DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139	05/01/2008 - 06/11/2008 FEI NUMBER 1833173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel H. Movens, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Caraco Pharmaceutical Laboratories, Ltd.	1150 Elijah McCoy Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Detroit, MI 48202-3344	Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

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.

A. The Quality Unit has failed to fully investigate (b) (4) incidents of contamination of drug product with another drug:

1. Tramadol HCL 50 mg Tablets, lot (b) (4), manufactured 1/26/08 was found adulterated with (b) (4) on 2/19/08 by the (b) (4)

2. Metoprolol Tartrate 50mg Tablets, USP, lot (b) (4), manufactured 2/4/08 (as (b) (4)) was found adulterated on 2/25/08 by the (b) (4) A contract laboratory confirmed the contaminate to be (b) (4) on 4/1/08.

This information was first presented at the Operations group meeting on 3/20/08. These two investigations (b) (4) remained open for the duration of this inspection.

B. Investigation under incident reports (b) (4) dated 3/17/07) and (b) (4) (dated 3/30/07) for Content Uniformity failures involving (b) (4)) of Metoprolol Tartrate Tablets, USP, 25 mg have not been completed. An extention to 6/1/07 was granted on 5/2/07.

C. Investigation under (b) (4) initiated 8/10/07 for (b) (4)) of Carbamazepine USP 200 mg tablets with failed dissolution test at (b) (4) minutes, remains open.

D. Investigation into the reason for the 4/10/08 Out of Specification for Content Uniformity of Tramadol HCl in Tramadol HCl/Acetominophen 37.5/325 Tablet lot (b) (4) had not begun as of 5/1/08.

E. Lack of adequate investigation into instances where raw material reconciliation failed to meet established allowable +/- difference. Examples include:

1. For Tramadol Hydrochloride raw material lot (b) (4), last dispensed 2/21/08 to Tramadol HCl & APAP lot (b) (4) (released 4/3/08) the investigation under (b) (4) initiated/dated 4/1/08 remains open for the (b) (4) (missing) discrepancy.

2. For Citalopram Hydrobromide lot (b) (4), short by (b) (4), the documented investigation focused on inventory

tolerance trends of other Citalopram Hydrobromide lots received and failed to evaluate other lots dispensed the same day(s) as lot RM81030.

F. Corrective Action Plan (CAPA)(b) (4) initiated as follow-up to OOS yields noted for Carbamazapine USP lots(b) (4) (b) (4) in October 2007 remains open as of 5/23/08.

G. There has been no investigation into the source of the metal contamination found 2/13/08 in the final blend of Metformin HCl 1000mg Tablets, USP, lot(b) (4) by the compression department, as noted on Incident Report(b) (4) . The due date for the investigation has been extended to 6/15/08.

H. Similarly, for Metformin HCl 1000mg Tablets, USP, lot(b) (4) there has been no investigation to date into metal scrapings and foreign matter found 2/27/08. The investigation has been extended until 5/30/08.

I. The 1/23/08 investigation into the finding of foreign matter in lot(b) (4) Metformin HCl 1000 mg Tablets, USP was incomplete in that the source of the wood identified, a wooden plug for the compression machine, has reportedly not been used in this facility since(b) (4) .

OBSERVATION 2

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

Product cross contamination incident investigations(b) (4) dated 2-19-08 and(b) (4) dated 2-25-08, did not extend to all other drug product lots dispensed within the same time period (01/25-29/08) as the lots impacted by each respective incident (Tramadol lot(b) (4) and Metoprolol lot(b) (4)) prior to 5/1/08. The following are examples:

Product	Lot	Date of Dispensing	Date of Quality Release
Carbamazepine Tabs, USP, 200mg	(b) (4)	1/26/08	2/22/08
	(b) (4)	1/26/08	2/22/08
	(b) (4)	1/26/08	2/28/08
	(b) (4)	1/27/08	2/28/08
	(b) (4)	1/27/08	4/22/08
Citalopram HBr Tabs, 40 mg	(b) (4)	1/27/08	2/23/08
	(b) (4)	1/27/08	2/21/08

	(b) (4)	1/27/08	2/21/08
	(b) (4)	1/27/08	3/18/08
Baclofen Tabs, USP, 10mg	(b) (4)	1/25/08	2/27/08
	(b) (4)	1/25/08	3/05/08
	(b) (4)	1/25/08	3/11/08
Oxaprozin Tabs, USP, 600mg	(b) (4)	1/27/08	3/08/08
	(b) (4)	1/27/08	2/29/08
	(b) (4)	1/27/08	2/29/08
	(b) (4)	1/27/08	3/08/08

(b) (4) in the Draft Investigations for each of the above Incident Reports attributed the cross contamination to inaccurate dispensing.

