

Establishment Inspection Report

L. Perrigo Co.
Allegan, MI 49010-9070

FEI: **1811666**
EI Start: 09/15/2008
EI End: 11/07/2008

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SUMMARY

The inspection of this large generic OTC/Rx Drug Manufacturer and Medical Device Repacker was conducted under CP 7356.002 “DRUG MANUFACTURING INSPECTIONS”, 7352.832 “PRE-APPROVAL INSPECTIONS/ INVESTIGATIONS”, 7356.021 “DRUG QUALITY REPORTING SYSTEM – DQRS NDA-FIELD ALERT REPORTING” and FACTS assignment #4504996. No coverage of the medical device products was accomplished during this inspection.

Pre-approval assignments for ANDA (b) (4) finished dosage manufacturer and ANDA (b) (4) finished dosage packager was attempted. It was determined that Perrigo’s Allegan facility no longer has equipment to manufacture creams and does not have the powder filling equipment necessary for packaging the (b) (4)

A 9/17/08 DFI assignment requested follow up to a (b) (4) contaminated lot of Heparin. It was determined that Perrigo had not purchased heparin, ever. The most recent (10/07) related purchase was for (b) (4), batch numbers (b) (4) and

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(b) (4) were purchased, but billed to (b) (4) (Exh. RTB-33) as stated on the purchase order, but delivered to the Perrigo plant in Greenville, South Carolina where dietary supplements are manufactured. There was no CoA for the material provided. Firm management stated that it was believed that it was purchased from a domestic supplier.

Current inspection revealed GMP deficiencies as follows: instances of drug product production and control records were not reviewed by Quality Control resulting in multiple lots for 4 different products released with extended expiration date assigned; multiple instances of failure investigations not including conclusion and follow-up and left open for up to a year after the stability failure was noted; failure to initiate follow-up to two batch failures experienced for a chewable APAP children's product; failure to file a Field Alert following a labeling error for ANDA (b) (4) (Naproxen Sodium) resulting in product being released and marketed with extended expiration dating; failure to follow Quality SOP's pertaining to drug products externally manufactured; multiple examples demonstrating the Quality Control Unit's lack of responsibility for approving or rejecting externally manufactured drug products that did not meet established release specifications; two examples where established statistical controls were triggered and/or not used and product was released; results of a stability testing failure was overlooked with examples of successful stability results cited; laboratory records lacking check for accuracy; and observation of two separate, unidentified, raw materials in production and warehouse areas of manufacturing Plant (b) (4)

Recalls of Senna Laxative Tablets, on 9/24/08 (1 lot) and 10/21/08 (multiple lots); and Sleep Aid Tablets (1 lot) on 10/2/08 were initiated during this inspection. Management promised written response to the FDA-483 list of inspectional observations.

ADMINISTRATIVE DATA

Inspected firm: L. Perrigo Co.
Location: 515 Eastern Ave
Allegan, MI 49010-9070
Phone: 269-673-8451
FAX:
Mailing address: 515 Eastern Avenue
Allegan, MI 49010

Dates of inspection: 9/15/2008, 9/16/2008, 9/17/2008, 9/18/2008, 9/19/2008, 9/22/2008,
9/23/2008, 9/24/2008, 9/25/2008, 9/26/2008, 10/1/2008, 10/2/2008,
10/3/2008, 10/15/08, 10/20/2008, 10/21/2008, 11/6/2008, 11/7/2008
Days in the facility: 18
Participants: Patsy J Domingo, Investigator

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Regina T. Brown, Investigator
Caroline H. Le, Investigator

HISTORY

This publicly owned company, incorporated in 3/23/88, was originally founded in 1887 by Luther Perrigo, and remains the largest manufacturer of over-the-counter (OTC) pharmaceuticals for store-brand markets in the country. The firm's corporate headquarters are located at 515 Eastern Ave., Allegan, MI 49010 (b) (4) addresses in total), with additional US manufacturing plants at the newly acquired (announced during this inspection) JB Laboratories, in Holland, MI; Greenville, SC (manufacturing and warehouse locations); Bronx, New York; Chemagis USA, Inc., Mountin Lakes, NJ; as well as international facilities in the UK, Germany, Denmark, Israel, Mexico, India and China (see **exhibit Pjd-995** for names and addresses). Perrigo repackages products from external manufacturers, a listing of these suppliers together with firm's providing intermediate manufacturing or packaging steps can be found attached as **Exhibits Pjd-932/950**.

Inspection History

Inspection conducted 9/5-15/07 was directed to cover reported recall situation involving five lots of Children's OTC cough/cold medications packaged with a dosing cup not containing the ½ teaspoon dosing mark for children ages 2-6. Recall No D-029-2008 was initiated as a result of this problem. Inspection findings noted packaging materials that were not representatively sampled and examined upon receipt and before use in packaging of a drug product; and SOPs associated with sampling of packaging materials were not followed.

The 11/7-12/15/06 GMP inspection revealed a lack of complete investigation conclusion and follow-up and lack of thorough review of an unexplained discrepancy; quality control unit responsibilities not in writing or fully followed; failure to visually examine reserve samples; failure to apply results of stability testing in determination of expiration dates; lack of written procedures for the cleaning and maintenance of certain equipment; written production and control procedures not fully followed; Equipment not of appropriate design; deviations from written production and control procedures not justified; incomplete training given; written stability testing program not followed; established sampling plans not followed; entries in equipment logs not in chronological order; record of major equipment maintenance not included in individual equipment logs; failure to clean certain equipment and utensils at appropriate intervals; incomplete batch production and control records; representative samples of each shipment of each lot of component for testing not obtained; and complaint records lacked known reply to complainants in cases cited. Recall D-403-7 was initiated as a result of finding the metal sieve wiring in the acetaminophen granulation blend received from a manufacturer in China.

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This firm has been inspected on a for-cause basis on two occasions: 7/2005 and 3/2006. The 7/2005 inspection resulted in the issuance of an 8 point FDA-483 regarding complaint handling and investigations while the 3/28/2006 inspection resulted in the issuance of a 3 point FDA-483 regarding complaint handling. The 7/2005 inspection lead to the recall of several pediatric use OTC drug products (D-474/477-5).

The 8/9-9/8/04 GMP inspection revealed no assurance of content uniformity for Loperamide HCl 2 mg tablets produced 6/02-5/04; failure to follow Quality procedures when a lot of Saline Nasal Spray was released without testing and for failure to document a production deviation for 800 mg Ibuprofen tablets; complaint investigations of foreign tablet found in marketed product failed to evaluate all possible sources of contamination; failure to follow Quality SOP's; stability data not supporting marketed product for hemorrhoid ointment; finished devices released for distribution before review of associated data and documentation; reserve samples not representative of the batch.

Inspectional history dated to 4/26-7/14/00 is described in the 8/9-9/8/2004 Establishment Inspection Report.

FMD-145

Correspondence and post inspection FMD-145 letter should be addressed to:

Joseph C. Papa, President and CEO
L. Perrigo Company
515 Eastern Ave.
Allegan, MI 49010-1327

INTERSTATE COMMERCE

The majority of all sales and distribution both to the firm and from the firm are from/to Interstate sources. Additionally, Perrigo operates as a Foreign Trade Zone for the importation of materials from China to be further processed (Acetaminophen, Aspirin and Ibuprofen).

A listing of own label/private label customers is attached as **Exhibit Pjd-993/994**. Examples include: **(b) (4)**.

DOC Samples 505736/505738 provide evidence of Interstate Shipment.

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JURISDICTION

The L. Perrigo Company continues to operate as a large scale generic drug manufacturer of both OTC and Rx products. Perrigo is also an own label distributor of devices including pregnancy test kits, ovulation kits, and back/neck/knee/arm wraps.

The following lists were collected as documentation of Perrigo's current product line:

1. Active Formula List (**Exhibit Pjd-925/931**)
2. Approved Purchased Product List (**Exhibit Pjd-932/950**) which is a listing of Name and the number assigned to products packaged at this location or received as finished goods and distributed. The name and address of the contract manufacturer or contract processor (i.e. gelatin coating) is also contained in this list as well as an indication (Y or N) whether the product produced is a Perrigo formula.
4. Tablet ID List (**Exhibit Pjd-951/954**) which contains the 3(b) (4) [REDACTED].

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Joseph C. Papa remains as President and CEO and is ultimately most responsible for the L. Perrigo Company. Dr. Louis W. Yu, Senior Vice President – Global Quality & Compliance is the most responsible for Quality Operations at the firm. John T. Hendrickson resides as second most responsible at the firm, titled Executive Vice President of Global Operations & Supply chain. Mr. Hendrickson received and accepted the FDA 483, List of Inspectional Observations at the close of the inspection in the absence of Mr. Papa, who was present on the phone. Paul Weninger, VP, CHC Global Quality Operations reports directly to Dr. Louis Yu. Paul Weninger was our primary contact during the inspection, and accompanied us in all daily inspection activities. A copy of the Perrigo Company organization chart is attached as **Exhibit Pjd-969**. The Global Quality & Compliance Organization Chart is attached as **Exhibits Pjd-955/968**. This Global Quality Organization Chart includes a page (**Exhibit Pjd-956**) documenting Perrigo's New York, South Carolina, Mexico and UK location Quality Directors reporting to Paul Weninger.

Subject matter experts and contacts addressed during the inspection include:

Steven Lum, Vice President Global Compliance & Quality Systems

Tami Frederick, Quality Director Liquids Value Stream

Renee M. Robbins, PMI QA Services/Project Director

Shannon Hukill, Associate Director, Technical Support

Bart D. Schrode, Quality Director Tablet Value Stream

Nicolas J. Ford, Quality Manager QC Lab Liquid Value Stream

Erika Ballman, Validation Manager

James R. Young, Associate Director Pharmacovigilance & Consumer Affairs

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Annette Kushner, Sr. Manager Development QA
Marta Williams, QC Stability Manager
John D. Brown, Quality Manager External Manufacturing/Contract Sales Value Stream
Val Gallagher, Regulatory Affairs
Mike Andrus, Packaging Manager
Steve W. Laninga, Tablet Manufacturing Manager

MANUFACTURING/DESIGN OPERATIONS

Perrigo both manufacturers, and repackages drug products, both Rx and OTC solid oral dose and liquid/suspension for children and adults. A copy of the Plant Tour Overview provided to the inspection team can be found attached as **Exhibits Pjd-996/1020**.

**QUALITY SYSTEM
(RTB)**

The written Quality Unit responsibilities procedure (b) (4) was reviewed; the department was made up of Analytical R&D, QA, QC and Quality Systems, which was responsible for all validations and qualifications. The QURT is a meeting of Directors where metrics, trends, quality initiatives and significant quality events and investigation progress is discussed with management. Minutes for the July 2008 Meeting were reviewed and included metrics from the previous 3 months.

I looked at the (b) (4) production reviews (APRs) for formulas (b) (4) nasal sprays, APRs and process validation reports for pediatric suspension formulas (b) (4) and (b) (4), for Loperamide (b) (4) and for Naproxen formulas (b) (4). Stability tables for the asterisked items were reviewed. The Master Validation plan showed that packaging validations for Plant (b) (4) tablets and the PIAB blister packaging line, an online TOC and an aspirin dispenser equipment were not yet done. The qualification of the HVAC system in Plant (b) (4) was reviewed. In addition some process validations from the 1990s had been misplaced and new validations were planned.

Validation reports were dense and neither the reasons for the grouping of formulations under one validation nor the previous validation work was readily apparent. Process Validations covered: a new USP grade material alternate API Oxymetazoline supplier and the packaging validation for all the Oxymetazoline nasal spray formulas (b) (4) the 6/05 (b) (4) manufactured Pediatric Suspension formulas (b) (4) Child Liquid, (b) (4) APAP Grape and (b) (4) APAP Bubblegum, Cetirizine Tablet, (b) (4) Pseudoephedrine 12 hour were reviewed. An explanation for a statement about product similarities that had appeared in the latest Nasal sprays validation was provided (**Exh. RTB-34**) by the Technical Operations group.

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Famotidine validation batch records and records of the destruction of several validation batch records were reviewed. Batches for destruction were sent to a particular warehouse location and waited for the destruction order to be issued. They were then transported by transport by (b) (4) [redacted] were reviewed. There were no records to verify the numbers of rejected bottles that left the facility for destruction, except the batch record yield numbers.

It was noted that the hold time for totes of Famotidine blend were not established until 5/07.

Validations were reportedly performed as a “Temporary Changes” to the routine control procedures.

One Profile Project was reviewed that examined and successfully accomplished, by controlled change, a reduction in the number of (b) (4) [redacted].

