (4). As a part of the investigation process, a request was made to Perrigo's QC Stability for a statistical analysis of the available stability studies for this formula. This analysis indicated that the shelf life of the product would be maintained, with a (b) (4) confidence interval, for product lots with initial assay results ranging from (b) (4) to (b) (4) (stability analysis completed on 08/10/2007). As a result of the investigation and QC Stability analysis, the batch was released by Perrigo's Quality Unit.

The incoming Certificate of Analysis for Perrigo batch 6F1641 reported a result of (b) (4) from JB Laboratories. At the time that this batch was released on June 21, 2006, internal alert limits were not in use at Perrigo and as such, the release limits for this material was (b) (4). The assay result from the CoA met the product release specification and the batch was released.

6C-1. Perrigo's investigation into the OOS assay results included an assessment of the master batch card formulation, the RM potency, and the batch yield. This assessment predicted that the assays of the subject batches would be in the acceptable specification range, consistent with the results generated by the manufacturer at the time of production. Additionally, the manufacturer indicated that it had worked with other customers on method execution. The method is a fluorescence based method on a plant extract. The assay results generated by Perrigo were not consistent with the results generated by the supplier or with the results predicted through an assessment of the formulation and the RM potency. Based on this initial investigation and assessment, Perrigo continued to distribute the product. As a step in the process of the investigation, Perrigo suspended new shipments from (b) (4) (b) (4) of this formula in June, 2008. The first confirmation of a failing result from the manufacturer was received in August, 2008. At that time, Perrigo suspended distribution of this product. The manufacturer has subsequently initiated a recall for 12 lots manufactured for Perrigo based on USP results. The manufacturer continues to work with the USP on method gaps for the Senna assay.

6C-2. The 32 batches referenced in this observation were batches packaged prior to January 18, 2008. As reviewed with the investigator during the site inspection, the available stability data in various packaging sizes (36 ct to 300 ct) and the packaging configuration difference for formula (b) (4) support release of these batches with 24-month expiry dating. The packaging configuration for formula (b) (4) differs from formula (b) (4) in that (b) (4) packaging configurations use a (b) (4) while the (b) (4) packaging configurations use a (b) (4).

The two 300 count lots referenced were packaged and initially distributed in 2007 with an additional (b) (4) units distributed on the February dates referenced. The corrective actions detailed in the response to observation 6D were also applied to the peach formula (b) (4).

- 6D. Perrigo has periodically reviewed the Enteric Aspirin status with the Detroit District Office, including a face to face meeting in January 2008. An action plan was shared, which included revalidation at the external manufacturing site of an optimized process, reduction in dating and suspension of additional high count packaging.

Perrigo's written response to the Detroit District regarding the November/December 2006 inspection communicated that the expiration dating for Enteric Aspirin, 81mg would be reduced from 36-month to 24-month dating with continued monitoring of current stability studies. Perrigo also communicated a stability batch failure, batch 5FE0473, on March 26, 2007. As part of this investigation, Perrigo initiated testing of the reserve sample for the batch in question, as well as for 15 additional related reserve batches from (b) (4) and five from Perrigo. The samples were analyzed at (b) (4) and Perrigo with all batches meeting the acid phase drug release specification.

In December 2007, when a stability failure was produced for formula (b) (4) in a 500 count packaging configuration, deviation investigation (b) (4) was initiated. As a part of this investigation, Perrigo took immediate action by suspending distribution of all Enteric Aspirin, 81mg for both formulas and all packaging configurations. This deviation investigation (b) (4) included completing testing of 17 reserve samples at or near 24-months, with all batches meeting specification for (b) (4) drug release testing; testing 11 reserve samples at or near 36-months, with 10 of 11 meeting specification for (b) (4) drug release; and an additional 10 batches tested at 21 months, with all batches meeting specification for (b) (4) drug release. Also included in this investigation was the testing of market samples collected from four different regions of the United States. All batches met (b) (4) drug release testing. A health hazard assessment was also obtained, and it concluded that the active is available at the described dose, and this (b) (4) (b) (4) drug release failure does not pose any increased health risk.

