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## SUMMARY

This was a limited inspection of a OTC and Rx drug manufacturer and Medical Device distributor. The inspection was accomplished in accordance with CP 7382845 Inspection of Medical Device Manufacturers and CP 7353.001 Enforcement of the Post Marketing Adverse Drug Experience Reporting Regulations. This inspection was completed under FACTS assignment 995931 and OP ID 5918419.

The previous ADE and Medical Device inspection of 08/09/04-09/08/04 was NAI. The previous cGMP drug inspection of 9/15- 11/07 was classified VAI.

The current inspectional focus was on the firm's medical device and ADE reporting and SOP's. No FDA 483 was issued. Items discussed with the firm at the conclusion of the inspection included: documentation of alerts and requests for investigation to (b) (4) and (b) (4) , cancel registration as a repacker if the firm does not intend to resume those operations for the medical devices, and caution was given to the firm to not rely too heavily on additional information when making a determination of serious or non serious AE's. Management promised corrections.

## ADMINISTRATIVE DATA

| | |
|---|---|
| Inspected firm: | L. Perrigo Co. |
| Location: | 515 Eastern Ave<br>Allegan, MI 49010-9070 |

| | |
|---|---|
| Phone: | 269-673-8451 |
| FAX: | |
| Mailing address: | 515 Eastern Avenue<br>Allegan, MI 49010 |
| Dates of inspection: | 1/14/2009, 1/15/2009, 1/16/2009 |
| Days in the facility: | 3 |
| Participants: | Martha Sullivan Myrick, Investigator |

On 1/14/08 a notice of inspection was issued to Mr. Louis W. Yu, Sr Vice President. Mr. Yu identified himself as the most responsible person at the facility at the start of the inspection.

## HISTORY

No changes to the history of the firm were reported from the previous inspection. As stated previously, 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 pharmaceuticals for store-brand markets in the country. The firm's corporate headquarters are located at 515 Eastern Ave., Allegan, MI 49010.

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/JURISDICTION

The L. Perrigo Company continues to operate as a large scale generic drug manufacturer of both OTC and Rx products. The firm is also involved in the distribution of pregnancy and ovulation test kits, along with single use heat wraps.

The following lists were collected to document the various types and classifications of products:

1- List of all Drug products with Perrigo name on label (EXHIBIT 1)
2- ANDA/NDA Marketed products (EXHIBIT 2)
3- ANDA/NDA Non Marketed product (EXHIBIT 3)
4- Unapproved product list (EXHIBIT 4)
5- Monograph marketed products (EXHIBIT 5)
6- Monograph NON marketed products (EXHIBIT 6)
7- External Manufacturer Responsible for filing adverse Events (EXHIBIT 7)

## INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

The firm's responsibility remains the same for the previous inspection of 10/2008. During the current inspection, a FDA 482 Notice of inspection was issued to Louis W. Yu, Senior Vice President who stated he was the most responsible person at the firm at that time.

James R. Young, Sr Manager Pharmacovigilance, provided information pertaining to the firm's ADE SOP and complaint handling operations.

Bart D. Shrode, Director Quality Assurance, provided additional information pertaining to complaints, and basic operations.

Nicolas J. Ford, Quality Control Manager acted as the scribe during the course of the inspection.

## MANUFACTURING/DESIGN OPERATIONS

### Medical Device

Medical devices include a heat wrap, pregnancy test kit, and ovulation test kits. Perrigo is not the specification developer or 510(k) holder. According to written contracts, Perrigo is responsible for receiving complaints and passing the results of internal investigations to the manufacturers of the devices. According to Bart Shrode, the firm is no longer repacking or relabeling any devices. This is being performed at PDM (Perrigo Mexico). Currently the firm is only a distributor for the devices. The neck heat wraps and Ovulation kits have always been repackaged at PDM (Perrigo Mexico). The last date of repackaging for Pregnancy test kits at Allegan was Feb 2006 and back heat wraps was Oct 2004. I informed the firm they may want to visit the issue of registration and possibly cancel the listing of repacker if they are not intending to do this in the future. The firm responded that they would discuss the issue.