(b) (4) series (Deviations) notifications as follows (b) (4) [redacted]

(b) (4) series (Production Advisories) investigations, as follows (b) (4) [redacted]

Quality System (Pjd)

(b) (4) series (deviations associated with externally manufactured product) notifications were reviewed as follows:

- (b) (4) [redacted] – Senna Lax Tablets (b) (4) [redacted]
- (b) (4) [redacted], -
81 mg Aspirin, (b) (4) [redacted]
- (b) (4) [redacted] – Chlorpheniramine Maleate (JB Labs)
- (b) (4) [redacted] – Loratadine D
- (b) (4) [redacted], – Cetirizine
- (b) (4) [redacted] – Nitetime PE Sinus Liquid gels (Accucaps)
- (b) (4) [redacted] – Nicotine Lozenges (Cardinal Health)
- (b) (4) [redacted] - Citirizine

(b) (4) series (deviations associated with externally manufactured product) notifications were reviewed as follows:

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(b) (4) , - blend uniformity sampling method
(Loperamide HCl)

(b) (4) - ,Loperamide impurity

(b) (4) – micro cleaning issues

(b) (4) APAP Allergy Sinus assay failure

(b) (4) (Draft) APAP 500 mg caplet metal contamination (b) (4) is APAP source)

(b) (4) – micro issues

(b) (4) – APAP Jr. Grape Chewable tablets

(b) (4) –Naproxen Sodium

(b) (4) – Sleep Aid Tablets

Inspection observation numbers (b) (4) all pertain to the Quality System failures.

PRODUCTION SYSTEM

Perrigo’s Allegan campus (b) (4). The following is a summary of the production related processes housed in each building:

Plant (b) (4) – houses stability labs and storage, and the liquid Pink Bismuth (Pepto) manufacturing (filling) line;

Plant (b) (4) - storage

Plant (b) (4) – Tablet manufacturing (dispensing, mixing, compression, coating)

Plant (b) (4) – Liquid manufacturing and packaging and Tablet Manufacturing

Plant (b) (4) – Consumer complaints and Regulatory Affairs

Plant (b) (4) – Tablet Packaging

ALC – Liquid labeling (bright stock) and Distribution/Finished product Warehouse

During this inspection visits, tours and inspection of Plants (b) (4) and the ALC facilities were accomplished. There have been no manufacturing activities in Plant (b) (4) since May 2008

(RTB/Pjd)

On 9/22/08 we (CSOs P. Domingo and R. Brown) revisited Building (b) (4) packaging to observe the recently (spring 2008) reconfigured vacuum dust collection connections to 14 tablet fillers that were recommended as a result of the Project Plan Team (PPT (b) (4)) and with results reported in document SAN #00017305.01. This Project Plant Team was reportedly formed to look for further improvement opportunities in response to complaints and or deviations noting mixed products which are categorized as “Perrigo foreign tablet”. Two such complaints are described below.

The soft parts of the vacuum system had been reconfigured within the past year such that the hose connecting the filler to the vacuum system now drops down in a (b) (4) then up to the main system at one end and up to the filler at the other. Prior to the lengthening and repositioning of the soft hose connections, the hard pipe joints could, when gravity and not vacuum was in effect, deliver

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dust/particles/tablets to the filler. The vacuum delivery hard piping has not been changed. It came down from the system mainlines just under the roof and the vertical piping had inverted “

(b) (4)

(b) (4)

” shaped joints that would permit material that “(b) (4)”, when the vacuum weakened or went off, to get closer to the tablet fillers. During our demonstration of the improvements made as a result of this project, we asked that dust duct inspection clean out port at the base of each hard pipe downward, be examined in our presence for non dedicated packaging line (b) (4) that had just finished a packaging run and had not been cleaned. We observed approximately 30 white tablets belonging to the Loratadine lot 8JE1328 that had just finished. In addition, we also observed a piece of a pink tablet and a chip from a green tablet. According to the packaging log, the pink tablet found was possibly from product packaged 4 lots prior to the most recently run lot. A similar demonstration was made on line (b) (4) where only tiny specs of previously run yellow and peach product were noted together with the white tablets of the current batch.

A map of this dust collector system is attached as **Exh. RTB-35** with a list of products filled on (which) packaging lines is attached as **Exh. RTB-36**. We were told the findings of the dust duct inspections were not recorded and therefore were not considered when complaint reports of foreign tablets were investigated at this firm.

In addition, it was noted that tablet filling lines located on the inside perimeter of the building showed long, ~20 foot plexiglass roofs over the covered conveyor holding/moving open bottles just inside pedestrian walkways.

Deviation (b) (4) dated 2/19/08 was initiated to investigate a complaint 72032 received for Batch 7KE0178 Famotidine 10 mg Tablets, 90's, which reportedly contained a white tablet embossed with “L194”, which described another Perrigo product, Famotidine 20 mg, Formula (b) (4), a product that had been packaged earlier and also on line (b) (4)

There were 3 complaints of the finding of a 20 mg tablet in a bottle of Famotidine 10 mg in the last 24 months. 27 incidents of foreign tablet findings were noted on the deviation list in the last two years.

Complaint #72588, dated 2/25/08, reported finding 3 caplets with L368 logo inside a bottle of Naproxen Sodium tablets lot (b) (4) (logo L490). Deviation (b) (4) was initiated to investigate this complaint as both L368 and L490 are Perrigo Naproxen Sodium products. The two products were packaged back to back on packaging line (b) (4). The investigation contained this statement from the Quality Unit Review Team (QURT) committee* that (b) (4)

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(b) (4) .” Reference to the above described Project Plan Team was listed in the disposition for complaint investigation (b) (4) .

*Committee members listed include: (b) (6)

Notably, since the last validations for pediatric suspensions manufactured in the (b) (4), the software used to control whole batch manufacture for the pediatric suspensions made in (b) (4) has not been used as programmed. Steps are manually programmed, one at a time, executed and then the next step, in a changed addition order, programmed into the PLC since a change control 4/08, that had been validated, after several years of moving away from the batch system. Cleaning procedure, preventative maintenance records and the equipment log for 08 were requested for the homogenizer equipped vessel.

Observation #10 describes two instances of failures of the manufacturing system to maintain identification of all raw materials

LABORATORY SYSTEM:

(RTB)

There was no impurity profile for Oxymetazoline Hydrochloride Nasal Spray products, and the Stability Specifications for Description for Formula (b) (4) finished drug products were changed 1/07 to add “light yellow” as acceptable color. A statistical analysis was reviewed that was used to show that the drug product assay would support aged material. It was noted that the USP has no related substances test for this drug product and that Perrigo does not test for drug product impurities.

The operation procedure for the (b) (4) laboratory instrument used by the firm for the identification of a limited number of incoming APIs was reviewed. It was noted that the standards to which APAP USP and (b) (4) APAP were different in two areas.

The Test Method validation procedure was reviewed.

Observation #9 concerns failures in the Laboratory system regarding verification of analytical values obtained.

The Microbiology Laboratory was not visited. The Supervisor and the senior microbiologist

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MANUFACTURING CODES

Perrigo uses different codes for their manufacturing and packaging operations.

Manufacturing or incoming (for externally manufactured lots) batch code assigned

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

Packaging batch code

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

COMPLAINTS

CSO P. Domingo accomplished follow-up to the following FDA received complaints:
62598 dated 8/26/08 which is the same as Perrigo complaints 93224 and 69251 (same lot)
61938 dated 7/28/08 for lot 7LE0477 L612 mixed with L10 – no complaints in Perrigo database
62990 dated 9/16/08 for Max Strength Antacid lot 8EK0314 (b) (4) label)
57868 dated 1/10/08 for Ibuprofen lot 7E0877 which is same as Perrigo complaint 67498
In each of these cases the complaint was isolated

CSO R. Brown reviewed complaints 49734, 49738, 96430, 33279, 73469, 86986, 80615, 74002, and 72032.

RECALL PROCEDURES

SOP (b) (4) (Exhibits Pjd-841/856) describes Perrigo’s recall process as starting with the Director of Quality Value Stream (Tablet or Liquid) notifying the Product Safety Committee of the preliminary product safety specifics. (b) (4)

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(b) (4)

Perrigo has had nine recalls since the previous GMP inspection 11/7-12/15/06. These include:

<u>Recall #</u>	<u>Product/reason</u>	<u>Date</u>
D-403-7	Acetaminophen products contaminated with metal	11/9/06
F-195-7	Vitamin E gelcaps labeled as Calcium with Vitamin D	1/31/07
D-029-2008	Dosing Cups lacking ½ teaspoon dose (various products)	9/6/07
D-041-2008	Enteric Coated Aspirin 81 mg acid phase failure stability	10/15/07
D-352-2008	Nicotine Gum 4 mg packaged inside box for 2 mg	5/19/08
D-037-2009	Sleep Aid tablets labeled with wrong expiration date	7/3/08
D-105-2009	Senna Lax Tablets stability failures super-potent	10/21/08
	Sleep Aid tablets labeled with wrong expiration date	10/2/08

A copy of the recall printouts from FDA’s tracking system, for the above listed recalls, is included as **Attachment #2**.

Follow-up to Recall D-037-2009 involving Sleep Aid Tablets lot 8EE0802 labeled with extended expiration date was accomplished during this inspection. The recall was the result of marketing this product in a new container type for which only accelerated stability data existed while assigning the extended expiration date approved for another packaging configuration. The error was not caught as a result of any of the established Quality Control checks prior to shipment. The error was noted by the stability department approximately one month later. The entire lot had not been shipped when the error was noted.

FDA’s follow-up as to the fate of the remainder of the lot, that had not shipped, resulted in the discovery that this same lot, which had been repackaged under lot number 8JE0699 had also been shipped with the same extended, 36 month, expiration date it had originally been packaged with (see FDA-483 observation 1.A). Again, established Quality Control checks had not caught this error. Since the bulk lot had already been placed on stability packaged as lot 8EE0802, additional samples had not been sent to the Stability Department. A second recall of the same bulk lot was initiated 10/2/08. A recall number has not been assigned for this 9th recall. See letter to FDA dated 10/3/08 and Field Alert also dated 10/3/08 attached as **Exhibit Pjd-1021/1023**.

Recall Information

Perrigo sent notification to customers, via a letter dated 10/1/2008, of a recall of Senna Laxative Tablets labeled under lot numbers 7EE0305, 7FE0474 and 7EE0671. These lots all originated from the same manufacturer’s **(b) (4)** bulk lot

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C049T assigned Perrigo bulk lot #7B0991. As an example of Perrigo's letter, a copy of the letter sent (b) (4) was collected and is attached as **Exhibits Pjd-1024/1027**. Also collected was the complete list of customers who received this lot of Senna Laxative Tablets which is attached as **Exhibits Pjd-1028/1035**. See also DOC 505737.

The portion of bulk lot 7B0991 packaged under the 7EE0671 lot number was finished under the following customer labels: (b) (4) (**Exhibits Pjd-1036/1040**); (b) (4) (**Exhibits Pjd-1041/1045**); (b) (4) (**Exhibits Pjd-1046/1050**) and (b) (4) (**Exhibits Pjd-1051/1055**). A total of (b) (4) bottles were packaged as documented on the Production Orders by Batch for lot (b) (4) (**Exhibit Pjd-1109**).

The portion of bulk lot (b) (4) packaged under the (b) (4) lot number was finished under the following customer labels: (b) (4) (**Exhibits Pjd-1056/1060**); (b) (4) (**Exhibits Pjd-1061/1065**); (b) (4) (**Exhibits Pjd-1066/1070**); (b) (4) (**Exhibits Pjd-1071/1075**); (b) (4) (**Exhibits Pjd-1076/1080**); and (b) (4) (**Exhibits Pjd-1081/1085**). A total of (b) (4) bottles were packaged as documented on the Production Orders by Batch for lot (b) (4) (**Exhibit Pjd-1110**).

The portion of bulk lot (b) (4) packaged under the (b) (4) lot number was finished under the following customer labels: (b) (4) (**Exhibits Pjd-1086/1089**); (b) (4) (**Exhibits Pjd-1090/1094**); (b) (4) (**Exhibits Pjd-1095/1099**); (b) (4) (**Exhibits Pjd-1100/1104**); and (b) (4) (**Exhibits Pjd-1105/1108**). A total of (b) (4) bottles were packaged as documented on the Production Orders by Batch for lot (b) (4) (**Exhibit Pjd-1111**).

More recalls of Senna Lax (Sennosides) Tablets 8.6 mg tablets were initiated by (b) (4) on 10/15/08 as documented in (b) (4) letter to Perrigo attached as **Exhibit Pjd-1112**. As can be seen in this 10/15/08 letter, (b) (4) bulk lot C049T, the same bulk as the above described recall, is also listed in this 10/15/08 letter together with 11 other bulk lots.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**Observations listed on form FDA 483**

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

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numbers 8EE0802 and 8JE0699 were assigned an unapproved 36 month expiration date and released.

B. Multiple lots of Naproxen Sodium 220 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 500 mg Gelcaps were assigned an unapproved 48 month expiration date and released. Examples include: 8GE0488, and 8GE0745

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

1.A. Sleep Aid Tablet lots 8EE0802 and 8JE0699 are from the same bulk lot (8D0825). The bulk was first packaged as lot 8EE0802 May 2008 as documented in the Customer Packaging Order for Batch 8EE0802 (**Exhibit Pjd-319**). This was the first lot to be packaged in this container (bottle) and all available stability data was for blister packaging. Samples of lot 8EE0802 were sent to the Stability Department for inclusion in a shelf life stability study.

