CARACO
PHARMACEUTICAL LABORATORIES, LTD

November 24, 2008

Judith A. Putz
Compliance Officer
Food and Drug Administration
Detroit District
300 River Place, Suite 5900
Detroit, MI 48207

Dear Ms. Putz:

This is in response to the Warning Letter (2008-DT-05) that we received from the Director of the Detroit District on October 31, 2008.

We recognize the seriousness of the violations and we would like to confirm that we have taken appropriate actions to correct the deficiencies in order to ensure compliance with the regulations.

The specific actions to correct the violations described in the warning letter are described in detail in the enclosed document. The document consists of a comprehensive and detailed analysis and explanation of completed and in progress corrective actions to ensure compliance. The corrective actions that have been undertaken reflect our commitment to compliance with the CGMP requirements and our pledge that the quality of our products will not be compromised. We believe that these corrective actions will alleviate the agency's concerns regarding the company's compliance history, the serious nature of the observed violations, and the risk to consumers.

We responded to each of the items cited in the warning letter. In addition to the corrective actions, we have made companywide changes that include the following:

- We hired an experienced individual from the pharmaceutical industry as the new Director of our Quality Control Unit to oversee management of the quality system.
- We are also in the process of hiring another experienced individual as the new Quality Assurance Manager.
- We expanded the scope of the in-house Regulatory Compliance group to audit all corrective actions based on previous inspections and external and internal audits.
- Implementation of [redacted] link by end of first quarter 2009 which tracks all quality control systems and will be integrated within our [redacted]. (b)(4)

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- Our Quality Review Board has implemented increased oversight of the Quality Unit through biweekly meetings to monitor and review compliance related issues, investigations, and other pertinent information.
- The corporate quality group of [redacted] will also help to monitor the effectiveness of the quality systems.
- We are in the process of engaging the regulatory consulting group of [redacted] as our outside consultant to conduct a comprehensive review of the quality systems implemented and provide any further remediation needed in our quality management system. (b)(4)
- In the last three years we made a considerable investment in human capital. We hired [redacted] people in quality and [redacted] in manufacturing.
- We acquired new equipment and systems to improve compliance and quality.
- Extensive and repetitive training of manufacturing and quality personnel

We would like to address the agency's concerns about our plans for expansion while we are also focusing on improving our compliance. The scope of the expansion at present is not to introduce new molecules (products) into the facility. Our expansion project actually allows the consolidation and modernization of our manufacturing activities as well as allowing executive management to be located in the manufacturing facility. The primary function of expansion is to improve the operation.

In order to alleviate FDA's concern we will delay moving any production related activities until after we have successfully implemented our [redacted] system. Our plan would remain to move our dispensing and storage of raw materials from a separate facility to provide seamless moving of material and product in the same building. This would enhance CGMP compliance by having the proper space allocation for these operations. We would also move executive management, accounting, and administrative functions in the building to coexist with the entire manufacturing operation. When we move the remaining production areas to the new area, we believe that our CGMP compliance would be further enhanced for the following reasons: (b)(4)

- More automation to reduce human interventions
- Man and Material movement for unidirectional flow
- Avoid unnecessary movement
- New equipment for better performance, easier cleaning, and maintenance
- New HVAC systems for controlling environment and air flow

- Improved space planning to further avoid potential cross contamination
- New finish for better cleaning

Our goal is to become a model of compliance. We would like the opportunity to discuss our action plan to convey our sense of urgency and address any remaining concerns from the agency. We would like to meet with you and your colleagues. I will contact you next week to set up a meeting.

Sincerely,

Daniel Movens
Chief Executive Officer
Caraco Pharmaceutical Laboratories, Ltd
Enclosure

Response to FDA Warning Letter issued October 31, 2008 to Caraco Pharmaceutical Laboratories, Ltd.

Inspection Date: May 1, 2008 to June 11, 2008
Form FDA 483 Issued June 11, 2008

Caraco has carefully reviewed the Warning Letter issued to Caraco Pharmaceutical Laboratories, Ltd. We have addressed the specific observations and comments below:

WARNING LETTER ITEM 1

Failure of the Quality Control Unit (QCU) a) to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed and b) to thoroughly investigate a batch or any of its components not meeting any of its specifications and extend investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure [21 CFR § 211,192].

a) Your QCU failed to fully investigate the contamination of Tramadol HCl, 50 mg tablets, lot [redacted] and Metoprolol Tartrate USP, 50 mg tablets, lot [redacted]. On February 19, 2008, Tramadol HCl, lot [redacted] was found contaminated with Metoprolol Tartrate. On February 25, 2008, Metoprolol Tartrate USP, lot [redacted] was found contaminated with Metformin HCl. More than two months after the contamination issues were discovered, the Directory of Quality provided only a draft investigation for the Tramadol HCl tablets and no information for the Metoprolol Tartrate tablets investigation. Rather than extending the investigation of two, closely-related, confirmed incidents of contamination of lots that were not released, to other potentially impacted drug products, the QCU placed these investigations into a low priority status, without isolating the source of the contamination, and continued releasing drug products from the same time period in which the two cross-contaminated lots were processed.

