

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

TABLE OF CONTENTS

Summary ..... 1

Administrative Data ..... 2

History ..... 2

Interstate Commerce/Jurisdiction..... 2

Individual Responsibility and Persons Interviewed..... 3

Manufacturing/Design Operations..... 3

Complaints ..... 5

Objectionable Conditions and Management's Response..... 6

Refusals..... 6

General Discussion with Management ..... 6

Voluntary Corrections ..... 7

Exhibits Collected ..... 7

Attachments ..... 8

**SUMMARY**

This was a PAI inspection of a manufacturer of OTC drugs (Over-The-Counter liquids, tablets, and capsules), nutritional supplements, vitamins and vitamin pre-mixes. The inspection was also a routine surveillance of an infant formula pre mix manufacturer. The PAI inspection covered the firm's packaging of Polyethylene Glycol and compliance with Drug GMP's. The inspection also covered the manufacturing of vitamin pre-mixes intended for infant formula. The inspection was conducted in accordance with Compliance Program 7321.006-"Infant Formula Program: Import and Domestic" CP 7356.002 Drug Product Surveillance, and DET-DO work plan FY '09 under FACTS Assignment # 5198362 and OP ID4128506 . The current inspection covered the processing, packaging, sanitation, and storage operations.

The previous inspection was conducted on 12/10,12-14,18-/2008 as a routine surveillance inspection of the firm's infant formula premixes and drug products. No FDA 483 was issued. Items discussed included unifying sampling and testing procedures with (b) (4) for Vitamin pre mixes., and documenting challenge testing for metal detection.

The current inspectional focus was on the firm's drug GMP's and infant formula premixes. At the conclusion of the inspection, no FDA 483 was issued. Items discussed included the ongoing issue of unifying sampling and testing procedures with (b) (4) for Vitamin pre mixes, stability protocol not matching the inspectional standards, and clear identification of identity samples. Management promised corrections.

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

**ADMINISTRATIVE DATA**

Inspected firm: Perrigo Holland Inc  
Location: 13295 Reflections Dr  
Holland, MI 49424-8220  
Phone: 616-738-8500  
FAX:  
Mailing address: 13295 Reflections Dr  
Holland, MI 49424-8220  
  
Dates of inspection: 6/1/2009, 6/2/2009, 6/3/2009  
Days in the facility: 3  
Participants: Martha Sullivan Myrick, Investigator

FDA 482 Notice of inspection was issued to Dave Schrage, Site Director and the most responsible person on site.

**HISTORY**

This firm is a manufacturer of OTC drugs (Over-The-Counter liquids, tablets, and capsules), nutritional supplements, vitamins and vitamin pre-mixes (EXHIBIT 1-5). This firm was acquired by L. Perrigo Co. in September 2008. All shareholders sold stock as a result of the acquisition. No business has changed. Organizational charts were supplied for upper level (EXHIBIT 1), Operations and Engineering (EXHIBIT 2) and Quality (EXHIBIT 3).

Normal office hours are 0800 Hrs. to 1630 Hrs. Monday through Friday. The firm's manufacturing plant operates (b) (4) around (b) (4). The first shift starts approximately (b) (4).

The vitamin pre-mixes intended for infant formula use are contract manufactured for (b) (4) and are either shipped to (b) (4) plant or to other plants (b) (4) (b) (4).

Any inspectional correspondence should be directed to Mr. Dave Schrage at the firm's address.

**INTERSTATE COMMERCE/JURISDICTION**

The firms operations have not changed since the acquisition in September 2008. The percentage of sales are as follows:

- (b) (4) Drug Sales (including prescription nutritionals)
- (b) (4) Infant Formula
- (b) (4) Nutritional Supplements

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

According to management, approximately (b) (4) of products are shipped directly into interstate commerce. Management stated that almost all other products end up eventually going into interstate channels.