Bulk lot 8D0825 was packaged under the (b) (4) brand label on 5/27/08 with Lot #8EE0802 and Expiration Date of 3/11 (**Exhibits Pjd-326/328**) assigned based on the information contained in Customer Packaging Order (b) (4) generated out of SAP (**Exhibit Pjd-325**). A Quality Assurance check on 5/23/08 approved the information associated with this packaging order stamping the document with a "COMPARED TO MASTER" stamp (**Exhibit Pjd-320**). A total of (b) (4) units were packaged (**Exhibit Pjd-325**). This material was released 6/10/08 (**Exhibit Pjd-319**).

On 6/30/08 stability personnel noted that a 36 month expiration date had been assigned to this product/packaging configuration when only 3 months of accelerated data existed. Deviation (b) (4) was initiated due to this error (**Exhibits Pjd-330/355**).

The Quality Review Team met and decided to retrieve any distributed product still in the customer's warehouse and to dump the undistributed portion of the batch back to bulk for reprocessing (**Exhibit Pjd-335**). A Field Alert was sent to FDA Detroit District on 7/15/08 (**Exhibit Pjd-342/343**). Investigation into the reason for the wrong expiration date being assigned lead to a change being initiated in SAP that affected all product formulas with multiple packaging configurations, "PDTs". This change, however, resulted in additional instances of product being assigned the wrong expiration date – see FDA-483 items #1.b & 1.c below for further explanation.

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Perrigo initiated a Rework Notification (b) (4) (Exhibit Pjd-356/360) to dump the now lot 8EE0802 back to 8D0825R (original bulk batch with an (b) (4)). This occurred on 8/20/08. In SAP the rework order simply indicated (b) (4). It did not specify how or where the expiration date was wrong, only that it was wrong (Exhibit Pjd-356).

As a follow-up to the original deviation of assigning the wrong expiration date I (Investigator Domingo) requested information regarding the reworked batch, whether it had in fact been repackaged following the rework and wanting to verify what expiration date had been assigned the reworked lot. This request was made early morning on 10/2/08.

On 10/2/08 Perrigo discovered, during review of the requested packaging batch record, that lot 8JE0669/8D0825R/8EE0802/8D0825 (these are all of the numbers associated with this lot, 8JE0669 being the most recent) was packaged and released with the same incorrect expiration date of 3/2011 as the first packaged portion that had been recalled. The batch, 8JE0669 had shipped 10/1/08 (see DOC 505736). Deviation (b) (4) was initiated 10/2/08 (Exhibit Pjd-361/370).

Perrigo SOP (b) (4) (Exhibit Pjd-371/380) work aid document (b) (4) (Exhibit Pjd-382) calls for a review of the rework paperwork for accuracy and completeness and to verify among other things that (b) (4) is assigned to the rework product. However, in the case of a rework, Quality Assurance has been trained to compare the expiration date on the rework paperwork to the information in SAP, which in this case would have been the incorrect expiration date that had originally been assigned to the bulk lot 8D0825. In addition at the time the lot is packaged for the second time, the paperwork available to the Quality Assurance that reflected the reason for the original rework, wrong expiration date assigned, is not made available. Quality Assurance has no other source or reference to use as verification of the correct expiration dating.

The Master Packaging Order for any packaging configuration is blank with regard to "Exp Date" in that this space will eventually hold the actual assigned expiration date for the individual batch, 03/11 in the case of lot 8EE0802. Nowhere on the Master Packaging Order is there an indication of the approved dating assignment, such as (b) (4), to the product in the particular packaging configuration represented.

1.B. & 1.C.

In an effort to prevent the reoccurrence of deviation (b) (4) described above, a change control was issued on 7/3/08 to make the change in SAP to all formula level designations for which multiple PDT level expiration dates exist (i.e. 24 months for one and 36 months for another package configuration for the same product). The change documentation for materials (b) (4) and (b) (4) are attached as Exhibits Pjd-385/386. The change called for the formula level dating to reflect the shortest dating at the packaging (PDT) level. There is a calculation performed in SAP associated with the assigning of the expiration date. When the change initiated on 7/3/08 was made,

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any lots that were in progress were adversely affected by this change. As a result formula (material) numbers (b) (4) had the potential for the wrong expiration date to be assigned. This error was not detected as part of Quality Assurance’s review prior to the release of product for distribution as the date assigned in SAP is the expiration date reflected on the packaging batch record. As was the case in 1.A. above, it is assumed the expiration date reflected in the record generated by SAP is correct. The only expiration date check is that the product labeling matches the batch record.

On 8/12/08, Stability personnel noted the expiration date on packaged batch 8HE0083 Naproxen Sodium 220 mg Caplets was at 48 month shelf life. Lot 8HE0083 is the packaged version of bulk lot 8E0180 which was manufactured 4/13/08 (prior to the 7/3/08 expiration date adjustment made in SAP). Naproxen Sodium 220 mg Caplets (material # (b) (4)) or Tablets (material (b) (4)) have an approved 36 month expiration dating assigned to them. Deviation 510000006578 was initiated with regard to this error. This draft investigation (Exhibits Pjd-387/427) identified (b) (4) batches affected by this deviation. I, Investigator Domingo requested a listing by product of the lots actually distributed (Exhibit Pjd-428). This list documents a total of (b) (4) lots of Naproxen Sodium 220 mg caplets, (b) (4) of Naproxen Sodium 220 mg tablets; and (b) (4) lots of APAP 500 mg Gencaps were distributed with 48 month expiration dates rather than the approved 36 month dating. It is unclear how a month went by and so many lots were released with 48 months expiration dating assigned when it is Perrigo practice to not allow greater than 36 month dating on any of their products. This business practice has been in effect since 2006.

In support of the labeled and released lots of Naproxen Sodium 220 mg Caplets and Tablets bearing 48 months, Perrigo provided the available stability data as follows:

Year Mfg	Product(s)	Data
1999	Caplets/Tablets	60 months
2000	Caplets/Tablets	48 months
2001	Caplets/Tablets	48 months
2002	Caplets/Tablets	48 months
2002	Caplets	48 months
2002	Caplets	48 months

(Exhibits Pjd-467/476)

There are no data supporting 48 months for recent years’ production. Batches manufactured in 2002 were the last to be placed on stability beyond 36 months.

The data provided in support of 48 month expiration dating assigned the APAP 500 mg Gencaps (Material (b) (4) does not go beyond 36 months (see Exhibit Pjd-429 gelatin coated by (b) (4) and Exhibit Pjd-430 gelatin coated by (b) (4)). Perrigo provided (b) (4)

(b) (4) (Exhibit Pjd-415). Minutes

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of Perrigo's Quality Unit Review Team (**Exhibit Pjd-422/423**) discusses the various other products' similar to the (b) (4) available stability data. The QURT ordered Correction Actions related to this labeling error included "(b) (4)

(b) (4)." I, Investigator Domingo, requested verification that this order had been set into action in the form of documentation that product (b) (4) had been placed under a stability protocol designed to continue out to 48 months. A summary of the available stability data for (b) (4) currently 6 months, is attached as **Exhibit Pjd-430**. To date only 6 months shelf life is available for the (b) (4) batches which are gelatin coated by a contract supplier (b) (4). Thirty-six (36) months of shelf life data is available for the (b) (4) batches (**Exhibit Pjd-429**) which were gelatin coated by contract supplier (b) (4).

The QURT ordered the release of all (b) (4) finished goods with 4 year expiration dating assigned on 9/12/08 based on the above mentioned worst case extrapolated expiration date based on the linear regression analysis (**Exhibit Pjd-423**).

Naproxen Sodium 220 MG tablets lot 8GE0281 was labeled with expiration date 01/12 (**Exhibits Pjd-519/526**) on 7/9/08.

Naproxen Sodium 220 Mg Caplets lot 8GE0304 was labeled with expiration date 02/12 (**Exhibits Pjd-528/534**) on 7/10/08,

APAP 500 mg (b) (4) lot 8GE0488, was labeled with expiration date 01/12 (**Exhibits Pjd-505/515**) on 7/16/08. On 9/18/08, a status change request form (**Exhibit Pjd-516**) was initiated by Quality Assurance to allow for the release of lot 8GE0488 prior to the close of deviation (b) (4) based on the attached QURT memo dated 9/12/08 (**Exhibit Pjd-517/518**) describing the stability data available for other APAP products "(b) (4)

Discussion with Management:

Discussions with Bart Schrode, Quality Director Tablet Value Stream and Paul Weinger, VP Global Quality Operations revealed decisions have not been made as to corrective actions to prevent such labeling errors from occurring again. An admitted lack of understanding the SAP system had caused the errors described in 1.b and 1.c to occur.

There was no discussion of this item during the exit interview.

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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) 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 for 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 deviation (b) (4) dated 6/12/2008, reported OOS 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 of (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) 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 7K2058, 8A2470, and 8C1587

C. Investigation of deviation (b) (4) dated 3/28/2008, reported an 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 81 mg Enteric Coated Aspirin tablet lot 6EE0500 manufactured by contract supplier (b) (4). This investigation remained open and unresolved. This lot expired March 2008.

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Reference: 21 CFR 211.192

Supporting Evidence and Relevance:**2.A.1.**

Deviation (b) (4), dated 12/18/07 (**Exhibit Pjd-535/583**), documents the 3-month stability failure (project (b) (4) for Senna Lax (Sennosides) Tablets, 8.6 mg lot 7B0991 (vendor batch C049T) packaged and released as lot 7FE0474 (also packaged as lots 7EE0305 and 7EE0671). This 3 month stability analysis represents the first analysis by Perrigo for this lot as Senna tablets are manufactured by (b) (4) and Senna tablets are routinely received/released based on C of A data supplied by (b) (4). As documented on the Stability Results Summary for Study (b) (4) **Exhibit Pjd-584**, this lot, 7B0991, was manufactured 4/2/07, packaged by Perrigo 6/27/07 and placed on stability as the once annual Senna Lax Tablet lot for the year 2007. The Three month sample was pulled 9/28/07 with the testing conducted 10/29/07 – 11/23/07.

It took additional failures 2/14/08 (6 month pull for lot 7B0991) and 3/10/08 (18 month failure for lot 6E0981 which had previously failed at 9 months on 8/21/07) and a 4 month time elapse (see Senna Potency Investigation Time Line attached as **Exhibit Pjd-559**) before a formal investigation was requested of (b) (4) (see page 3 of (b) (4) letter dated 4/17/08, **Exhibit Pjd-566**.) (b) (4) reported no root cause identified.

A third party testing laboratory, (b) (4), was involved beginning April 2007 with confirmation of OOS results reported in May of 2008 (see analytical C of A's **Exhibits Pjd-568/573**). This third party laboratory was deemed necessary as (b) (4) analytical results were not confirming the OOS results obtained by Perrigo. Attached as **Exhibit Pjd-571**, is (b) (4) 5/22/08 Certificate of Analysis reporting OOS analytical results for Senna laxative lot 7FE0474. Item #16 of Perrigo's (b) (4) "Materials" section (**Exhibit Pjd-547**) states "(b) (4)" that Perrigo pushed out the due dates for any open Purchase Orders that existed in their SAP system in an effort to not receive any new batches and no new orders were placed. The (b) (4). On 8/25/08, Perrigo placed all batches within expiry period on hold in SAP.

This deviation document also contains a time line section (**Exhibit Pjd-566**). The first entry is 8/21/07 for deviation "E-note" (b) (4) "for confirmed 9 month assay failure of stability project (b) (4) (Perrigo batch 6E0981)". The last entry was 9/16/08 which states "PMI received internal investigation from (b) (4) for notification (b) (4). No root cause identified by (b) (4)".

After discussions and review of this and other investigations involving Senna Lax tablets, investigation time line, the various stability failures and requests for all stability data, I, Investigator

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Domingo was told on 9/23/08 that Perrigo retain samples were being assessed. On 9/24/08 I was told (b) (4) was recalling lot C049T which is Perrigo bulk 7B0991 marketed as lots 7FE0474, 7EE0305 and 7EE0671. Per (b) (4) recall letter dated September 23, 2008 (**Exhibit Pjd-585**), this is the only lot involved in this recall. On 9/26/08 Perrigo sent a letter informing FDA Detroit District of the recall stating Wholesalers would be notified by letter issued by 9/29/08 (**Exhibit Pjd-586**). A copy of Perrigo's recall letter is attached as **Exhibit Pjd-1024/1025**.

2.A.2.

Deviation (b) (4) ("Draft") documents the 8/6/08 9-month stability failure of project 21247 for Senna Lax (Sennosides) Tablets, 8.6 mg lot 7G0903 (vendor batches G041T) packaged and released as lots 7JE0528, 7JE0529, and 7ME0269 labeled with expiration date of 07/09 (**Exhibits Pjd-587/629**). This stability failure represents the most recent in a series of stability or release assay failures for this product. The first page of the DMAID Deviation Document section of this deviation, Section A describes the deficiency as "(b) (4)

(b) (4) (**Exhibit Pjd-589**). The subject lot, together with numerous other lots, was, on August 25, 2008, added to the scope of the investigation. I, Investigator Domingo, was told by John Brown, Quality Assurance Director-External Operations that all lots within expiry were placed on hold and further shipment, if inventory existed, was stopped. Since only the most recent received product would be available in inventory, this hold was strictly a formality. (b) (4) investigation report attached as **Exhibits Pjd-610/612** reported no root cause for this failure.

