CARACO
PHARMACEUTICAL LABORATORIES, LTD

Orig: DCB w/Manual
cc: DD w/o Manual
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ljk 1/22/09

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January 21, 2009

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

Re: Form FDA 483 issued December 22, 2008, to Caraco Pharmaceutical Laboratories, Ltd.

Dear Ms. Givens:

Caraco Pharmaceutical Laboratories, Ltd. (Caraco) has carefully reviewed the Form FDA 483 observations presented by the agency investigators at the conclusion of the inspection of our Farmington, MI packaging facility. We appreciate the professional manner in which the investigation was conducted.

We are disappointed at the findings and have taken immediate action to correct the systems that caused these lapses. Please see the enclosed response to each of the observations.

As you know we have invested significantly in our infrastructure in order to improve the quality systems in place while at the same time improving productivity. We have invested in people, equipment, and facilities in order to provide an improved outcome. For example, last year we purchased and retrofitted the Farmington packaging plant that we acquired from our former third party packager. We replaced the manual packaging lines and moved to automated lines that require less human intervention.

As mentioned in our previous letters, prior to this inspection we expanded our manufacturing, management, and supervisory staff as well as re-positioned the responsibility of certain departments to provide enhanced oversight and accountability.

From the inspection it is clear that we must still take positive steps to enhance our quality systems, primarily in the area of employee training and supervision. In spite of the specific lapses found during the inspection, Caraco has no evidence that any product commercially distributed failed to meet its quality, purity, or identity standards

We hope that Caraco's commitment to continuous improvement was evident during this recent inspection. We have hired an outside firm for additional training and self audits to ensure that we stay on track and to assist in addressing the issues found during the inspection.

As specified during the closeout meeting held on December 22, 2008, we are providing this written response to the observations presented by the investigators.

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We understand that the observations are not all inclusive and could represent broader issues. Therefore, we reviewed the observations from a global perspective. Actions taken in response to the observations apply not only to the specific observations, but to the systems they represent.

As committed previously, we have continued to undergo annual external audits by outside consultants. In the enclosed response, we have followed a format of re-stating the five written observations in bold and followed each observation with Caraco's response. We have included copies of all relevant procedures and supporting documents.

We request that a copy of our response to the Form FDA 483 be included with each FOIA request for the 483 and Establishment Inspection Report.

Caraco is strongly committed to supplying the highest quality generic pharmaceuticals in compliance with all Federal, State, and Local regulations. If the FDA requires any additional information or explanations, please do not hesitate to contact us. We will be happy to meet with you to discuss any concerns or questions you may have concerning our response or our Plan.

Sincerely,

Daniel Movens
CEO
Caraco Pharmaceutical Laboratories, Ltd.

Enclosures

OBSERVATION 1

Inspection of the packaging facilities immediately before use is not done to assure that all drug products have been removed from previous operations.

There have been numerous instances, 5/2008 through the present, where the failure to perform an adequate cleaning procedure (b) (4) has resulted in the necessity to conduct (b) (4) inspection of packaged finished product lots for the presence of foreign tablets noted to be present in/on/near the packaging equipment after Quality Assurance release of the equipment/room for use. Examples include:

a. ***Meloxicam Tablet lot (b) (4) inspected under SPO (b) (4) dated 5/1/08 for the presence of Carvedilol 25 mg***

b. ***Metformin HCl Tablet lot (b) (4) inspected under SPO (b) (4) dated 8/7/08 for the presence of Mirtazapine 45 mg***

c. ***Metformin HCl Tablet lot (b) (4) inspected under SPO # (b) (4) dated 8/21/08 for the presence of Metoprolol Tartrate 100mg***

d. ***Tramadol HCI tablet lot (b) (4) inspected under SPO (b) (4) dated 8/24/08 for the presence of Metoprolol Tartrate 50 mg tablets***

e. ***Methimazole Tablets lot (b) (4) inspected under SPO (b) (4) dated 9/6/08 for the presence of Clonazepam 0.5 mg tablets.***

f. ***Metformin HCl tablet lot (b) (4) inspected under SPO (b) (4) dated 10/20/08 for the presence of Metoprolol Tartrate 100mg tablets***

g. ***Tramadol HCl Tablets lot (b) (4) inspected under SPO (b) (4) dated 11/3/08 for the presence of Atenolol Tablets 25 mg***

h. ***Zolpidem Tartrate Tablets lot (b) (4) inspected under SPO # (b) (4) dated 11/18/08 for the presence of Carbamazepine Tablets 100 mg***

i. ***Metformin HCI Tablets lot (b) (4) inspected under SPO (b) (4) dated 12/2/08 for the presence of Metoprolol Tartrate 100 mg***

Response

In every instance noted in the observation, all lots impacted were inspected and not a single foreign tablet was found during the bulk tablet inspections. However, we have made the following changes which have been implemented to minimize the potential for foreign tablets in the packaging operation.