The vitamin premixes, intended for infant formula are manufactured for (b) (4) and shipped to (b) (4) plant or to the other plants outside of Michigan. The vitamin premixes manufactured at Perrigo Holland Inc. are packaged and shipped in bulk size containers.

Drug products are manufactured for various customers including Perrigo (b) (4) and (b) (4). The firm's largest product is (b) (4) for (b) (4).

Polyethylene Glycol is received from (b) (4) (b) (4)

The product list (EXHIBIT 4) was supplied. In addition, a list of all lots of infant formula lots produced in 2008 was supplied. (EXHIBIT 6,7,8,9)

**INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**

Mr. Dave Schrage, Site Director, stated he was the most responsible person at the firm at the time of the inspection.

Others present during the inspection included:

- Gary Carlson, Compliance Manager
- Paul Walker, Director of Quality
- Gretchen Starr, Quality Assurance Manager
- Jill Bronkema, Raw Material Supervisor
- Kirk Walter, Director Operations

**MANUFACTURING/DESIGN OPERATIONS**

Receiving of Raw Ingredients:

All of the firm's products are received under the same General Receiving Procedure. Each raw material purchased is identified by a code number. When a lot of raw material is received, it is inspected for damaged containers and identified with a label listing the name, code number, date and quantity received, manufacturer's lot number, and a reference number. The reference number (receiving number) is assigned in the order in which the material is received. The label also indicates the lot is quarantined. As of March 2009, the firm uses (b) (4) system to control the status of all materials from receipt to shipping.

The sample technician transfers the lot of raw ingredient to a sampling area. The amount of sample needed to be collected is determined by the laboratory. The Material Control Card and the sample of material are taken to the Quality

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

Control Laboratory, where the sample is tested in accordance with established procedures. At minimum, description, identification, and foreign matter are performed each time a material is received, with other required testing accepted from the manufacturer's certificate of analysis. Testing accepted on certificate of analysis is verified on one lot (b) (4) for materials used in drug products, and for other materials on request. The Quality Control Laboratory has the capability to perform normal and reversed-phase HPLC, flame atomic absorption, and UV-Visible spectrophotometric assays, fluorimetry, titrimetric techniques, and dissolution testing. Compendial methods are used for these tests. As of the last inspection the firm now has use of (b) (4) scans.

Review of sample receipts and testing for the PAI Polyethylene Glycol, found the firm has received (b) (4) of product. This shipment consisted of (b) (4) Each tote was sampled and tested for identity. Further examination of the samples found that the bags were not clearly identified from which of the (b) (4) totes each sample was taken. This was also not cross referenced onto the lab notebooks (EXHIBIT 24). According to the firm, the totes were identified with the corresponding sample. I informed the firm that the cross reference should not only be identified on the totes but on the sample bags and lab notebooks.

**INFANT FORMULA PRE MIXES**

Raw Ingredient Weigh Operations:

A list of all raw material suppliers (EXHIBIT 5) was provided during this inspection. All raw ingredients meeting specifications is released in (b) (4) Raw ingredients are weighed out as specified in the batch record and the amount weighed accounted for taken out of inventory in (b) (4) Each step of the weighing operation is checked by a second person in addition to the individual performing the weighing operation. Labels are attached to each container of bulk ingredients, identifying the contents by name, code number, and the product name, code number, and lot number for which they are to be used.

All ingredients needed for one batch of product are weighed and assembled on one pallet or group of pallets and transferred to a staging area located on the second floor for the appropriate manufacturing operation.

Infant formula Mixing Operations:

After the designated mixer is checked for cleanliness, staged ingredients are verified against the batch record, then added and processed according to the manufacturing instructions.