2.A.3.

Deviation (b) (4) (Draft) (**Exhibits Pjd-630/695**), dated 8/23/07, documents the 9-month stability failure (project 20020) for Senna Lax (Sennosides) Tablets, 8.6 mg lot 6E0981 packaged and released as lot 6GE0670. Lot 6E0981 was assigned a 24 month expiration date of April 2008. The "18 month" stability pull resulted in OOS results 3/10/08. According to the deviation report (**Exhibit Pjd-630**), the 12 month stability pull was not tested due to the ongoing investigation. The 9 month failure of this batch was the first of three stability lots to exhibit failing sennosides assay results in the one year time span. In addition, one incoming lot also failed 10/30/07 and was not released. Attached to this deviation investigation report is a report of "Stability and Investigational Testing of Product 021AB" that lists chronologically each of the assays performed and the results obtained (**Exhibits Pjd-670/671**). This deviation investigation remained open for over a year prior to this inspection.

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2.B.

Deviation **(b) (4)** (Draft) **Exhibits Pjd-696/746**, dated 12/21/07, documents the failed bulk tablet Uniformity of Dosage assay generated 10/30/07 for incoming lot 7E1788 (vendor batch F052T) Senna Lax Tablets. Lot 7E1788 was the 2007 confirmation batch for external manufactured Senna Lax (Sennosides) Tablets 8.6 mg, product 021AB. Only one lot per year is analyzed upon receipt as confirmation of the C or A provided by the external vendor. According to the April 17, 2008 letter from **(b) (4)** attached to this deviation, Perrigo did not report the failing results to **(b) (4)** until 4/10/08 (**Exhibit Pjd-725/727**). This lot was placed on hold and remained on hold at the time this inspection brought attention to this failure and the other related failures.

A memo dated 6/24/08 regarding Rejected Confirmation batches (**Exhibit Pjd-744/745**) is attached to this investigation. This memo contains the statement "**(b) (4)**"

This 6/24/08 memo concludes "**(b) (4)**". As stated above, this deviation was not closed. Per John Brown, Quality Manager External Manufacturing Value Stream, confirmation testing was not conducted on subsequently received lots of Senna Lax (Sennosides) Tablets 8.6 mg, product 021AB. See Inspection observation 5.A. for more pertaining to this externally manufactured lot confirmation testing failure.

2.C.

Deviation **(b) (4)** (**Exhibits Pjd-755/776**), dated 3/28/08, documents the 18 month stability failure for Chlorpheniramine maleate lot 6F1641, packaged as lot 6GE0558 with a 48 month expiration date. The assay result obtained, **(b) (4)** is outside the specification range of **(b) (4)**. The original investigation copy provided was signed for the investigator 7/25/08 (**Exhibit Pjd-759**). The investigation disposition was blank.

Following my (Investigator Domingo) inquiry regarding this deviation a second copy of this deviation was provided (**Exhibits Pjd-777/808**). The following differences were noted between the two deviations: This second copy contains a different conclusion page signed by the investigator 9/24/08 and contains the statement "**(b) (4)**" also dated 9/24/08 (**Exhibit Pjd-781**). The Quality Unit Review Team meeting minutes, also dated 9/24/08, states the stability profile indicates little or no degradation further stating "**(b) (4)**" (**Exhibit Pjd-783**). The Ishikawa/Fishbone Root Cause Analysis section of the investigation is also different in this second copy. The Materials section contains an additional two points, 5 & 6 (**Exhibits Pjd-785/786**) and reference is made to an additional investigation conducted by J. B. Labs which is attachment 4 (**Exhibits Pjd-801/807**). JB Labs' original investigation report is included as attachment 2 (**Exhibit Pjd-798**). This batch at the time

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of receipt was released with C of A result from manufacturer (JB Labs) listing an assay value of (b) (4). See also Observation 6.B.

2.D.

Deviation (b) (4) (Exhibits Pjd-277/283), dated 7/31/08, documents the 24-month stability failure (Project 19954) for Aspirin 81 mg enteric coated Peach tablets, product 277AC, lot 6EE0500 (bulk lot 6C1427). The problem statement section states “A (b) (4)

(b) (4) “(b) (4)

.” Although this product expired 4 months prior to this stability pull, the section entitled (b) (4) states “(b) (4)

.” The investigator signed and dated this document 8/22/08. The “Investigation Disposition” and “Quality Reviewer” signature box and “Date” are blank.

See observation 6.D. for a discussion of deviation (b) (4) (Exhibits Pjd-54/137) and its association with (this) deviation (b) (4).

Discussion with Management:

There was no discussion of this item during the exit interview.

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 experienced 4 months apart for APAP 160 mg Jr Grape Chewable Tablets were both inconclusive. A Project Plan Request was issued 6/18/08. To date no activities have been initiated:

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Lot #	Date	Assay Result	Specification
7B0254	3/11/07	Acetaminophen Content Uniformity Assay (b) (4)	(b) (4)
7F1074	7/1/07	Acetaminophen Content Uniformity Assay (b) (4)	(b) (4)

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

Review of deviation database revealed two deviations referencing failing content uniformity results, below Perrigo’s specification limit of (b) (4), for product 449AF which is APAP 160 MG JR Grape Chewable tablets. Deviation (b) (4), dated 3/11/07 (**Exhibit Pjd-477/489**), was initiated for Acetaminophen Assay result of (b) (4). The investigation determined no root cause for the failure. “(b) (4)” was the statement for the “Improve” section of the investigation (**Exhibit Pjd-480**). The batch was rejected 4/5/07.

On 7/1/07 a second deviation was initiated, (b) (4) dated 7/1/07 (**Exhibits Pjd-490/499**), following confirmation of the content uniformity failure experienced for lot 7F1074. The investigation determined no root cause for the failure. The “Analyze for root cause” section states “(b) (4)” (**Exhibit Pjd-493**) The Improve section states “(b) (4)” (**Exhibit Pjd-499**) lists the target date of 10/1/07 for the corrective action of a Project Plan Profile QE 054-064 with a Failure Mode statement “(b) (4)” (**Exhibit Pjd-499**) This lot was rejected 7/30/07 (**Exhibit Pjd-493**).

The Annual Product Review for Product #449 Grape Chewable 160 mg, for the review period 4/1/07 – 3/31/08, was noted to contained a Project Plan Request document dated 6/18/08 (almost one year after the above failure investigation). A Project Team has not begun work for this product.

Discussion with Management:

There was no discussion of this item during the exit interview.

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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 Naproxin Sodium Caplets and Naproxin Sodium Tablets being released labeled with expiration dating exceeding the 36 months filed in the application ((b) (4)) by 12 months (48 months). Examples include: Lot (b) (4)

Reference: 21 CFR 314.81(b)(1)(ii)

Supporting Evidence and Relevance:

Field Alert was not generated following the discovery that multiple lots of (b) (4) tablets and caplets were released with expiration dating exceeding that filed in the application. Perrigo SOP (b) (4) ” (Exhibits Pjd-500/504) calls for form FDA 3331 to be submitted in the event of a labeling error. As described in observation 1.B. above, the assignment of 48 month expiration dating to (b) (4) tablets or caplets was as a result of a labeling error. Quality Assurance failed to identify the errors for over a month after the system change that caused the errors was initiated.

(b) (4) was packaged and released 7/11/08. As documented on pages from the Packaging Order for Customer Material Number (b) (4) Exhibit Pjd-531 and product label copy (Exhibit Pjd-532/534) this lot was assigned an expiration date of 02/12. This lot contained a portion of two bulk caplet lots – (b) (4) (Exhibit Pjd-529).

(b) (4) was packaged 7/9/08 and released 7/10/08. As documented on the Packaging Order (Exhibit Pjd-519) and product label copy (Exhibit Pjd-523/526) this lot was assigned an expiration date of 01/12. This lot contained bulk tablet lot (b) (4) (Exhibit Pjd-520).

Discussion with Management:

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Perrigo believes they are exempt from the Field Alert reporting requirement because the above (see observation 1.B) 48 month stability data had been included in their 2005-2007 Annual Reports to the Agency. The investigation team pointed out that the release of lots bearing 48 month expiration dating was an error and not the "minor change" described as annual report reportable in the 2004 Guidance Document. This error had the potential of not being realized except for the fact that one of the affected lots was submitted into the stability program where a second look at the expiration date assigned triggered the discovery.

There was no discussion of this item during the exit interview.

OBSERVATION 5

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

A. SOP (b) (4)

" calls for investigation of any failed/OOS confirmation batches. It further calls for QA to determine (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)

" 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) (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); (b) (4), and 325 mg enteric coated aspirin.

2. For JB Laboratories quarterly evaluations for (b) (4) 2007 and (b) (4) 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) (b) (4) evaluations for (b) (4) 2008 were both dated 9/26/08. (b) (4) manufactures Loratadine D 10 mg and Loratadine 10 mg QD tablets for Perrigo.

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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 two (b) (4), the majority concerning the condition of incoming shipping cartons of Omeprazole products. There was no written plan to ameliorate the problem.

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:

5.A.

SOP (b) (4)

“(Exhibit Pjd-747/754), Section G. a. states “(b) (4)

(Exhibit Pjd-750)

Deviation (b) (4) dated 12/21/07 documents the 10/30/07 failure of confirmation lot 7E1788 for Senna Lax Tablets (Exhibit Pjd-696/746). DMAIC Deviation Document section D. (Exhibit Pjd-700) states “(b) (4)

.” It is unclear as to the date this statement was added to this deviation investigation, although section B of this same DMAIC Deviation Document makes reference to the following activities:

- Perrigo analysts went to (b) (4) in November 2007
- (b) (4), a third part lab, performed the sennoside assay in May 2008
- In June 2008, all open Purchase Orders in SAP for material 021AB had their due dates extended
- The sennosides assay was performed at (b) (4) with a (b) (4) analyst in August 2008

A 6/24/08 memo, attachment #12 to this deviation, regarding Rejected Confirmation batches (Exhibit Pjd-744/745) lists “(b) (4)

The following documentation pertains to Senna Lax Tablet lots received from external manufacturer (b) (4) after the confirmation failure. Per John Brown, Quality manager External Manufacturing/Contract Sales no analytical testing of these lots (received in 2008) had been conducted by Perrigo. A list of Senna confirmation batches was provided and is attached as (Exhibit Pjd-907). Release of these lots was based on (b) (4) CofA:

1. Natural Senna Laxative Tablets assigned Perrigo Batch Number 7K2058 (b) (4) batch number K057T) was received 1/8/08 as documented in the purchased material receiving record

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attached as **Exhibits Pjd-857/865**. As can be seen on the Perrigo Certificate of Analysis prepared for this lot; assay, identification, content uniformity and dissolution results were taken from the CofA provided by (b) (4) Perrigo prepared Certificate of Analysis (**Exhibit Pjd-858**) is dated 1/13/08, almost 3 months after obtaining failing results for 2007 confirmation batch.

2. Perrigo prepared Certificate of Analysis attached as **Exhibit Pjd-866** documents Perrigo approved Natural Senna Laxative Tablets batch 8A2470 on 4/17/2008. This document also serves as evidence that the lot, Perrigo lot 8A2470, (b) (4) lot A188U was accepted based on (b) (4) CofA as "Method# C OF A" is documented in the Test Description column.

3. Natural Senna Laxative Tablets assigned Perrigo Batch Number 8C1587 (b) (4) batch number B054U) was received 4/7/08 as documented in the purchased material receiving record attached as **Exhibits Pjd-868/876**. As can be seen on the Perrigo Certificate of Analysis prepared for this lot (**Exhibit Pjd-867**); assay, content uniformity and dissolution results were taken from the C of A provided by (b) (4) (**Exhibit Pjd-874**). Perrigo's C of A is dated 4/11/08.

5.B.1.

SOP (b) (4) (Exhibit Pjd-877/881), calls for Quality Assurance to "compile data on a quarterly basis for all external manufacturers. The data will be presented in a quality scorecard which will be sent to manufacturers." (Exhibit Pjd-878) On 9/23/08, I (Investigator Domingo) requested the quarterly scorecards for (b) (4) January 2007 to the present. The requested documents were provided on 9/24/08. The last three quarterly reviews for (b) (4) (10/1/07-12/31/07), (1/1/08-3/31/08) and (4/1/08-6/30/08) were all provided with the Evaluation Completed Date listed as 9/23/08 (Exhibits Pjd-882/892). John Brown, Quality Assurance, Director- External Operations verified this meant the evaluations had not been shared with the manufacturer as specified by this SOP.

Of interest is the Quality Status documented for (b) (4) which is listed as "(b) (4)" meaning "(b) (4)". Three deviations listed on the second page of this 4/1/08-6/30/08 evaluation include (b) (4) (Exhibit Pjd-883). In each case the column "LT/CA Required" (Long Term Corrective Action) is documented as "NO". See Inspectional Observation 2.A. regarding these deviations. In addition, one consumer complaint listed for mixed tablets (both manufactured by (b) (4) indicates root cause could not be determined (Exhibit Pjd-883).