Caraco SOP (b) (4) "(b) (4) [redacted], **(Attachment 1)** was revised to include:

- Enhanced cleaning instructions. Included are specific cleaning and inspection points based on our historical findings and physical review of the equipment. Attachments B, for (b) (4) Cleaning, and (b) (4) for (b) (4) Cleaning, are included to ensure compliance to the cleaning and inspection requirements. Included in the (b) (4) Cleaning Record are signature fields with date and time requirements for the person performing each cleaning step and the person performing the verification. This by itself will allow for personnel accountability and determine their performance relating to the effectiveness of their training.
- Equipment pictures are provided to illustrate potential points on the machine where tablets may potentially lodge. A copy of the pictures have been placed in binders and issued to each slat counter line (b) (4) These pictures are used as an aid for operators and Quality Assurance personnel to ensure effective line

clearance following cleaning.
- Detailed safety warnings
- An Exhibit to illustrate the machine/equipment parts
- Common slat patterns

All affected personnel (e.g., line operators, supervisors, mechanics, and Quality Assurance line personnel), have been trained on the new procedure that was effective on January 2, 2009. The result of the recent internal equipment cleaning inspection has proven that the procedure and personnel training is effective.

OBSERVATION 2

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

SOP (b) (4) (b) (4) (b) (4) ***". Section*** (b) (4) ***of this SOP calls for "*** (b) (4) (b) (4) ***'. It was determined that there has been no trending of SPO's issued for 2008, although*** (b) (4) ***SPO's have been issued in 2008 as of the start of this inspection. The following is a partial summary of the reasons for SPO issuance for 2008 as listed in the database provided:***

Foreign Tablets	(b) (4) ***instances*** (b) (4) ***since May 2008)***
Thick/Thin Tablets	***instances Thick) -*** (b) (4) ***of which were for Clonazepam***
Foreign Contamination	***instances since September)***
Inspection of " (b) (4) ***lots from*** (b) (4)	(b) (4) ***instances***
Inspection of "' lots from	(b) (4) ***instances***
Inspection (non discript)	***instances*** (b) (4) ***since 6/27/08)***

Response

Section (b) (4) of procedure (b) (4) (**Attachment 2**) indicates that Special Processing Operation numbers are assigned to ensure traceability of SPO's to other cGMP documentation (e.g., BMR's, Incidents, Complaints). For each SPO that pertains to a product inspection due to quality-related matters, such as foreign matter and tablet appearance, a reference is provided for the incident tracking number associated with that lot. SOP (b) (4) specifies that (b) (4)

The tracking includes maintenance of an SPO database which provides the traceability back to the incident. Incidents are currently trended on a (b) (4) basis by Quality Assurance. The Incident Trend Report includes a breakdown of incidents which require Special Processing Operations, typically in the form of product inspections. This report includes the further breakdown of quality-related issues relative to the type of incident (e.g., foreign matter, foreign tablets, tablet appearance, etc.), the department where the incident occurred (e.g., (b) (4) compression, packaging, etc.), and the product produced. Section (b) (4) (b) (4) " (**Attachment 3**), specifies that incidents "(b) (4) (b) (4) " A copy of the most recent Incident Trend Report for the past quarter is included with this response (**Attachment 4**). We have taken as a result of this trending specific corrective action where applicable. We apologize for any confusion we may have caused by presenting a histogram from the previous year instead of the most current one. That document was a result of a (b) (4) analysis conducted as part of our on-going investigations.

The incident process is specific to Caraco-produced products. A system does exist for those products manufactured by contract partners, such as (b) (4) Components that are contract manufactured are issued a Contract Partner Complaint (CPC) tracking number, which tracks the issue through the suppliers' investigational process. Section (b) (4) of Caraco SOP (b) (4) " indicates that Quality Assurance (b) (4) (b) (4) " A copy of the most recent Contract Partner Complaint Trend Report is included with this response (**Attachment 5**).