The corrective actions included a revalidation of the process at (b) (4) (b) (4) to reduce process variability and tighten the control range on critical coating variables, reduction of the expiration dating from 24 months to 18 months and suspension of new production in packaging sizes greater than 180 count until additional work is completed. The status of enteric aspirin and the action plan to address the (b) (4) drug release was reviewed at a meeting requested by Perrigo at the Detroit District Office on January 14, 2008.

Observation 7

The quality control unit lacks the responsibility and authority to reject all drug products.

Appropriate statistical controls were triggered and/or not used and product was released.
For example;

- A.) The 4/29/2008 packaging tote of (b) (4) of (b) (4) (b) (4) lot (b) (4) an AQL test for foreign particles was performed and was failed for particles. A deviation report showed that the result was overturned, the tote filled and released. Review of the (b) (4) (b) (4) Formula (b) (4) the source batch record showed that the manufacturing batch was aborted and then begun again, and the cleaning / use log showed that there had been no cleaning done after the previous (b) (4) batch or during the manufacturing of the batch.
- B.) There was no explanation for the 10/01/2007 – 12/31/2007 APAP ER 650mg tablet formula (b) (4) within specification dissolution profile changes in (b) (4) of the batches. In addition, the reason for the rejection of batch (b) (4) for which the immediate release tablet layer failed, was not determined.

Response:

Perrigo Quality Control Unit demonstrated the authority and responsibility for the disposition of the drug products cited in the examples in the observation. Perrigo had taken appropriate actions as required per SOP to thoroughly assess and investigate the reported quality events. These products were appropriately released by the Quality Unit based on our investigational findings.

- 7A. *The quality event which occurred on April 29, 2008 involved very small dark red particles that were noticed floating at the bottom of the bottle during the packaging of the batch. These particles were evaluated by the quality technician on the floor following the Operational Risk Assessment Form (ORAF) Process per SOP (b) (4) in which an AQL analysis for foreign particulate was performed. Per the ORAF procedure, the event was elevated by the quality technician to QA Management as it failed the AQL for foreign particles. The ORAF, the product, and the process were evaluated independently by the Quality Management team with technical assessments provided by Technical Operations Management. The particles were determined by Quality Management not to be foreign, but to be consistent with the (b) (4) product ingredients. These few particles were darker as the dye had adsorbed to the surface of the (b) (4) particles within the suspension creating a darker hue. The product met all acceptance sampling and analytical criteria for release of the batch.*

Cleaning activities were executed appropriately for the manufacturing and packaging of this formula batch. Manufacturing batch 8C1577 was packaged into two finished bottle batches, 8CD0115 and 8CD0116, both of which were contained during the evaluation of this quality event. There is no requirement to clean between two packaging batches bottled from the same manufacturing batch.

- 7B. *During the period from October 1, 2007 to December 31, 2007, APAP ER 650mg tablet formula (b) (4) did experience a trend in drug release stage testing. This trend was noted during internal OOS trending and a project team was initiated in March 2008. A review of the laboratory investigations initiated during the time period identified seven batches which did not meet Stage 1 criteria but met Stage 2 criteria, and one batch that failed all 3 stages for drug release and was rejected.*

Due to the failure to meet drug release specification at Stage 3, an investigation was initiated for batch 7J1433. The investigation detailed a review of materials, manpower, machines, methods, and measurement as part of the (b) (4) root cause investigation tool for potential root cause scenarios. As noted and discussed during the audit, the root cause for the failure was not determined. This batch was subsequently rejected.

The other seven batches associated with laboratory investigations all met USP drug release specifications for S2 testing as approved in the ANDA filing and were released appropriately. Stage testing is permissible by the USP and ANDA filing. The shift that occurred in the second quarter for 2007 was identified through internal OOS trending and a project team is investigating the potential cause. As noted during the audit, the rate of batches moving to S2 testing has returned to the normal rate, and the project team is concentrating on the cause for the shift during this particular quarter including laboratory equipment review, raw materials, and potential compression factors.