5.B.2.

Requested (b) (4) scorecards for JB Laboratories are attached as **Exhibits Pjd-908/918**. As can be seen, the (b) (4) 2007 report and the (b) (4) 2008 are both dated 9/22/08 indicating they

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had not been completed before my request to see them and subsequently have not been provided to JB Laboratories.

5.B.3.

Requested (b) (4) scorecards for (b) (4) are attached as **Exhibits Pjd-919/924**. As can be seen, the (b) (4) for 2008 reports are both dated 9/26/08 and have not been submitted to (b) (4). There is a corrective action listed (b) (4) 3) on the 4/1/08-6/30/08 evaluation which references deviation numbers (b) (4) and (b) (4) and the statement "(b) (4) (Exhibit Pjd-919). This corrective action had a due date listed as 9/22/08.

The two deviations referenced, (b) (4) dated 2/13/08 and (b) (4) dated 2/20/08 were both initiated in response to a portion of the referenced lot not meeting Perrigo's internal limit of (b) (4) and available stability data did not support 24 month expiration given the release value(s) obtained. In each case a portion of the batch, subplot 4, was rejected. There was no indication in the deviation documentation that the get together to align release limits has taken place. Both deviations were signed off by the Quality Unit Review Team on 6/11/08 – prior to the end of the review period for the quality evaluation.

5.B.4.

(b) (4) vendor quality evaluations show 18 (Exh. RTB-25) and 100 (Exh. RTB-26) advisories, respectively for the past (b) (4), the majority concerning the condition of incoming shipping cartons of the drug product Omeprazole. Mr. John Brown stated that there was nothing in writing that had been sent to (b) (4) and no written plan to arrange for improvements in the shipping methods or containers.

Discussion with Management:

There was no discussion of this item during the exit interview.

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 7J1978, released with a (b) (4) assay although your internal alert limit is (b) (4)

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B. For Chlorpheniramine Maleate from JB Labs, lot 6F1641exp. Date 4/2010, the OOS 18 month stability assay of (b) (4) was not predicted by "(b) (4)" from the release assay of (b) (4).

C. 1. For Natural Senna Laxative Tablets from (b) (4) 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)". However, distribution of previously received lots including (b) (4) continued through 8/25/08 or until gone.

C. 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:

Package Size	Lot Number	Expiration Date	Dating Assigned	Dates Shipped
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 Aspirin 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:

Package Size	Lot Number	Expiration Date	Dating Assigned
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

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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

Reference: 21 CFR 211.22(a)

Supporting Evidence and Relevance:

6.A.

Perrigo purchases Chlorpheniramine Maleate from J B Labs. Perrigo assigns Material number (b) (4) to this product. Upon receipt Perrigo inspects the product for defects and performs an ID test comparing the (b) (4). Assay, Content Uniformity and Dissolution values are taken from JB Labs' C or A and transferred to Perrigo's C of A for the lot. On or about 11/08/07 Perrigo received lot 7J1978 from JB Labs as documented on Perrigo Receiving Form for Batch 7J1978 dated 11/9/07 (Exhibit Pjd-815) and Sample Drawing Instructions for lot 7J1978 stating Date Received 11-08-2007 (Exhibit Pjd-813). The C of A for this lot, received (b) (4) that same day (Exhibit Pjd-816). Samples were drawn and submitted for description, defects, identification assay, and verification of C of A (see Exhibits Pjd-813/835). Perrigo's Certificate of Analysis for lot 7J1978 includes in the TEST RESULT column a "WARN" together with the (b) (4) result taken from the supplier's C of A. According to John Brown the Warning generated by LIMS is due to the Perrigo's Internal Alert Limit being (b) (4) % which as documented in the ESTABLISHED PRODUCT INTERNAL ALERT LIMIT APPROVAL FORM (Exhibit Pjd-839), was established 8/4/06.

A memo to the file, dated 12/14/07, (Exhibit Pjd-837), states "(b) (4)". This memo also states "(b) (4)". I question John Brown as to why they accepted this lot with assay values below their (Perrigo's) internal limit and why JB Labs would offer product not meeting Perrigo's limit. John Brown stated they had not advised JB Labs of this limit further stating it would not be fair to hold them to a specification they had not been made aware of. Deviation (b) (4) also substantiates this statement of failure to communicate Perrigo's Internal Alert Limit to JB Laboratories (Exhibit Pjd-761). JB Laboratories' release limit was (b) (4).

6.B.

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As described in deviation (b) (4) (Exhibit Pjd-781) and as documented on Perrigo Certificate of Analysis for lot 6F1641 (Exhibit Pjd-840) the Chlorpheniramine maleate release assay value for lot 6F1641, manufactured 5/24/06, was (b) (4) Perrigo memo dated 8/10/07 prepared “(b) (4)” describes an analysis of available stability data for Chlorpheniramine maleate manufactured by J.B. Labs (product #PC463AJ). According to this memo “(b) (4)

.” (Exhibit Pjd-838) This (b) (4) is outside Perrigo’s internal release alert limit approved 8/4/06 (Exhibit Pjd-839) which was the “(b) (4)” . As described in deviation (b) (4) dated 3/28/08, the 18 month analysis of product PC463AJ manufactured by JB Labs and assigned lot 6F1641 and an expiration of 4/2010 was found to be (b) (4) which is out of specification.

6.C.1.

Deviation investigations associated with Natural Senna Laxative Tablets manufactured for Perrigo by (b) (4) were described previously under observations 2.A.1 thru 2.A.3 and 2.B. The first being deviation (b) (4) (Exhibits Pjd-696/746) dated 8/23/07. As described previously in observation 2, each of these deviations remained open and unresolved. The investigation document, item #16 of Perrigo’s “(b) (4)” (Exhibit Pjd-547) describes the confirmation of Perrigo’s OOS findings by a third party laboratory and that on 6/6/08 Perrigo made the decision to stop receipt of future lots of Senna. Following this decision to stop purchasing, Perrigo continued, however, to distribute existing inventory of Senna as documented in the following lot history reports:

Packaged lot #	Dates distributed	Remaining quantity	Exhibits
8GE0279	7/18/08 – 8/25/08	(b) (4)	Pjd-970/976
8FE0688	7/11/08 – 8/18/08	(b) (4)	Pjd-977/983
8FE0141	6/13/08 – 8/6/08	(b) (4)	Pjd-984/989
8CE0043	6/9/08 – 6/27/08	(b) (4)	Pjd-990
8BE0070	2/11/08 – 8/10/08	(b) (4)	Pjd-991/992

6.C.2.

As a result of the various investigations pertaining to the stability failures experienced for 81 mg enteric coated aspirin products 535AD (yellow colored) and 277AC (peach colored) (see FDA-483 observation 6.D. below), change control orders to reduce the expiration date of both the 535AD (Exhibits Pjd-284/287) and 277AC (Exhibits Pjd-288/291) products were effected 1/18/08.

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Portions of these two 277AC lots, 7KE0619 (**Exhibit Pjd-301**) and 7HE0550 (**Exhibit Pjd-303**) packaged in 300 count bottles with 24 month expiration dating assigned were re-released and shipped after 1/21/08 despite the change control lowering the expiration dating to 18 months and after telling FDA at a meeting on 1/15/08 (see Perrigo post meeting summary letter dated 1/23/08 as **Attachment 1**) that dating had been reduced and marketing in the large containers had been discontinued. In fact, all 277AC (peach colored 81 mg enteric coated aspirin) lots labeled with 24 month expiration dates that had been on hold prior to the meeting with FDA were released (see QURT document attached to deviation **(b) (4)** (**Exhibit Pjd-60**)). The 277AC lots with current inventory at that time are listed on **Exhibit Pjd-65**. Similar lots of 535AC (yellow colored 81 mg enteric coated aspirin) were deemed acceptable to be reworked back to bulk provided they were labeled with an 18 month expiration date. A business decision concluded the 535 AC lots were destroyed rather than reworked. A listing of those lots can be found on **Exhibits Pjd-62/63**.

6.D.

This is a repeat of Inspectional Observation #5 from the previous (11/7-12/15/2006) inspection. That observation documented Perrigo's 24 month stability failure for 81 mg enteric coated aspirin product 535 AD, Lot 4DE0756 (bulk lot 4C1963) manufactured by **(b) (4)** packaged in 500 count bottles and labeled with 36 month expiration date. The investigation was conducted under E-Notification 51000002714 and the conclusion was some tablets in the batch may be damaged causing the release of the active ingredient to not be properly delayed. Recall D-355-6 was initiated for bulk lot 4C1963 and its associated packaged lot numbers only. Any lots still in house at that time were to be dumped back to bulk and repackaged with 24 month expiration date assigned. Lot 4C1953 had been the only stability lot for 81 mg aspirin tablets manufactured by **(b) (4)** packaged in the 500 count bottles. Marketed lots with 36 month expiration dating assigned were left on the market. A copy of the change control initiated to change the expiration dating from 36 to 24 months, dated 6/29/06, is attached as **Exhibits Pjd-304/306**.

The following are evidence of the continued stability failures experienced for enteric coated 81 mg aspirin products 535AD (yellow) and 277AC (peach) manufactured by **(b) (4)** **(b) (4)** and packaged and distributed by Perrigo:

1. As documented in the stability summary report for study **(b) (4)** (**Exhibit Pjd-16**), a similar failure was experienced for product 535AD lot 5F1484 packaged in 120 count bottles, with one desiccant, at the 18 month stability pull 2/14/07 and again at the 24 month pull 8/15/07. This lot, like lot 4DE0756 above, had been labeled with a 36 month expiration date. Deviation **(b) (4)** (**Exhibits Pjd-27/53**) was initiated 9/12/2007 following the 24 month failure. A check of the deviation database supplied this investigation team finds no record of a deviation initiated for the 18 month failure. Perrigo's investigation, which included an investigation report provided by manufacturer **(b) (4)** dated 10/04/07 (**Exhibits Pjd-43/53**), concluded lot 5F1484 (packaged lots 5GE0118, 5HE0086 and 5HE0589) should be recalled citing an incident that occurred during coating, that caused the agitation of the coating solution to be disrupted, as the

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reason (**Exhibit Pjd-33**). This document is silent as to the reason it took from 10/11/07 (the date the quality reviewer signed off on the report) until 2/11/2008 when the Quality Unit Review Team finalized their decision (**Exhibit Pjd-33**), the lot expired March 2008.

2. The stability summary for study 20004 (**Exhibit Pjd-18**) documents the 15 month failure experienced in November 2007 for product 535AD packaged in 500 count bottle, with two desiccants, under lot 6GE0396, from bulk lot 6D1309 ((b) (4) lot D012S). This lot was assigned a 24 month expiration date. Deviation (b) (4) (**Exhibit Pjd-54/137**) dated 11/30/07 was initiated to investigate this failure. The investigation report includes as attachments 7&8 an investigation report provided by (b) (4) (**Exhibits Pjd-120/127**). The Conclusion statement by the Quality Unit Review Team states "(b) (4)

Disposition section states "(b) (4) ."

" (b) (4) ."

3. The stability summary for study (b) (4) (**Exhibit Pjd-17**) documents the 18 month failure experienced 1/7/08 for product 535AD packaged in 500 count bottle, with one desiccant, under lot 6FE0361 which was a mixture of two bulk lots (6D1306 and 6D1307) from (b) (4) batches C090S and D011S. This lot had been labeled with a 24 month expiration date of March 2009. Deviation (b) (4) dated 1/7/08 (**Exhibit Pjd-138/162**) documents Perrigo's investigation with (b) (4) investigation as an attachment (**Exhibits Pjd-153/160**). The Quality Unit Review Team's findings (dated 3/4/08) made reference to the investigation conducted under deviation (b) (4) (above) again concluding no root cause found and no market action (**Exhibit Pjd-144**).

4. The stability summary for study (b) (4) (**Exhibit Pjd-20**) documents the 18 month and 24 month failures experienced March 2008 and September 2008 respectively for product 535AD packaged in 120 count bottle, with one desiccant, under lot 6HE0045 from bulk lot 6E0985 ((b) (4) lot D062S). This lot bore a 24 month expiration date of May 2008. The investigation of this failure is documented in deviation (b) (4) dated 3/10/08 (**Exhibits Pjd-163/198**) which includes (b) (4) investigation (**Exhibits Pjd-192/195**) dated 3/31/08 as well. This deviation report references deviation report (b) (4) stating "(b) (4)

" (b) (4) ."

5. The stability summary for study (b) (4) (**Exhibit Pjd-21**) documents the 18 month failure experienced March 2008 for product 535AD packaged in 300 count bottle, with one desiccant, under

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lot 6HE0167 from bulk lot 6F0893. This lot bore a 24 month expiration date of May 2008. There was no investigation of this failure (no deviation listed in data base provided this investigation team).

6. The Summary of Stability Projects and Data Available for PC-535, Level AD Aspirin 81 mg Coated Enteric Tablet (**Exhibit Pjd-1/2**) did not list study (b) (4) and a Stability Results Summary for study (b) (4) was not provided when copies of all stability projects for Product 535AD was requested.