(b) (4)

(b) (4) The final packaged containers of vitamin pre-mixes are labeled and placed on pallets for shipment. The firm receives the (b) (4) liners from (b) (4) located in (b) (4) The (b) (4) liners are manufactured by (b) (4) located in (b) (4) The (b) (4) drums with (b) (4) lids and seals are manufactured and received from (b) (4) located in (b) (4)

## Establishment Inspection Report

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

This firm manufactures (b) (4) vitamin premixes for (b) (4). A list for each product manufactured during the last year was provided. These are: (b) (4) Vitamin Pre-Mix # (b) (4) (EXHIBIT 7), (b) (4) Vitamin Pre-Mix # (b) (4) (none produced), (b) (4) Vitamin Pre-Mix # (b) (4) (EXHIBIT 6), (b) (4) Vitamin Pre-Mix # (b) (4) (EXHIBIT 8), and (b) (4) (b) (4) Pre-Mix # (b) (4) (EXHIBIT 9).

During the discharging of the vitamin premix into the (b) (4) drums, the company employees select the first, middle, and last master container of finish product for lab testing. The three master containers of vitamin premix are shipped to the (b) (4) laboratory for full testing. The (b) (4) containers serve as representative of the production lot. Perrigo Holland INC., collects samples of the vitamin premix and test for certain indicators in each lot before they are released. The indicators tested by Perrigo Holland INC., are Niacinamide, Riboflavin (Vitamin B2), Pyridoxine HCL (Vitamin B6) and Cyanocobalamin (Vitamin B12). A "Certificate of Analysis" (C.O.A.) is issued for each lot of finish product.

This firm has not made any formulation changes since the last inspection.

### POLYETHYLENE GLYCOL

The firm receives polyethylene glycol from (b) (4) (EXHIBIT 21). The product is dumped into (b) (4) hoppers where it is packed into one of four finished containers. 4.1, 8.3, 17.9, 29.9 oz containers. The firm does no mixing, blending, compression, milling, or any other manufacturing of the product. The firm uses only line (b) (4) (EXHIBIT 18). This line is also used to package (b) (4). Cleaning validation was completed for the packaging for (b) (4) in 04/2002. Cleaning verification was completed for Polyethylene Glycol on 4/29/09 and 5/7/09 (EXHIBIT 20). The firm is in the process of performing cleaning validation studies.

The firm has packaged (b) (4) (EXHIBIT 28). The (b) (4)

The firm hopes to have all validation lots completed by July 2009.

The packaging of (b) (4) was observed during the current inspection. No observations were noted. The Polyethylene will be packaged on the same line using the same equipment with minor changes to the (b) (4) and (b) (4).

### METAL DETECTION

There are currently metal detection units on all the packaging lines. The firm has completed installing portable metal detectors on all compression units. Magnets are currently used on the blenders. All bulk products are currently metal detected prior to shipping. Products that are packaged at Perrigo Holland Inc., are detected on the packaging line. The firm is working to install metal detection on all compression units so that products being packaged will be metal detected both on compression and during packaging.

### COMPLAINTS

Infant formula complaints (EXHIBIT 10) were reviewed. The firm receives complaints directly from (b) (4) for vitamin pre-mixes. The firm continues to receive complaints for OOS results. Perrigo Holland Inc. retests the product and

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

determines the results are within limits. Perrigo Holland Inc. stated they composite the samples before analysis and (b) (4) does not. This in turn can lead to differences in results. Currently the firm is conducting comparative studies (EXHIBIT 17) with (b) (4) to review differences in testing methods and results. Previous studies on test methods (EXHIBIT 12) and process variance (EXHIBIT 11) were inconclusive.

**OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**

No FDA 483 was issued at the close of the inspection.

**REFUSALS**

No refusals were encountered during the current inspection.