OBSERVATION 3

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

A. Process Validation attempt conducted under protocol (b) (4), involving Carbamazepine Tablets, USP 200 mg lots (b) (4) was ultimately repeated under protocol (b) (4) following the (b) (4) minute dissolution failure of preliminary compression samples for all (b) (4) lots. Despite no difference in the manufacturing process for these (b) (4) lots, lot (b) (4) was released following validation under (b) (4) manufactured with additional water in the process, while lots (b) (4) were rejected. In addition the subsequent Carbamazepine validation lots produced under (b) (4)) were not placed on stability.

B. Validations conducted on Carbamazepine Tablets manufactured using (b) (4) revealed failing dissolution results for lots exhibiting low LOD ((b) (4) in-process values. Current Batch Master Record (BMR) (b) (4) for Carbamazepine Tablets, USP, 200 mg tablets, still contains the statement "(b) (4) . There is no documented justification for LOD specification (b) (4) referred to in this BMR.

C. The acceptable range for the LOD, a critical control for the quality of Tramadol HCl 50 mg Tablets granulation dried, was inadequate to distinguish acceptable material from not acceptable material. Seasonal exceptions to the Master Batch Record directions were used to compensate for undefined unacceptable variance inside of the LOD specification (b) (4) For example on 5/1/08, we observed that approved (b) (4) was used to decrease the time that granulation of lot (b) (4) other Tramadol HCl 50 mg Tablets granulation lots would spend in the tray driers (b) (4) ; the CR was a response to low humidity of the season. In addition, there was no procedure or written criteria for revalidation of manufacturing processes.

D. No documentation exists to support the current in process hardness tolerance extremes as listed in the Master Batch formula for Mirtazapine Tablets, USP, 15 mg and 45 mg as follows:

Drug Product	Current Batch Record Hardness Tolerance (Kp) -Indiv.	Hardness Ranges Established (Development/Validation, Kp)
Mirtazapine Tabs, USP, 15mg	(b) (4)	[redacted]
Mirtazapine Tabs, USP, 45mg	(b) (4)	

OBSERVATION 4

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

A. SOP(b) (4) [redacted] was not followed in that(b) (4) [redacted] However, a total of(b) (4) bottles of Methimazole Tablets, USP, 10mg lot (b) (4) were distributed on 5/27/08 to(b) (4) different customers though this lot was subject to open investigation,(b) (4) [redacted]

B. No QA hold was issued 1/19/08 when a nut and bolt went missing during coating of Choline Magnesium Trisalicylate Tablets 500mg lot(b) (4) Incident ((b) (4), SPO(b) (4)) and QA Hold(b) (4)) were issued 1/22/08 when the nut and bolt were found during packaging. The QA Hold was lifted 5/3/08 although the lot was released 1/29/08.

C. SOP(b) (4) [redacted] was not followed in that step(b) (4), is to include '(b) (4) [redacted] however: the in process tablet compression data provided in the 1-1-2006 through 4-30-2007 Mirtazapine Tablets, USP ((b) (4) [redacted]) Annual Product Review (APR) do not represent actual in-process compression values obtained during batch processing. For example, the compression values represented in the APR for lot(b) (4) are the start of compression set-up values.

D. The following deviations from SOP(b) (4) [redacted] were observed on 5/14/2008 in the dispensing area:

1. (b) (4) contained raw materials Povidone and Mannitol for Carvedilol 25 mg Tablets Lot#(b) (4). Sucrose was also brought to the room and was eventually removed.

2. (b) (4) contained raw materials Microcrystalline Cellulose and Lactose Hydrous for Metoprolol Tartrate Lot#(b) (4) .

3. (b) (4) contained Microcrystalline Cellulose and multiple ingredients already dispensed and labeled for Citalopram Hydrobromide 40 mg Tablets Lot #(b) (4) .