Deviation (b) (4) dated 6/12/08 (**Exhibits Pjd-199/229**) documents the investigation of 21 month pull stability failure experienced for product 535AD lot 6F0898 (project number (b) (4) packaged in 180 count bottles under lot 6HE0322 with a 24 month expiration date of 5/30/08. The investigation includes (b) (4) investigation (**Exhibits Pjd-220/225**) of their lot #E096S. In their investigation (b) (4) told Perrigo they were “(b) (4)”. A copy of the signature page from (b) (4) recent process validation report for “Aspirin Delayed Release (Enteric Coated) Tablets USP, 81 mg (b) (4) Product Code Numbers 135R and 219R) is attached to this deviation report as Attachment 5 (**Exhibit Pjd-229**). Perrigo referenced deviation (b) (4) s conclusion as the conclusion for this failure. The investigator has requested the Quality Unit Review Team make the disposition for this deviation on 7/31/08 (**Exhibit Pjd-202**). This deviation remained open at the time of this inspection.

The Stability Summary for study (b) (4) (**Exhibit Pjd-233**) documents the 18 month stability failure for product 277AC bulk lot 5F1324 packaged in 180 count bottles labeled as lot 5FE0743 and expiration date 4/2007 (24 months). Deviation (b) (4) dated 1/18/07 (**Exhibits Pjd-238/276**) documents Perrigo’s investigation of this failure. Included is (b) (4) investigation (**Exhibits Pjd-250/254**), (b) (4) C of A for lot D037R (**Exhibit Pjd-255**) and the available stability data for this product (**Exhibits Pjd-256/265**). Bulk lot 5F1324 was used in multiple packaged lots, 5GE0858, 5GE0593, 5GE0434, 5GE0174, 5FE0927, and 5HE0162 which were all placed on hold on 2/1/07 after the failure was confirmed analytically. As described in the DMAIC Deviation Document (**Exhibit Pjd-242**) the stage 1 results failed such that S2 and S3 testing would not have changed the OOS result. No definitive Root Cause determined. The Conclusion (Recommendation for Disposition) states “(b) (4)” (**Exhibit Pjd-243**). The Investigation Disposition states “(b) (4)”. This is dated 3/23/07.

Deviation (b) (4) contained no statement from the QURT, however; Perrigo representatives had contacted FDA’s Detroit District office regarding this failure on 3/15/07 via telephone to inform FDA of the problem. In the follow-up letter dated 3/26/07 (**Exhibit Pjd-298/300**) Eric Koldziej, Vice President Quality & Compliance stated “(b) (4)”

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The Stability Summary for study (b) (4) (Exhibit Pjd-234) documents the 24 month stability failure for product 277AC bulk lot 6C1427 packaged in 180 count bottles labeled as lot 6EE0500 and expiration date Mar 2008 (24 months). Deviation (b) (4) dated 7/31/08 (Exhibits Pjd-277/283) states “A (b) (4)

(Exhibit Pjd-280) This document further states “(b) (4)

.” The Investigator signed this document 8/22/08 with the usual statement “(b) (4) .” This deviation remains open as of this inspection.

Stability Summary for study (b) (4) (Exhibit Pjd-236) documents a 9 month stability failure for product 277AC bulk lot 7E1400 packaged in 180 count bottles labeled as lot 7HE0052 and expiration date May 2009 (24 months). No investigation was initiated for this failure (no deviation found in data base provided this investigation team). The 12 month Acid Phase did not yield a failing result.

The following is a chart that summarizes the available stability data for product codes 535AD and 277AC 81 mg enteric coated aspirin manufactured by (b) (4) for Perrigo.

STABILITY SUMMARY

(b) (4) mfg Product Code 535AD 81 mg enteric coated aspirin (Yellow)

Lot	Exp Date	Date Mfg.	Size/Des**	Stability Data	Failure
4DE0756	1/2007	2/6/04	500/1	30 months*	24 month
6FE0361	3/2009	4/27/06	500/1	12 months	18 month
6GE0396	4/2008	5/8/06	500/2	12 months	15 month
7FE0096	1/2009	2/15/07	500/2	12 months	N/A
6HE0167	5/2008	6/23/06	300/1	24 months*	18 month
6HE0169	5/2008	6/26/06	365/2	24 months	N/A
2DE0148	1/2005	4/11/02	120/1	12 months	18,24,30 mon.
4EE0157	1/2007	5/18/04	120/1	30 months	N/A
5GE0118	3/2008	4/14/05	120/1	12 months	18 & 24 mon.
6HE0045	5/2008	6/8/06	120/1	21 months*	18 & 24 mon.
7EE0179	12/2008	1/23/07	120/1	12 months	N/A
7KE0158	6/2009	7/25/07	120/1	9 months	N/A

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(b) (4) mfg Product Code 277AC 81 mg enteric coated aspirin (Peach)

Lot	Exp Date	Date Mfg.	Size/Des**	Stability Data	Failure
4JE0165	4/2006	5/12/04	180/1	18 months	24 months
4KE0402	4/2006	5/14/04	180/1	18 months	24 months
4LE0626	4/2006	5/17/04	180/1	24 months	N/A
5FE0743	4/2007	5/6/05	180/1	12 months	18 & 24 ***
6EE0500	3/2008	4/3/06	180/0	18 months	24 months
<u>7HE0052</u>	<u>5/2009</u>	<u>6/11/07</u>	<u>180/1</u>	<u>12 months*</u>	<u>9 months</u>
7HE0550	5/2009	6/11/07	300/2	12 months	N/A

* months of stability with a prior failure

** Des = Desiccant (number in container)

*** See 3/26/07 letter regarding this failure from Perrigo to DET Compliance Officer J. Putz

A List of marketed 81 mg enteric coated aspirin lots assigned greater than 18 month expiration dating that had not expired was requested and is attached as **Exhibits Pjd-292/296** for Product 535AD and as **Exhibit Pjd-297** for Product 277AC. The lots listed for this observation represent all packaging sizes on the market.

Discussion with Management:

There was no discussion of this item during the exit interview.

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 4/29/08 packaging of tote **(b) (4)** of **(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)** Formula **(b) (4)** the source batch record, showed that the

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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 10/1-12/31/07 APAP ER 650 mg Tablet formula (b) (4) within specification dissolution profile changes in (b) (4) of batches. In addition, the reason for the rejection of batch # (b) (4) for which the immediate release tablet layer failed, was not determined.

Reference: 21 CFR 211.22(a)

Supporting Evidence and Relevance:

7A

A. The 4/29/08 Perrigo Production Tracking sheet (**Exh. RTB-1 pg. 3**) showed that a deviation had been raised for foreign particles in a product being packaged. Tracking sheets were considered non-cGMP and were not kept by the firm for longer than 3 months. The sheet that is subject of this discussion was found in a waste tote in the filling area. The codes used on the sheet were also collected (**Exh. RTB-2**). The packaging sheet showed that during (b) (4) packaging on line (b) (4) packaging had been stopped for foreign particles. The Risk Assessment Form (**RTB-4 pg. 3**) showed the floating particles on (b) (4) liquid # (b) (4) in tote (b) (4) and also particles embedded in the bottles. An AQL for the bottles passed and for the floating particles, was failed (**RTB-4 pg. 5, 6**). Canceled Notification Event (b) (4) (**Exh. RTB-4 pg. 2**) showed that the lot was related to packaging of lot (b) (4), also, (b) (4). The (b) (4) specialists team, packaging the batch in the evening followed procedure and had identified failing drug product and the QA person had signed the Risk Assessment 4/28/08.

The Production Advisory report (b) (4) (**Exh. RTB-4 pg. 1**) showed that the failed result was overturned (also see **Exh. RTB-4 pg. 4**) because they appeared to be raw materials, and the tote was filled without further investigation and released. The note made on the reverse side of the risk assessment was dated 5/01/08 was signed by a packaging supervisor, Mr. T. Sinalla. The Risk Assessment decision was overturned and a different QA person signed the document showing the product was approved, based on the production persons' assessment. Documents showing that the lot (b) (4) was packaged and released (**Exh. RTB-7**) were reviewed during this inspection.

The (b) (4) Formula (b) (4) source batch record showed that the manufacturing batch was aborted (**RTB-5 pg. 34, 37**) because of a mixer scale malfunction, after drum rolling spills, and then begun again, with new raw materials weighed out (**RTB-5 pg. 2, 3, 5, 6 & 7**) (new-**RTB-5 pg. 19-25**). The cleaning/use log for the work center (the room(s) holding

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the production equipment) showed that there had been no cleaning done after the previous batch (b) (4) or during the manufacturing of the batch (b) (4) (Exh. RTB-6).

During the discussion with management, it was stated by management that both the initial decision and the decision overturning the first had been approved by the Quality Unit.

7.B.

B. A list of Projects was obtained that described the focus for groups working on several production, packaging and product issues (Exh. RTB-8). Open Project Profile (b) (4) was set up to examine the reason for the sudden necessity for (b) (4) stage testing for bilayer tablet APAP Extended Relief 650 mg Tablet Formula formula (b) (4) batches in (b) (4) of output during 10/1-12/31/07, the firm's (b) (4). There were no meeting minutes available for the progress of this group, according to Mr. B. Shrode, who also stated that the problem disappeared, so that there was no longer a necessity to meet. A chart describing the problem and the (b) (4) released product lots and active pharmaceutical ingredient (API) lot numbers involved were made available (Exh. RTB-9).

The 10/26/07 investigation (b) (4) showed that Batch (b) (4) was rejected for not meeting release specifications at (b) (4) dissolution specification was not met; the immediate release tablet layer failed. There was no reason for the failure revealed; however, it was established that the disintegrant had indeed been added to the layer (Exh. RTB-10).

There was no investigation into the failure and the follow-up batches that necessitated second level dissolution testing to meet the release specification. CSO Brown's inquiry into the API quality, showed that the API lots had all been accepted based upon a reduced testing scheme, reportedly, a Near IR identification in the QC laboratory; the API CoAs from the supplier, (b) (4) were the only source of information such as particle size. (b) (4) API 2007 CoAs were collected (Exh. RTB-11).

Vendor Qualification for APAP (b) (4) was requested and provided for review. It showed that the vendor was approved 6/08 in SAP and that the vendor (b) (4) t, had assigned a 5 year retest date to the substance and, a document was reviewed that showed that this suppliers material was used in product formulas that began with the numbers (b) (4). There were several other APAP raw materials purchased by this firm-they included APAP (b) (4) Coarse (from (b) (4)), with a three year retest date, unapproved APAP Granulation (b) (4) (from (b) (4)) and APAP USP (b) (4) with a three year retest date (from (b) (4)). When I, CSO Brown asked which one was used in the lots that were statistically variable as described above, it was stated at first, by Mr. John D. Brown, Quality Assurance, Director - External Operations that it was the Kangle Wenzho manufactured product supplied by (b) (4) which had been approved 10/24/07 in SAP. When Mr. J. Brown returned to the topic, he stated that (b) (4) had manufactured and supplied the same material to Perrigo and was the supplier before 6/08 also. The approval document for the supplier prior to 6/08 was reportedly 6/18/07 and this was seen on an

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image of the SAP screen provided. There was no information in the (b) (4) vendor file that indicated that any raw material variance had been observed at Perrigo.

In summary, statistical controls showed that there was a problem and that it was not defined and that it disappeared. There was no investigation into the difference between (b) (4) released drug product and other production materials. It appeared that for QA, production department success in subsequent drug product lots after a lot failure and unusual lot laboratory data and results, was permitted to overcome the authority and the responsibility of QA to better define the initial problem and to initiate corrective and preventative activities.

There was no discussion of this item during the exit interview.

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 #6GO998 failed for assay at 18 and 21 mo. (b) (4) Relative Humidity. For Investigation (b) (4) there was no reason given for the failure. And for deviation (b) (4) the 18 mo. stability failures for largest unknown impurity for this same lot under project (b) (4) had no assignable cause. The deviation report stated that the current 24 mo. expiration dating period was justified by other data.

Reference: 21 CFR 211.166(a)

Supporting Evidence and Relevance:

A 1/06 communication with FDA about the ANDA 77-007 for Nicotine for the products was determined to be necessary (Exh. RTB-12).

The stability indicating test method was reportedly the chromatographic Impurities test method dated 4/08 (Exh. RTB-13). The 9/08 assay test method was also reviewed (Exh. RTB-14). This product is manufactured at (b) (4)) and the quality agreement between the firms was provided (Exh. RTB-20).

Ms. Marta Williams, QC Stability Manager, who ran the (b) (4) for this firm, provided a summary for the 2 mg lots of blister packaged Nicotine Lozenges in the stability program (Exh. RTB-15)(the 4mg product has not been in demand). It was noted in a data

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summary that Lot 6C1741-6G0998, manufactured 6/06 had been OOS for assay at 21 mo (**Exh. RTB-16**). Notably, the 18 mo. largest unknown impurity failure at (b) (4) for the same lot was not noted on the summary. The 5/08 assay investigation (b) (4) (**Exh. RTB-17**) showed no root cause identified. The 4/08 unknown impurity investigation showed (**Exh. RTB-18**) that the expiration date on the product was 8/07 or 14 mo. after manufacture. The suspect peak was not noted during forced degradation (see **Exh. RTB-22**) and was determined to be a degradation product that appeared when the product was stressed dry, that is believed to be related to degradation of components in the tablet matrix, which the firm calls placebo, and not to the degradation of nicotine in the drug product.