Observation 8

Results of stability testing are not used in determining expiration dates.

Review of the Nicotine Lozenges stability indicating assay test method validation showed that 4 of 6 forced degradation were ineffective. The study did not adequately anticipate observed degradation in the drug product; for example, Nicotine 2 mg Lozenge batch 6G0998 failed for assay at 18 and 21 months (b) (4) relative humidity. For investigation (b) (4) there was no reason given for the failure. And for deviation (b) (4) the 18 month stability failures for the largest unknown impurity for this same lot under project (b) (4) had no assignable cause. The deviation report stated that the current 24 month expiration dating period was justified by other data.

Response:

This observation will be broken down into specific points for ease of review and discussion in addressing each item.

1. Results of stability testing are not used in determining expiration dates.

Perrigo uses stability testing data (results and trending of results) to assign and maintain shelf life for products. The expiration date assigned to a specific batch is derived from the shelf life. For Monograph and ANDA products, the initial shelf life is established based on three months stability data generated on product stored under accelerated storage conditions (b) (4). The initial shelf life assignment for a product is then supported by stability data collected on product stored under room temperature storage conditions (b) (4). The initial shelf life can be changed based on the data collected on the product stored under (b) (4) storage conditions. When confirmed out of specification stability data are generated, a deviation investigation is initiated to identify root causes and corrective actions to provide direction to eliminate the causative forces, following the procedures defined by SOP (b) (4) (b) (4) (b) (4).

2. Review of the Nicotine Lozenges stability indicating assay test method validation showed that 4 of 6 forced degradation were ineffective.

Results of the stress studies for nicotine lozenges did yield degradation in all conditions (see summary in table below). Therefore, the forced degradation studies were effective for the assay method validation. Furthermore, the manufacturer of the Nicotine Polacrilex drug substance also performed forced degradation studies and concluded that Nicotine Polacrilex 15%, USP is a relatively stable material and that degradation of the compound only occurs while refluxing in oxidative conditions or applying extreme heat for a period of time, which are consistent with the data generated by Perrigo.

Condition	Experiment	% Degradation
(b) (4)	(b) (4)	

** For the acid/base hydrolysis, the drug product was exposed to a (b) (4) and base with (b) (4) applied for (b) (4) hours.*

Forced degradation studies on the drug product were conducted for assay test method validation (test method # (b) (4) titled Assay and Identification of Nicotine in Nicotine

2mg and 4mg SF Lozenges by HPLC) to determine the stability indicating property of the assay test method to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components.

As justified above, results of the studies did yield degradation in all stressed conditions. The forced degradation studies were effective for the assay method validation.

3. The study did not adequately anticipate observed degradation in the drug product; for example, Nicotine 2 mg Lozenge batch 6G0998 failed for assay at 18 and 21 months (b) (4) relative humidity.

It should be noted that there was no assay failure at the 18 month stability time point for Nicotine 2 mg Lozenge batch 6G0998 (manufacturing batch 6C1741). There was a confirmed assay failure only at the 21 month stability time point.

The purpose of the forced degradation method validation study is not to anticipate degradation of the drug product in the marketed package, which is accomplished through accelerated stability studies, but rather to show specificity of the assay test method for the drug substance. The assay method is not the primary method for determining the level of degradation products in the drug product. A separate impurity method is used (test method # (b) (4) titled (b) (4) (b) (4) which is validated to not only be specific for the API, but to also be specific for known degradation products

The assay forced degradation validation study adequately demonstrated that the measurement of the drug substance was unaffected by the presence of degradation products and concluded that the method is specific for the drug substance. The example provided by the agency demonstrates that the validation of the method was appropriate in that it did detect degradation of the drug product as manifested by the potency failure.