OBSERVATION 3

Batch production and control records do not include complete information relating to the production and control of each batch.

a. On 12/11/08 we observed a problem that occurred during packaging of Zolpidem Tartrate Tablet lot (b) (4) ***where, due to an alignment issue bottles were shorted tablets as the tablets were observed to be spilling onto the floor. The line had to be stopped, adjustments made, and bottles removed and their contents dumped. Review of the packaging record following the completion of the run revealed no notation of the problems we witnessed.***

b. Review of the batch record for Zolpidem Tartrate Tablet lot (b) (4) ***reveals no indication of a problem during packaging. However, review of Caraco's complaint data base reveals there have been*** (b) (4) ***complaints of incorrect tablet count received for lot 80311A.***

Response

Caraco has created a new Form (b) (4) (**Attachment 6**). Caraco SOP No. (b) (4) was also revised to include Form (b) (4) in subsection (b) (4) (**Attachment 7**). This provides a specific repository for any additional information to be added during a packaging run for each product without limiting the space, thus allowing for robust documentation of the specific issue during the packaging process.

Form (b) (4) and SOP (b) (4) were made effective on January 2, 2009, and training was provided to all affected personnel: operators, supervisors/managers, mechanics, and Quality Assurance line personnel. To enhance and simplify instructions in the packaging batch record, the entire packaging batch record format is in the process of being revised to include stepwise instructions to be followed during packaging. This process should be completed by the end of second quarter 2009

Additionally, the packaging lines are being fitted with (b) (4) which will eliminate bottle movement during packaging. This provides for (b) (4) (b) (4) The parts are being delivered this week, and the equipment will be qualified and implemented by February 15, 2009.

OBSERVATION 4

The persons performing and double-checking the cleaning and maintenance are not dating and signing or initialing the equipment cleaning and use log.

a. On 12/12/08, review of the Line [redacted] Maintenance Use and Cleaning Record noted the clean-up of this area, last used 12/11/08, was not documented on this log or on the Cleaning and Washroom Area log where [redacted] cleaning of the various rooms are documented. The area referred to as Line [redacted] was clean with no sign of "inspection" activities for the lot of Metformin, [redacted] that was in process on 12/8-11/08. Inspection of Lot [redacted] was not complete.

b. Failure to document [redacted] cleaning between packaging of Atenolol Tablet lot [redacted] and Tramadol HCl tablet lot [redacted] both packaged on Line [redacted] on 10/31/08. Tramadol lot [redacted] was ultimately inspected for the presence of Atenolol following the discovery of Atenolol Tablet(s) in the packaging room after packaging the Tramadol lot.

Response

Caraco SOP [redacted] requires that all personnel performing the cleaning and inspection of equipment sign the record concurrent with the operation. Personnel have been re-instructed in this procedure. All personnel during this training were reminded that appropriate actions up to and including termination will be taken for infractions or deviations from our procedures.

Additionally, to provide assurance that the procedure is complied with, SOP [redacted] (**Attachment 8**) has been updated. Instructions provided in section [redacted] require all personnel [redacted]

OBSERVATION 5

Written records of major equipment cleaning, maintenance, and use are not included in individual equipment logs.

Induction sealer, Caraco asset # [redacted] located in "Line [redacted]" area does not have a usage log. This moveable equipment was utilized for unsealing and sealing finished product containers subjected to inspection for various reasons as assigned by the Quality Unit via a Special Processing Operation (SPO) order.

Response

Caraco SOP [redacted] (**Attachment 7**) has been updated to address the use of portable or moveable equipment. The addition of section [redacted] states that "[redacted]

All operators, supervisors/managers, mechanics, and Quality Assurance line personnel have been trained to ensure that this requirement is followed when a packaging operation is performed that does not require use of the complete packaging line.

The stand alone Induction sealer Caraco asset # [redacted] was previously employed for off packaging induction sealing, however this equipment was taken out of service on December 16,

2008. As previously stated above all packaging operations that require the use of less than a complete line to complete the operation must be performed on one of the established packaging lines. The use of previously designated room (b) (4) has been discontinued.