I, CSO Brown, compared the hardness values for this lot to that of a few of the other lots on the stability program (**Exh. RTB-19**) and it was noted that they were lower, on average for the failed batch. It was also noted that lots 7A0887-7D1941, 7A0855-7D1940 had a largest unknown impurity at the limit at 9 mo. (**Exh. RTB-19 pg. 1, 3**) and 6H0933-6M1312 at 15 mo. (**Exh. RTB-19 pg. 6**). Notably, the product is currently assigned a 24 month expiration period.

Review of the Nicotine Lozenges stability indicating assay validation showed that 4 of 6 forced degradation studies had failed to degrade the stressed product to the extent that it was outside of the assay specification of (b) (4) (see product specification, **Exh. RTB-21**) and showed extensive degradation in acid and peroxide of well over (b) (4) (**Exh. RTB-22 pg. 7**). The study concluded that the impurity test method was stability indicating. The stability study design, forced degradation in various aqueous solutions, did not adequately permit the anticipation of unknown impurity that has been now seen during product degradation. The determination of expiration dating of 24 months for the 2 mg drug product has not been reconsidered since the impurity has been observed.

There was no discussion of this item during the exit interview.

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 7/23/08 showed 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 FDA's review.

B. Microbiological raw data is placed directly into LIMS, with no check for accuracy.

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Reference: 21 CFR 211.194(a)(8)

Supporting Evidence and Relevance:

A. A sheet showing stability lots available for Cetirizine 10 mg was provided (**Exh. RTB-23**). Review of the stability impurity test data for the 36 mo. data for Cetirizine 10 mg Tablets, lot #3M1257V-4AD0008V. Black and white copies of the notebook pages were provided that showed the raw weighing data for the impurity standards were marked with writing in blue ink on the print outs from the balances (**Exh. RTB-24 pg. 1** (pg. 2 is reduced in size)). The changes to the copies were not dated. The laboratory review of data had not been a complete check; the missing impurity reference standard lot numbers. The analyst, (b) (6), was interviewed and he stated that he had made the change right before the data was brought into the room for my (CSO Brown) review. The original notebook was requested and provided for review and it did not have the standard materials identified on the print outs stuck onto the notebook page (b) (4).

There was no discussion of this item during the exit interview.

B. A Microbiologist and his Supervisor, brought a chart with water system microbiological test results that were greater than one for review. The Microbiologist stated that R2A was the media used and that it was good for finding injured microbes and that 7 days was the typical incubation time total. He stated that the system in Plant (b) (4) was sanitized on the (b) (4) and samples were taken on (b) (4). The sample analyzed was 1 mL on a plate. The USP test methodology was reportedly followed. The Microbiologist explained that growth promotion was done on each batch of media prepared.

There was no written test method specific to the water testing.

When the raw data for selected water samples from 2008 trend listings were brought into the room, they were in the form of printed images from a computer system screen. The Microbiologist and his Supervisor both stated that plates were read and the results entered directly into the (b) (4) system and that there was no second person who looked at the growth on the plate. There was no laboratory review of the data, the plates, and no record to show accuracy and completeness of the results recorded.

The Microbiologist reported that the system in Plant (b) (4) were sanitized with hot water and steam on the (b) (4) and that sampling was done on (b) (4). I explained that the best time to sample to see the same conditions that the water is in when going into products, would be (b) (4) before system sanitization.

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Discussion with Management:

Management asked for the clarification during the exit interview that it was indeed that the raw data was directly entered into the (b) (4) system without a check for accuracy.

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, weight or measure, and batch for which component was dispensed including product name, strength and lot number.

A. On 9/15/08, a pallet holding two unidentified drums and several raw material containers was observed in a hallway between several work centers in Plant (b) (4) 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 of the 9/8/08 discovery of foreign material during milling on the batch record, as required by standard operating procedure.

B. On 9/15/08, 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 7/25/08 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)

Reference: 21 CFR 211.101(b)

Supporting Evidence and Relevance:

A. During walk through on 9/15/08 a pallet holding two unidentified and unlabeled drums as well as several raw material containers was observed in a hallway. Late in the day, the material on the pallet was identified as the remaining material from Batch #8J2663, the Batch Record #8J2663 IM APAP ER MIX formula # (b) (4) (Exh. RTB-27 pg 11) showed that the operator had stopped at a fitzmilling step. There was no notation about the reason for aborting the batch in the Batch Record, as required by SOP (b) (4) Exhibit Pjd-312).

Notification (b) (4) (Exh. RTB- 28) was initiated 9/15 for the 9/8 events that, according to the ORAF, led to the aborted batch. The supervisor statement (Exh. RTB-28 pg. 3) stated that the previous batch 8H2334 (as shown on the cleaning and use logs (Exh. RTB-29 pg. 3)) should be

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reviewed because it had used the same (b) (4) (EIN 102995 and 111665). All materials were removed from the work area and a major clean done.

The reason for the presence/source of the pieces of foreign material was not further investigated.

No assessment of the previous product lot was performed.

The foreign matter was observed and identified on the baggie enclosing it. On 9/15/08 an investigation was begun.

I asked for the scorecards for the vendor of methocil, which was projected to be the bagged item that was the source of the blue paper on 9/15/08. There were 3 other foreign matter deviations found in this IM Mix in the last 24 months).

In addition, it was noted on the cleaning records that passivation of equipment was mentioned (**Exh. RTB-29 pg. 4**). Ms. Erika Ballman, Validation Manager, stated that there were no operational or scheduling written procedures describing the passivation of equipment.

B. An unlabeled box with "MAG" handwritten on it contained a bag of white powder and was observed on 9/15/08 on a pallet with other raw materials. Later in the day, the batch the pallet had been involved with was identified as batch #8G0284 and Batch Record #8G0284 APAP ER Release Mix Formula (b) (4) was provided (**Exh. RTB-30**).

The batch was aborted during Pre-grind-1 (**Exh. RTB-30 pg. 5**) due to (Perrigo source (**Exh. RTB-31 pg. 2**)) metal razor blade pieces caught by a magnetized grid (see ORAF **Exh. RTB-30 pg. 15**). Earlier campaigned batches of Formula (b) (4) that had been through the same (b) (4) and grid were not examined as part of the investigation; mill cleaning records were examined (**Exh. RTB-32**).

Discussion with Management:

There was no discussion of this item during the exit interview.

REFUSALS

None

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GENERAL DISCUSSION WITH MANAGEMENT

Prior to the inspection close out, I, Investigator Domingo, attempted to present documentation and Affidavits prepared to document GMP deficiencies noted during the course of this inspection. Mr. Hendrickson stated they would not acknowledge affidavits as a matter of corporate policy. The subject of these documentation samples is described under the heading SAMPLES COLLECTED.

At the conclusion of the inspection, form FDA-483, Inspectional Observations, was issued to John T. Hendrickson, Executive Vice President of Global Operations & Supply Chain in the absence of Joseph C. Papa, President and CEO who was present via telephone. Other individuals present included: Dr. Louis Yu, Sr. VP Global Quality & Compliance; Paul Weninger, VP CHC Global Quality Operations; Steven Lum, VP Global Compliance & Quality Systems; John D. Brown, Director QA External Operations; Greg Kurdys, Senior VP Operations; Steve Steffes, Director, Liquid Value Stream; Shannon Hukill, Director Technical Operations; Bruce Haney, Director Analgesic Tablet Value Stream; Charles Terpstra, QA Manager, Tablet Value Stream; Renee Robbins, Director QA Services; Bart Shrode, Director – QA Tablet Value Stream; Tami Frederick, Director Quality Liquid Value Stream; Nicolas Ford, Manager QC Liquid Value Stream; and Steve Laninga, Director Non-Analgesic Tablet Value Stream. Each observation was read aloud with opportunity given for questions, clarification or response. With the exception of a typo noted for observation #5, and a couple of clarification questions no response was offered for any of the observations.

SAMPLES COLLECTED

Documentary Samples 505736, 505737, and 505738 were collected to document GMP deficiencies noted during this inspection.

DOC 505736

Sample #1 ANDA #40-167 Sleep Aid Tablets lot 8JE0699

Sleep Aid Tablet lot 8EE0802, produced from bulk lot 8D0825, was the subject of a recall D-037-2009 following the release of packaged lot #8EE0802 with an extended expiration date of 36 months (3/2011). Field Alert dated 7/1/08 also documents this labeling error (**Exhibit Pjd-337/338**). The portion of packaged lot 8EE0802 not shipped prior to the discovery of the error was ordered by Quality Unit Review Team to be reworked (dumped from the bottles back into bulk containers) and made available to be repackaged. This order, which is in the form of the Product Safety Meeting (7/7/08) minutes, was attached to the deviation associated with the labeling error **(b) (4)** dated 6/30/08) and is attached as EIR **Exhibit Pjd-334/335**. The meeting minutes bear prepared by and approved by signatures dated 7/25/08.

A Rework Notification dated 8/1/08 was issued for batch 8EE0802 labeled with an expiration date of 3/24/2011 as documented on rework notification **(b) (4)** attached as EIR **Exhibits Pjd-356/358**. This same document states the rework was completed 8/26/08 and the lot # assigned this reworked bulk material was 8D0825R.

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Bulk lot 8D0825R (previously 8EE0802) was packaged on 9/10/08 into bottles of 96 tablets each as documented in the packaging order for material number (b) (4) Exp Date 03/11 (Exhibits A-1/21) and finished (labeled) for customer (b) (4) as documented in packaging order (Exhibit A-22/37). A total of (b) (4) bottles (Exhibit A-23) were labeled under the (b) (4) brand label (Exhibits A-30, 33/35).

On 10/1/08 a total of (b) (4) were picked up (shipped) by customer (b) (4) for delivery to (b) (4) truck as documented on Straight Bill of Lading #442924-1 (Exhibits B-1/4) for purchase order (PO) numbers (b) (4) (Exhibit B-2) bearing carrier agent representative signature dated 10/1/08; and by Perrigo Company Packlists for PO # (b) (4) (Exhibits B-5/6).

On 10/2/08, Perrigo representatives' review of the packaging record for lot 8JE0699, prior to providing it to FDA for review, noted lot 8JE0699 was labeled with the same expiration date of 3/2011 as recalled lot 8EE0802. Established Quality Perrigo recalled the shipment from their customer and issued a Field Alert (Exhibit C-1/3).

DOC 505737**Sample #2 Senna Laxative Tablets lot 7EE0305**

Senna Laxative Tablets lot 7EE0305, packaged from bulk 7B0991, was manufactured by external manufacturer (b) (4) and assigned (b) (4) lot number C049T. Perrigo placed bulk lot 7B0991, packaged as lot 7EE0305 into their stability program as the once annual stability lot for this product. Perrigo noted OOS results for lot 7EE0305 at the 3 month stability pull which was Perrigo's first analysis of this lot.

Perrigo ranked (b) (4) as an acceptable supplier which equated to performing one confirmation analysis per year and the placement of one lot on stability per year. The confirmation and stability lots are not the same. Senna Laxative Tablets assigned incoming bulk lot number 7B0991 is (b) (4) lot C049T. This lot was received 4/23/07 as referenced by Perrigo Goods Receipt Slip for lot 7B0991 (Exhibit A-6) which references the manufacturer's lot number C049T, the quantity of tablets (3,977,519) and the date received 4/23/07. (b) (4) Certificate of Analysis that accompanied this shipment is attached as Exhibit A-7.

Perrigo prepared their own Certificate of Analysis for bulk lot 7B0991 (Exhibit A-3) which documents Identification, Total Sennosides, Sennosides Content Uniformity, and Total Sennosides Dissolution are listed as method "C of A" and a comparison of Perrigo's C of A to (b) (4) C of A finds identical results.

Bulk lot 7B0991 was packaged as lot 7EE0305 on 5/13/07 as documented in Customer Packaging Order for lot 7EE0305 attached as Exhibits B-1/7, yielding (b) (4) bottles (Exhibit B2).

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Attached to the page entitled Goods Issue List (**Exhibit B-4**) is one of the (b) (4) labels, removed from the incoming bulk container, which contains Perrigo related identification such as product #021AB and the bulk # 7B0991 as well as the Purchase Order (b) (4)

A portion of packaged lot 7EE0305 was labeled under customer label (b) (4) as documented in Packaging (Finished Goods) record attached as Exhibits C-1/5.

On 5/27/07, sixteen cases of Senna lot 7EE0305 were sold to (b) (4) and shipped via (b) (4) as documented by Perrigo Packlist for PO 48317326 and Bill of Lading #380243-1 attached as Exhibit D-1.