The firm's Medical device SOP'S were reviewed, including the firm's Medical Device reporting SOP (b) (4) (EXHIBIT 8). A review was performed of the complaint handling system, as they are contracted by the manufacturer to handle the complaints and alert the manufacturer so that a complete investigation can be performed if warranted. A copy of the firm's written contract with both (b) (4) (EXHIBIT 9) and (b) (4) (EXHIBIT 10) including medical device reporting agreements with both firms (EXHIBIT 11-12) documents that Perrigo is responsible for completing complaint investigations and recording all reportable events. 8 complaints and 5 of 9 device AE's from 2007-2008 (EXHIBIT 13) were reviewed. The firm did not always completely document the communication to the manufacturer to alert, or request an investigation as required by the contractual agreements.

## ADVERSE EVENT REPORTING

An ADE inspectional review was conducted during this inspection. Inspection included review of development reports, batch records, and analytical data. Minor deficiencies were noted. This was accomplished in accordance with CP 7353.001 Enforcement of the Post Marketing Adverse Drug Experience Reporting Regulations. The primary focus was to insure the firm had adequate written procedures for the surveillance, receipt, evaluation and submission of post marketing

ADE reports to the FDA. Also reviewed was the firm's compliance with ADE regulations and the submission of accurate and complete reports to the FDA in a timely manner. Minor deficiencies were noted during the review of the firm's ADE program.

A list (EXHIBIT 1-6) of the firm's ANDA and NDA products was obtained. Products selected for the complete review were chosen based on the most recent drug approval dates (EXHIBIT 14). These products included; Simvastatin Tablets USP 5,10,20,40,and 80 mg Rx (PC613, 093, 540, 879, 292), Omeprazole 20 mg tab (PC 915), and Nicotine Gum 2 mg Regular (PC 029).

In addition, a random sampling of reports from the 15 day submission list (EXHIBIT 15) were selected and reviewed. Products reviewed included: Ibuprofen Oral Suspension USP 100mg (PC 166), Nitetime free 6hr liquid gel (PC 041), Nitetime Free Original 6hr liquid (PC 977), Loperamide liquid (PC 377), Migraine Caplets 350's (PC 374), Dibromm PE (PC 906), Cetirizine 10mg tablets (PC 4H2), Diphedryl elixir (PC 379), Carbamide 6.5% ear Ph drops (PC 284), APAP 80mg Infant (PC 289), and APAP 500mg (PC 227).

All reports issued for the above products were submitted to the agency within the required timeframe. This included the 15 day alerts. Quarterly and annual periodic safety reports submitted to the FDA were also reviewed and appeared to have been submitted within the required timeframes and included all the correct information.

A discussion was held with firm's management regarding the classification of a complaint issue "ineffective" as a labeled/ expected event. I informed the firm that ineffectiveness is not a labeled event. Mr. Young informed me that not all drugs work for all people. I assured the firm that while this may be the case, there is nothing on their labels that states that the drug may be ineffective and therefore is not a "labeled event". Review of the firm's adverse events and complaint reports found the firm records all types of complaint issues separately and if a complainant has an issue because of lack of effect, both the lack of effect and symptom it caused are entered and each is reviewed separately. Review of the firm's complaints and AE's found no instance where the firm did not address the symptoms caused by an ineffective complaint separately. I continued to caution the firm about using the term "labeled" when referring to ineffective. One complaint (EXHIBIT 20) case number 101611 dated 10/17/08 had two problem codes including drug ineffective and gastrointestinal issues. Review of the complaint found that each problem code was reviewed and investigated separately. In addition complaint 80541 dated 4/30/08 (EXHIBIT 21) had three problem codes including drug ineffective, stroke, and hepatobiliary disorder. Review of this complaint found the firm reviewed and investigated each problem code separately and as a result, a 15 day report was submitted to the FDA.