**GENERAL DISCUSSION WITH MANAGEMENT**

Individuals present during the closeout inspection including myself (representing the FDA) and the following persons for Perrigo Holland Inc.:

- Gary Schrage, Site Director
- Kirk M. Walter, Director Operations
- Paul Walker, Director Quality
- Jill Bronkema, Raw Material Supervisor
- Gretchen Starr, Quality Assurance Manager
- Gary R. Carlson, Director Quality Assurance

Items discussed during the close out inspection including the following:

- 1- The testing standard (b) (4) used and submitted by the firm (EXHIBIT 27), does not match the stability protocol in existence (EXHIBIT 28). Currently the stability protocol calls for (b) (4) (b) (4) The testing method (EXHIBIT 27) only states that a (b) (4) (b) (4) The firm stated that the stability protocol was (b) (4) (b) (4) I stated that the release C of A (EXHIBIT 26) only referenced the Testing standard (b) (4) which again (b) (4)
- 2- Labeling of the ID test samples should be clearly identified so as to cross reference the container from which it was sampled, not only on the sample bags but also in the lab notebooks. This will help to identify the sample in the case of any OOS, and to assure the employees are taking non composite samples of the product for ID testing.
- 3- Corrective subscripsts should document the true reason for the changes. The firm uses "entry error" for changes to method codes without clear documentation as to why the change is made. Review of the C of A for Material (b) (4) lot 08M002 (EXHIBIT 29) showed that the control result code was changed from 266 to 265 and then

## Establishment Inspection Report

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

back to 266 without true documentation as to the reason for the changes except for "entry Error". I informed the firm that entry error should be reserved for those error such as writing an "A" when it should be a "B" or a "2" when it should have been a "3"

Management promised corrections.

### VOLUNTARY CORRECTIONS

Corrections made to the previous inspectional discussions include:

1-Documenting their results of all three challenge tests for metal detection. Review of batch records determined the firm had made corrections.

2-Discuss with (b) (4) the sampling and test procedures of vitamin premixes to assure uniformity. The firm is in the process of performing comparative studies.

### EXHIBITS COLLECTED

- 1- Organizational chart Manufacturing support
- 2- Organizational chart Operations and Engineering
- 3- Organizational chart Quality
- 4- Product list (4 pages)
- 5- Approved Supplier List of materials used in infant formula premix manufacturing (5 pages)
- 6- Batch list (b) (4) Premix (b) (4)
- 7- Batch list (b) (4) premix (b) (4)
- 8- Batch list (b) (4) Premix (b) (4)
- 9- Batch list (b) (4) Nucleotide-Choline (b) (4)
- 10- Infant formula complaint list (2 pages)
- 11- Process Variance Assessment dated 2/22/08 (8 pages)
- 12- Assay Method evaluation for complaint BN7-0076 dated 9/27/08 (2 pages)
- 13- CAPA V70014 interim report dated 3/31/08
- 14- CAPA V70014 interim report dated 4/29/08
- 15- CAPA V70014 interim report dated 6/27/08
- 16- CAPA V70014 interim report dated 10/26/08
- 17- CAPA V70014 interim report dated June 2,2009
- 18- Blue print of line (b) (4)
- 19- Cleaning verification protocol (7 pages)

**Establishment Inspection Report**

Perrigo Holland Inc  
Holland, MI 49424-8220

FEI: 1000518646  
EI Start: 06/01/2009  
EI End: 06/03/2009

---

- 20- Cleaning Verification Report (8 pages)
- 21- (b) (4) C of A dated 4/30/09 for Polyethylene Glycol (2 pages)
- 22- Certificate of Analysis purchase requirements for Polyethylene Glycol Lot 9D4102 (2 pages)
- 23- Sample drawing instructions for Polyethylene Glycol Lot 9D4102 (2 pages)
- 24- Lab notebook (b) (4) pages 172 and 173 for lot 9D4102 for Polyethylene Glycol (2 pages)
- 25- (b) (4) for lot 9D4102 Polyethylene Glycol (2 pages)
- 26- Perrigo Holland Product Specifications for Polyethylene Glycol from (b) (4) (3 pages)
- 27- Method (b) (4) for Dispersion of Polyethylene Glycol
- 28- Perrigo Holland Stability Protocol Polyethylene Glycol (8 Pages)
- 29- C of A Material (b) (4) lot 08M002 dated 11/9/08

**ATTACHMENTS**

- 1- FDA 482 Notice of Inspection



Martha Sullivan Myrick, Investigator