On 10/29/07 the 3 month stability sample failed as documented in deviation (b) (4) attached as EIR **Exhibits Pjd-535/583**. On 10/1/08 Paul Weninger informed FDA Detroit of their sub-recall of lots 7EE0305, 7FE0474 and 7EE0671 all packaged from the same external manufacturer's bulk lot C049T/Perrigo bulk 7B0991. An example of the October 1, 2008 letters sent represented by the letter to (b) (4) was provided and is attached as EIR **Exhibits Pjd-1024/1027**.

DOC 505738

Aspirin 81 mg enteric coated tablets, bulk lot 7H1520, were manufactured by external manufacturer (b) (4) and assigned (b) (4) lot number H065T. Lot 7H1520 was received 11/1/07 as documented on Perrigo's Goods Receipt Slip for Batch 7H1520 which documents the purchase order #450354326, vendor name (b) (4) Inc. and the expiration date of 8/19/09 (Exhibit A-1). Bulk lot 7H1520 was issued to and packaged under lot number 7LE0692 as documented on the Good Issued List for batch 7LE0692 (Exhibit A-2). This document also has attached to it the (b) (4) label taken from the bulk container which lists Perrigo's product number 277AC, P.O. #450354326, Perrigo's assigned bulk number 7H1520, (b) (4) address and phone number and (b) (4) lot number H065T

VOLUNTARY CORRECTIONS**Voluntary Corrections:**

(CHL)

Follow-up to Perrigo's response to the FDA 483, Inspectional Observations, for Establishment Inspections dated November 7 – December 15, 2006 and September 5 – 13, 2007 found all corrective action documentation and SOP updates to be consistent with reported response.

The Following documents were reviewed in support of the EI dated November 7 – December 15, 2006 FDA 483, Inspectional Observations.

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SAN (b) (4)	Metal Detection Action Limits for Tablets Products
SOP (b) (4)	Processing and Investigation of Perrigo Product Complaints
SOP (b) (4)	Trending of Deviations and out-of-Specification Test Results
SOP (b) (4)	Quality Event Risk Assessment Process
SOP (b) (4)	Finished Goods Reserve Sample Management
SOE (b) (4)	Perrigo Quality Control Stability Program
SOP (b) (4)	Purified Water Rinse
SOP (b) (4)	Equipment/Suite Start-up Inspection
SOP (b) (4)	Deviation Investigation Tools and Process
SOE (b) (4)	Coating of Tablets
SOP (b) (4)	Equipment Cleaning and Use Log
Policy (b) (4)	Equipment Log Requirements
SOE (b) (4)	(b) (4) Cleaning
SOP (b) (4)	Packaged Product Sample Collection and Control
SOP (b) (4)	Target Control Sheet for Liquid Fillers
SOP (b) (4)	Packaging Component Inspection Plans

The Following documents were reviewed in support of the EI dated September 5 – 13, 2007 FDA 483, Inspectional Observations.

SOP (b) (4)	Inspection of Incoming Packaging Components
SOP (b) (4)	Learner Item Status training documentation
SOE (b) (4)	Component/Pre-Print Inspection Form training documentation
JOB- (b) (4)	Sampling of Incoming Components
PDC# -008	Physical Defect Criteria Quality Levels
SAN (b) (4)	PMI Component Acceptance Sampling Plans
Specification for Perrigo Plastic Cups	
Attach 054-235-3	Packaging Component Inspection Form, dated 7/22/08, batch# 120507

EXHIBITS COLLECTED

Pjd-1/26	Summary of Stability Projects for PC535, 81 mg enteric coated aspirin (yellow color) and associated individual study results
Pjd-27/53	Deviation (b) (4) stability failure for 81 mg enteric coated aspirin, bulk lot

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- 5F1484
- Pjd-54/137 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 6D1309
- Pjd-138/162 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 6D1306
- Pjd-163/198 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 6E0985
- Pjd-199/229 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 6F0898
- Pjd-230/237 Individual stability results summaries for Product Code 277AC 81 mg enteric coated aspirin (peach color)
- Pjd-238/276 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 5F1324
- Pjd-277/283 Deviation (b) (4) stability failure for 81 mg enteric coated aspirin bulk lot 6C1427
- Pjd-284/287 Change Control documentation reducing expiration dating for 81 mg enteric coated aspirin product 535AD from 24 to 18months
- Pjd-288/291 Change Control documentation reducing expiration dating for 81 mg enteric coated aspirin product 277AC from 24 to 18months
- Pjd-292/297 List of marketed Formula (b) (4) and (b) (4) lots, within expiry date, labeled with more than 18 months
- Pjd-298/300 March 26, 2007 letter to FDA regarding 81mg Enteric coated aspirin stability failure
- Pjd-301/303 Where used reports from SAP documenting post 1/23/08 shipment of 300 count bottles of 81 mg enteric coated aspirin lots 7KE0619 and 7HE0550
- Pjd-304/306 Change control document for Formula 535AD dated 6/29/06
- Pjd-307/318 SOP (b) (4) ”
- Pjd-319/329 Packaging records for Sleep Aid lot 8EE0802 Exp. 3/11
- Pjd-330/355 Deviation (b) (4) 0 regarding incorrect expiration date assigned Sleep Aid Tablets lot 8EE0802
- Pjd-356/360 Rework Notification for Sleep Aid Tab batch 8EE0802
- Pjd-361/370 Deviation (b) (4) dated 10/2/08 regarding incorrect expiration date assigned Sleep Aid Tablets lot 8JE0699
- Pjd-371/383 SOP (b) (4) ” and associated work aid document SWI (b) (4) ”
- Pjd-384/386 Change Control Documents for Expiration Dating
- Pjd-387/427 Deviation (b) (4) regarding incorrect expiration date assigned Naproxen NA

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- Caplets, Tablets, and APAP Geltabs
- Pjd-428 Listing of lots (Naproxen Sodium Caplets, Tablets and APAP Geltabs) actually released with incorrect expiration date assigned
- Pjd-429/461 Stability data and Regression analysis and pooling data for Gelatin Coated APAP tablets product # 187
- Pjd-467/476 Stability data for Naproxen Sodium Caplets and Tablets
- Pjd-477/489 Deviation (b) (4) regarding content uniformity failure APAP 160mg Jr Grape Chewable tablets lot 7B0254
- Pjd-490/499 Deviation (b) (4) regarding content uniformity failure APAP 160mg Jr Grape Chewable tablets lot 7F1074
- Pjd-500/504 SOP (b) (4) ”
- Pjd-505/518 Packaging documents pertaining to APAP 500 mg Geltabs lot 8GE0488
- Pjd-519/526 Packaging documents pertaining to (b) (4)
- Pjd-527/534 Packaging documents pertaining to (b) (4)
- Pjd-535/583 Deviation (b) (4) regarding 3 month stability failure for Senna Lax Tablets lot 7B0991
- Pjd-584 Stability Results Summary for Natural Senna Laxative Tablets lot 7B0991
- Pjd-595 Recall letter (b) (4) retarding Senna Lax Tablets Control #C049T
- Pjd-596 Perrigo notification letter to FDA Detroit District regarding the “recall of one batch of Senna Laxative Tablets”
- Pjd-587/629 Deviation (b) (4) regarding 9 month stability failure for Senna Lax Tablets lot 7G0903
- Pjd-630/695 Deviation (b) (4) dated 8/23/07 regarding 9 month stability failure for Senna Lax Tablets lot 6E0981
- Pjd-696/746 Deviation (b) (4) dated 12/21/07 regarding content uniformity failure for incoming Senna Lax Tablet lot 7E1788 (annual confirmation lot)
- Pjd-747/754 SOP (b) (4) ”
- Pjd-755/776 Deviation (b) (4) dated 3/28/08 regarding 18 month stability failure for externally manufactured Chlorpheniramine Maleate lot 6F1641 (copied 9/19/08) bearing investigator’s signature date of 7/25/08 but remaining open as of this inspection.
- Pjd-777/808 Deviation (b) (4) dated 3/28/08 regarding 18 month stability failure for externally manufactured Chlorpheniramine Maleate lot 6F1641 bearing investigator’s signature date of 9/24/08
- Pjd-809/837 Release documents pertaining to Chlorpheniramine Maleate lot 7J1978

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Pjd-838 Memo regarding statistical analysis of available stability data for Chlorpheniramine Maleate

Pjd-839 Master Control copy of Established Product Internal Alert Limit for product 463AJ Chlorpheniramine Maleate

Pjd-840 Certificate of Analysis for Chlorpheniramine Maleate lot 6F1641

Pjd-841/856 SOP (b) (4) ”

Pjd-857/876 Receiving documents and CofA’s for Senna lots 7K2058, 8A2470, and 8C1587

Pjd-877/881 SOP (b) (4) ”

Pjd-882/907 (b) (4) Quality evaluations,

Pjd-896/905 Quality Assurance Agreement

Pjd-906 list of products manufactured by (b) (4)

Pjd-907 list of confirmation lots for Senna Lax Tablets.

Pjd-908/918 (b) (4) Quality evaluations

Pjd-919/924 (b) (4) Quality evaluations

Pjd-925/931 Active Formula List

Pjd-932/950 Contract Manufacturers list

Pjd-951/954 Tablet ID List

Pjd-955/969 Organization Charts

Pjd-970/976 Lot distribution history and Where Used Reports for Senna lot 8GE0279

Pjd-977/983 Lot distribution history and Where Used Reports for Senna lot 8FE0688

Pjd-984/989 Lot distribution history and Where Used Reports for Senna lot 8FE0141

Pjd-990 Lot distribution report for Senna lot 8CE0043

Pjd-991/992 Lot distribution report for Senna lot 8BE0070

Pjd-993/994 Customer List

Pjd-995 Perrigo Sites

Pjd-996/1020 Plant Tour Overview

Pjd-1021/1023 Letter dated 10/3/08 and Field Alert also dated 10/3/08 for recalled Sleep Aid Tablets Lot 8JE0699

Pjd-1024/1027 Perrigo Recall letter dated 10/1/08 for Senna Laxative Tablets

Pjd-1028/1035 Distribution List for Senna Lax Tablets

Pjd-1036/1055 Labeling for Recalled Senna lot 7EE0671

Pjd-1056/1085 Labeling for Recalled Senna lot 7FE0474

Pjd-1086/1108 Labeling for Recalled Senna lot 7EE0305

Pjd-1109/1111 Quantity packaged for each of the recalled lot numbers 7EE0671, 7FE0474 and 7EE0305

Pjd-1112 (b) (4) 10/15/08 Recall letter for Senna Lax Tablets (12 batches)

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- RTB-1. Production Tracking Sheets (3pp)
- RTB-2. Codes for Production Tracking Sheet (2pp)
- RTB-3.
- RTB-4. (b) (4) foreign particles investigation (6pp)
- RTB-5. Batch Record 8C1577 (58pp)
- RTB-6. Work Center cleaning record
- RTB-7. COA for 8C1577.
- RTB-8. Profile Project List
- RTB-9. Release test Q2 for APAP 544AB information (2pp)
- RTB-10. Batch failure for drug release investigation (10pp)
- RTB-11. APAP API CoAs (4pp)
- RTB-12. ANDA (b) (4) excerpt
- RTB-13. Nicotine Lozenge Impurity TM (6pp)
- RTB-14. Nicotine Lozenge Assay TM (5pp)
- RTB-15. Stability data summary (2pp)
- RTB-16. Nicotine Lozenge 6C1741-6G0998 stability results (2pp)
- RTB-17. Nicotine Lozenge 6C1741 Assay failure investigation (3pp)
- RTB-18. Nicotine Lozenge 6C1741 Largest unknown impurity investigation (43pp)
- RTB-19. Other Nicotine Lozenge 2 mg stability results (8pp)
- RTB-20. Quality Agreement with Nicotine Lozenge Manufacturer Catalent (10pp)
- RTB-21. Nicotine Lozenge 2 mg specification (3pp)
- RTB-22. Validation report for Nictine Lozenge impurity TM (43pp)
- RTB-23. Cetirizine lots on stability program
- RTB-24. Notebook copy copies (2pp)
- RTB-25. 4-6/08 (b) (4) vendor Quality evaluation (7pp)
- RTB-26. 1-3/08 (b) (4) vendor Quality evaluation (4pp)
- RTB-27. BR 8J2663 excerpts (18pp)
- RTB-28. Investigation 570000001718 (9pp)
- RTB-29. Cleaning Logs (4pp)
- RTB-30. BR 8G0284 excerpts (34pp)
- RTB-31. Deviation (5pp)
- RTB-32. Cleaning Logs (4pp)
- RTB-33. Perrigo PO for Chondroitin Sulfate from ~3/08
- RTB-34. Perrigo family validation for Nasal Spreays explained (3pp)

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RTB-35. Map of ventilation system (8pp)

RTB-36. Products made on packaging lines (4pp)

ATTACHMENTS

- #1 January 2008 Perrigo/FDA meeting follow-up letter and meeting slides
- #2 MARCS Recalls Details
 - a. D-403-7
 - b. F-195-7
 - c. D-029-2008
 - d. D-041-2008
 - e. D-352-2008
 - f. D-037-2009
 - g. D-105-2009

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