4. For investigation (b) (4) there was no reason given for the failure. And for deviation (b) (4) the 18 month stability failures for the largest unknown impurity for this same lot under project (b) (4) had no assignable cause. The deviation report stated that the current 24 month expiration dating period was justified by other data.

Both deviations listed in the observation are related to the same batch (# 6C1741), stability project (# (b) (4) and time points (18 and 21 months). Deviation (b) (4) is related to a potency failure investigation at 21 months and deviation (b) (4) is related to an impurity investigation at 18 months. Batch # 6C1741 was marketed with a 15 month expiration date and was expired before the 18 month stability time point that triggered deviation (b) (4)

It should be noted that there was no impurity failure for deviation (b) (4) at the 18 month stability time point or any other stability time point. Deviation (b) (4)

was an impurity investigation and was subsequently not confirmed. The identification of the peak that triggered the investigation was found to be related to the excipients (summarized in Analytical Report # (b) (4) which is included in the deviation report reviewed by the agency) and, therefore, was no longer identified as the largest unknown impurity. The reported largest unknown impurity for this batch is (b) (4), which meets the stability specification of (b) (4).

Deviation (b) (4) was a confirmed assay failure at the 21 month stability time point. No assignable cause has yet been determined for the potency failure. A thorough investigation, including the review of manufacturing records, packaging records, API & excipients records, investigation report from the manufacturer as well as testing of a reserve sample from another batch (#6G0999) using the same drug substance lot, was conducted. No abnormalities were found.

It is suspected that the cause of the potency failure is due to oxidation since the two known (b) (4) were also found to be at atypical levels in this batch although still within their acceptance criteria. These degradants were confirmed and identified as (b) (4) degradants based on the method validation forced degradation studies.

Six remaining stability batches have met all stability acceptance criteria through 24 month testing. The trending of assay data indicates that specifications would also be met beyond 24 months. Other stability studies initiated after subject batch (#6C1741) are consistent with these six studies through their current duration (longest at 21 months from date of manufacture).

The potency failure was not confirmed in reserve samples for the same batch that were tested at 25 months from the date of manufacture. This potency investigation remains open as Perrigo continues to seek out the cause for this failure. As indicated above, the overall analysis of all the stability studies supports the 24 month dating. Perrigo continues to initiate new annual studies and will continue to monitor the results of both open and new studies. At the closure of this deviation investigation, Perrigo will provide an update to the Detroit District Office.

Observation 9

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.

- A.) Black and white copies of raw weighing data for the impurity standards for stability testing of Cetirizine tablets on 7/23/2008 showed the weight ticket lot numbers added in blue ink and these changes were not dated. These changes were made as the documents were previewed prior to the FDA's review.
- B.) Microbiological raw data is placed directly into LIMS, with no check for accuracy.

Response:

Laboratory records are reviewed for accuracy, completeness and compliance with established standards and are governed by the following SOPs. SOP (b) (4) “(b) (4) (b) (4) SOP (b) (4) (b) (4) (b) (4) (b) (4)”, SOP (b) (4) (b) (4) and SOP (b) (4) “(b) (4)”

Laboratory records include the initials and/or signatures of a second level review in the notebook and/or (b) (4)

9A. We acknowledge that this particular incident, the addition of the reference standard lot numbers was not documented. The analyst and lab auditor have been counseled on this error. In addition, documented retraining for all of Quality Control-Stability analysts and Management Staff on SOP (b) (4) was completed on November 26, 2008 to ensure compliance with this standard laboratory documentation practice. It is the practice and expectation that the analysts will footnote with an explanation, initials and date, any additions or changes made on completed documentation per SOP (b) (4) (b) (4) Section (b) (4).