4. Use and Cleaning Log for(b) (4) [redacted] documents Type II Cleaning; however, all products were not removed from the rooms prior to reported cleaning.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139	05/01/2008 - 06/11/2008 FEI NUMBER 1833173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel H. Movens, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Caraco Pharmaceutical Laboratories, Ltd.	1150 Elijah McCoy Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Detroit, MI 48202-3344	Drug Manufacturer

E. QA (b) (4) for a foreign tablet made of tooling polishing compound found in Tramadol HCl 50 mg lo(b) (4) was issued 1/18/08, after the QA Hold was signed closed 1/17/08, and after the lot was reprocessed (sorted) under SPO(b) (4). There was no record of investigation into the source of the identified contaminant and no consideration given to examining other lots of potentially similarly contaminated product.

F. SOP (b) (4) Quality Complaint Procedure was not followed with regard to Complaint (b) (4) 3 received 10/23/07. The complaint indicated Gabapentin tablets lot (b) (4) had off white or tan hue on the tablets and inside the bottle. As of 6/3/08 this complaint remains open with no documented investigation available at Caraco.

OBSERVATION 5

Component weighing, measuring, and subdividing operations are not adequately supervised.

A. Contaminated Tramadol HCl ((b) (4)) and Metroprolol Tartrate (b) (4)) lots were dispensed during a shift not staffed with a supervisor.

B. Multiple lots observed on 5/14/08 in (3) dispensing rooms, in the presence of supervisor and manager.

C. Employee observed on 5/14/08 wearing jewelry while working in dispensing area, contrary to SOP (b) (4) and with the knowledge of the Supervisor on duty.

OBSERVATION 6

Records fail to include an individual inventory record of each component and reconciliation of the use of each component with sufficient information to allow determination of any associated batch or lot of drug product.

A. The following are examples where the raw material inventory was adjusted following the total depletion of available material. Such adjustments involved serveral kilograms of material without investigation as to where the extra material came from, or where it might have gone depending on the type of adjustment necessary to achieve a zero balance. Beginning/starting quantities are not verified upon receipt:

1. Metformin HCl, lot (b) (4) , (b) (4) Kg documented as "Excess found"
2. Carbamazepine USP lot, (b) (4) 0, (b) (4) Kg
3. Metformin HCl lots (b) (4) 8 adjustments of (b) (4) Kgs respectively
4. Metformin HCl lo(b) (4) (b) (4) Kg
5. Tramadol HCl lot (b) (4) 1 (b) (4) Kg
6. Tramadol HCl lot (b) (4) (b) (4) Kg

B. The following are examples where the raw material inventory information was not entered/reconciled at the time of use resulting in inaccurately documented inventory records:

1. Tramadol HCl lo(b) (4) (b) (4)) dispensed 2/16/08, inventory history record updated 2/26/08
2. Metformin HCl lots (b) (4) dated 1/24/08) dispensed 1/16&17/08, inventory history record updated 1/22/08

3. Metoprolol Tartrate lot (b) (4) wrong quantity of Magnesium Sterate dispensed to the batch (b) (4) 5 dated 4/29/08).

OBSERVATION 7

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

A. Metformin HCl Tablets, 1000 mg lo (b) (4), coating record dated 4/14/08, fails to document the nature/type(s) of the defects noted for each of the part lots (b) (4) sampled.

B. Metformin HCl Tablets, 1000 mg lo (b) (4) coating record dated 4/23/08, fails to document the nature/type(s) of the defects noted for each of the part (b) (4) sampled.

C. Metoprolol Tartrate Ready to Compress Granules, lot (b) (4), batch record does not reflect the fact that a portion of the (b) (4)) dispensed to the batch, is from Receiving No. (b) (4) . (b) (4) 5 dated 1/28/08 investigation of dispensing documentation error involving SSG lots (b) (4) was closed 4/26/08 but did not include a correction of the batch record for lot (b) (4)

OBSERVATION 8

Equipment and utensils are not cleaned and maintained at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

A. Routine preventative maintenance was not performed on the air handling system with HEPA filter associated with the (b) (4)) according to written Preventative Maintenance procedures and prior to use in manufacturing operations.
Specifically, the integrity of this HEPA filter and the associated air handling unit had not been verified prior to use in drying Methimazole (b) (4) . These (b) (4) lots were then issued to compressed tablet, finished product lots including (b) (4) each released by quality on 01-31-08.