James R. Young, Sr Manager Pharmacovigilance, provided me with the information relating to the ADE procedures. Adverse Events are handled under SOP (b) (4) Adverse Drug Experience Reports (EXHIBIT 16). In addition the firm has SOP's for Literature Adverse Reporting SOP (b) (4) (EXHIBIT 17), and Clinical Trial Adverse Event Reporting SOP (b) (4) (EXHIBIT 17).The Field Alert Reports SOP (b) (4) (EXHIBIT 18) is used to define the procedure for issuing and submitting a Field Alert Report for distributed ANDA and NDA drug products in accordance with 21 CFR 314.81. In addition, the Processing and Investigation of Perrigo Product complaints SOP (b) (4) EXHIBIT 19) is used to ensure that all quality related product complaints are documented and investigated.

**OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**
No FDA 483 was issued at the conclusion of the inspection.

**REFUSALS**

No refusals were encountered during this inspection.

**GENERAL DISCUSSION WITH MANAGEMENT**

On 1/16/09 a close out meeting was held with the firm. Those present included:
Louis W Yu, SR Vice President
John D Brown, Director Quality Assurance External Operations
James R Young, Sr Manager Pharmacovigilance
Bart D Shrode, Director Quality Assurance Tablet Stream Assurance
Nicolas J Ford, Quality Control Manager

Items discussed with the firm included;

1- Documentation of alerts and requests for investigation to (b) (4) and (b) (4) .
   a. Management promised to address the issue of clearer documentation of all correspondence between Perrigo and the manufacturer of the devices.

2- Cancel registration as a repacker if the firm does not intend to resume those operations for the medical devices. I informed the firm that if they are no longer going to be repacking the devices, then they should consider canceling their registration. I informed the firm that they can re-establish the registration in the future if needed.
   a. Management stated they would consider this option.

3- Caution was given to the firm to not rely too heavily on additional information when making a determination of serious or non serious AE's. The firm received one complaint who stated she had an allergic reaction and went to the hospital and received two drugs. At the time of the initial complaint, the complainant did not know the name of the drugs. After some time the complainant was able to remember that one of the drugs was prednisone. I stressed to the firm that if there is potential evidence that the complaint should be elevated to serious then the firm should not wait until minor clarifications are obtained before submitting a 15 day notice. I informed the firm that they were relying on the lack of information to make a determination of not filing a 15 day submission, when in some instances they had the basic information just maybe not the exact drug name or treatment. I informed the firm that they should be looking closer at the underlining problem not just the actual treatment when determining the seriousness of an event.
   a. Management promised to consider this and make corrections as needed.

4- In addition, caution was again given to the firm against using the terms "labeled or expected" when referring to complaints of ineffective. I informed the firm's management that they may want to consider rewording the SOP to more clearly reflect the firm's procedure and to clarify their understanding of ineffective complaints.
   a. Management promised to review the SOP's and make corrections as needed.

**EXHIBITS COLLECTED**

1- List of all drug products with Perrigo name on label
2- ANDA/NDA Marketed products
3- ANDA/NDA Non marketed products
4- Unapproved product list
5- Monograph Marketed
6- Monograph Non Marketed
7- External manufacturer responsible for filing adverse events
8- Medical Device Reporting SOP (b) (4)
9- Quality assurance agreement between Perrigo and (b) (4)
10- Perrigo agreement of responsibility with (b) (4)
11- Medical device reporting requirements with (b) (4)
12- Medical device reporting requirements with (b) (4)
13- Medical device Adverse events from 01/2007-01/2009
14- Periodic reporting schedule for ANDA. NDA products
15- 15 day submission list from 01/2008 to 01/2009
16- Adverse Experience Reports SOP (b) (4)
17- Literature Adverse Event Reporting SOP (b) (4)
18- Clinical Trial Adverse Event Reporting SOP (b) (4)
19- Field Alert Reports SOP (b) (4)
20- Processing and Investigation of Perrigo Product Complaints SOP (b) (4)
21- Complaint case number 101611 dated 10/17/08
22- Complaint case number 80541 dated 04/30/08

**ATTACHMENTS**
1- FDA 482 Notice of Inspection

Martha Sullivan Myrick, Investigator