9B. Per our SOP (b) (4) and SOP (b) (4) total aerobic plate counts, combined mold and yeast counts, bile-tolerant gram-negative quantitative tests, specified organism and gram stain results are entered into (b) (4) (b) (4) (b) (4) as raw data along with the required sample information. SOP (b) (4) (b) (4) requires a laboratory management second level review of counts whenever a test result is equal to or greater than the alert limit. This management level review is documented within (b) (4) for the corresponding test. The use of the (b) (4) to record raw data and sample information within the Microbiology Lab is analogous to the use of a laboratory notebook. Information entered into (b) (4) is reviewed and approved by a second qualified individual and electronically documented. The (b) (4) program utilized by Perrigo is validated and is compliant with CFR Part 11 requirements.

The counting and recording of enumeration counts, gram stain reactions, and enrichment results are core training for the microbiology analyst and documented during the training and periodic retraining of the laboratory professionals per SOP (b) (4)

The analyst's ability to read and record the plate counts accurately is demonstrated by proficiency assessment after completion of each training session. To further challenge and verify the analysts' proficiency in reading the plate counts accurately, Perrigo is committed to initiate a program in which

analysts will be periodically required to read plates with known plate counts as part of the continuing certification process.

Observation 10

For components removed from the original containers, the new container fails to be identified with component name or item code, receiving or control number, weights or measure and batch for which component was dispensed including product name, strength and lot number.

- A.) On 9/15/2008 a pallet holding two unidentified drums and several raw material containers was observed in a hallway between several work centers in Plant ⁰¹⁶ Tablet Manufacturing. Batch record 8J2663 IM APAP ER mix formula (b) (4) was later identified as an aborted batch that had been the source of the pallet in the hallway. There was no note on the 9/8/2008 discovery of foreign material during milling on the batch record as required by the standard operating procedure.
- B.) On 9/15/2008 an otherwise unidentified box with "MAG" handwritten on it, containing a bag of white powder was observed in a warehouse on a pallet with other raw materials. Batch record 8G0284 APAP ER Release mix formula (b) (4) was later identified as an aborted batch that had been the source of the pallet of goods. The 7/25/2008 investigation into the metal found during Pregrind-1 was incomplete and did not include earlier batches for which the Pregrind-1 had employed the same (b) (4).

Response:

We acknowledge the incidents cited in observation 10 A and B. Both of these incidents involved a batch that was aborted prior to completion. Additional training and revisions to clarify SOP's have been initiated as outlined below to prevent similar labeling errors in the future.

The specific labels had been removed per procedure prior to charging, but the containers were never charged due to the batch processing interruption. SOP (b) (4) "(b) (4) (b) (4)" requires confirmation of labels against the batch record. The unidentified materials noted above could not have been used for future batches. Investigations were initiated and corrective actions identified for both incidents referenced above.

- 10A. *Unplanned Deviation (b) (4) was generated for this incident. Further investigation confirmed the materials in question were RM# (b) (4) and RM# (b) (4) that had been dispensed for use in batch 8J2663. The material had been checked in per procedure, but the batch was aborted prior to the two containers in question being charged. SOP (b) (4) will be revised to include the requirement that a scale print-out sticker be applied directly to all secondary containers. This label will remain on the container throughout check-in and use*

of material, rather than being placed in the receptacle as required by current procedures. This corrective action is targeted for completion on December 10, 2008. We acknowledge that the supervisor who generated the ORAF for the original incident should have footnoted the batch record as the quality event procedure states. The incident was reviewed with the supervisor as part of the investigation.

- 10B. Unplanned Deviation (b) (4) was generated for this incident. The unlabeled raw material product was confirmed to be RM # (b) (4) Magnesium Stearate. Raw materials were being charged for a batch of (b) (4) when the process was aborted and materials were returned to the warehouse. Scale printout stickers for the Magnesium Stearate had already been attached to the batch card. The specialist hand wrote "Mag" on the box but failed to attach a formal label. The same corrective actions identified for Item A will resolve the root causes for Item B.

Previous batches that used the same raw material and (b) (4) were reviewed to confirm that the incident did not impact or contaminate other batches. The contamination was very abrupt and immediately evident. The original investigation (b) (4) is now complete.

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