B. On 5/1/08, during compression of Clonazepam Tablets USP lot (b) (4) we observed the compression operator spraying dilute isopropyl alcohol to clean tableting dust from the tablet press base. The area sprayed was near the discharge chute through which compressed tablets were being guided into the collection containers.

OBSERVATION 9

Written production and process control procedures are not documented at the time of performance.

For the following manufacturing operations, a portion(s) of the batch record was transcribed and not prepared concomitant with the operation:

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139	05/01/2008 - 06/11/2008 FEI NUMBER 1833173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel H. Movens, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Caraco Pharmaceutical Laboratories, Ltd.	1150 Elijah McCoy Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Detroit, MI 48202-3344	Drug Manufacturer

A. Special Processing Operation (b) (4) record for Choline Magnesium Trisalicylate Tablets 500mg lot (b) (4) (b) (4), a sorting operation was executed without documentation and approval on 1/19/08. The record also showed the sorting activity was performed 1/22/08.

B. Use and Cleaning Log for Dispensing (b) (4) dated 5/13-14/08, lacks the required Type II cleaning documentation by the operators working the overnight shift but was later (approx. 1:00 pm) recorded by the day shift supervisor as having been completed.

OBSERVATION 10

Employees engaged in the manufacture and processing of a drug product lack the training required to perform their assigned functions.

Review of training records of four employees in the Dispensing Department show incomplete documentation of minimum training requirements to enable a person to perform the assigned functions according to (b) (4) Effective Date 04/17/2007 (b) (4). Examples:

A. Four of four employee training records reviewed lack documentation of Job Specific SOP trainings, specifically: (b) (4)

Core Quality SOP training lacking documentation include (b) (4)

B. (b) (4) employee training documentation lack instructor's name, date, and signature. For example employee PT the 08/02/2005 training on (b) (4) and for employee RC the 02/26/2008 training on (b) (4).

OBSERVATION 11

GMP training is not conducted on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

The Quality Unit has not assured that corrective action taken to retrain analysts in the dilution procedure for dissolution tests involving SLS was complete in that; for (b) (4) persons involved in the initial dissolution failure of Carbamezapine Tablets lots (b) (4) were not retrained until this inspection.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139	05/01/2008 - 06/11/2008 FEI NUMBER 1833173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel H. Movens, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Caraco Pharmaceutical Laboratories, Ltd.	1150 Elijah McCoy Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Detroit, MI 48202-3344	Drug Manufacturer

OBSERVATION 12

Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance.

A. (b) (4) does not require documentation of the replacement and re-assembly of the hose tubing associated with the dispensing pumps.

For example, Log Book entries for Granulation Dispensing Pump, asset (b) (4), show evidence of a Type I clean between granulation of Glipizide Tablets, USP, 10 mg lot (b) (4) and Clonazepam Tablets, USP, 1 mg lot (b) (4), however, record of the destruction of the previous hose and installation of a new segment of hose is not documented in this log record or each respective batch record.

B. The practice of dedicated use for a 'difficult to clean' sample thief, observed labeled for use in sampling of Tramadol HCl and Acetominophen 37.5/325 Tablet batches, was not controlled by a written procedure.

OBSERVATION 13

Procedures describing the warehousing of drug products are not established.

On 5/1/08 there was no documented control of the contents of the warehouse at Elijah that held in-process goods and dispensed raw materials as well as 'QA Hold' in process goods.

OBSERVATION 14

For components removed from the original containers, the new container fails to be identified with receiving or control number.

On 5/1/08 we observed that the identity of 4/12/08 weighed active ingredient Metformin HCl (b) (4) was changed after the weighing (and check), based on the lack of reconciliation between inventory records observed on 4/14/08, for Metformin HCl Tablets, USP, RTC lo (b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139	05/01/2008 - 06/11/2008
	FEI NUMBER 1833173

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel H. Movens, Chief Executive Officer

FIRM NAME	STREET ADDRESS
Caraco Pharmaceutical Laboratories, Ltd.	1150 Elijah McCoy Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Detroit, MI 48202-3344	Drug Manufacturer

FDA EMPLOYEES' NAMES, TITLES, AND SIGNATURES:

Patsy J Domingo, Investigator

Andrea F. White, Chemist

Regina T. Brown, Investigator

Rebecca E. Dombrowski, Investigator

Caroline H. Le, Investigator

Tracey L. Taylor, Investigator

SEE REVERSE OF THIS PAGE

DATE ISSUED
06/11/2008