(b)(4)

Your July 10, 2008 response regarding the failure to thoroughly investigate discrepancies and out-of-specification (OOS) results, states in part that products under investigation were "[redacted]" We note significant inadequacies in your response, including inconsistencies with other explanations you provided previously during the inspection. First, none of the other drug products that may have been associated with the same failure during the cross-contamination incidents (i.e., Jan 2008) were placed on QA Hold or rejected (e.g. Carbamazepine, Citalopram HBr, Baclofen, Minocycline HCl).

(b)(4)

CARACO RESPONSE A

The two lots associated with the cross contamination incidents (i.e., Tramadol HCl, 50mg Tablets, lot [redacted] and Metoprolol Tartrate USP, 50mg Tablets, lot [redacted]) were placed into rejection at the time of the discovery of the cross contamination. These lots have been destroyed. (Attachement 1) Due to the nature of the contamination, with the material being substituted, it left the investigators with the impression that it was an isolated incident and no other products were affected. Inventory adjustments made by the Dispensing Manager that were the approximate

(b)(4)

amount of the calculated contamination further supported the investigator's position of being an isolated incident. The investigation reports were previously submitted.

Caraco has a procedure, SOP [redacted] (Attachment 2), which has been revised to include a checklist of requirements which must be signed prior to batch release. One of these requirements is to ensure satisfactory closing of any open incidents.

(b)(4)

In addition, Caraco SOP [redacted] (Attachment 3), and the associated Form [redacted] have been revised to include a formal assessment of the product quality impact on other lots. This assessment will be completed as soon as an incident has occurred and been reported to the Quality Engineering Unit (QEU). This assessment will be approved by the QA Manager and will be included in the investigation file.

(b)(4)

b)(4) SOP [redacted] contains detailed procedures for how to perform investigations, how to extend investigations to potentially impacted products, what needs to be taken if some products and marketed released products are potentially impacted. It also specifies the extension of investigation to various activities including equipment, personnel, methods and materials, as necessary. The SOP also requires an evaluation to determine if any repetitions relative to incident type, product and/or personnel are involved.

(b)(4) As part of our revised SOP [redacted] an interim investigation report will be prepared to summarize the on-going activities and an approved product quality impact analysis will be attached to the extension request before an extension is granted. All the granted extension requests will be reviewed by the Quality Review Board (QRB). Need to verify the SOP

b)(4) SOP [redacted] includes the need for root cause and if not possible then the most probable cause must be detailed and the applicable CAPA identified.

In addition Caraco's Quality Review Board (QRB) which includes the CEO, heads of Quality, Regulatory Affairs, Manufacturing, Human Resources, Purchasing, and Sales Operations has implemented an increased oversight of the Quality Unit.

[redacted] reports are provided by Caraco's Quality Control Unit to the QRB, which indicates the status of core quality systems. This requirement has been included in the updated Caraco SOP [redacted] (Attachment 4). Included in this information is the current investigation status pertaining to the current total number of incidents, status of outstanding; number, type and products with incidents and complaints generated; and the number of investigations that are open beyond [redacted] days. In addition, a status report of active process improvement projects designed to reduce the number of incidents is also provided to the QRB. Caraco started conducting Quality Review Board meetings in June 2008 on a [redacted] basis and intends to continue these meetings in the future as well.

(b)(4)

As indicated in the [redacted] letters issued to the FDA, Caraco has recently implemented changes within the Quality Assurance Department that places additional Quality Auditors within each of the manufacturing and packaging areas throughout the daily operations. This change provides QCU

b)(4)

representation on the production floor for immediate identification and reporting of any potential issues.

Since the inspection we have expanded the scope of the investigation in an effort to determine the source and extent of the potential contamination. We have tested [redacted] lots and reviewed the applicable records for the products manufactured during the same period. The [redacted] lots dispensed during the period in question that could have been potentially impacted were identified and placed on QA Hold. For lots that had already been released to the market at that time, any remaining inventory was placed on QA Hold until the investigation and testing confirmed that there was no cross contamination on finished product with no impact on the quality of these lots The test was performed by employing methods capable of detecting low level specific contaminants. We also tested representative samples of lots produced one month prior to the period in question and one month after the incident (Attachment 5).

(b)(4)

Caraco is also in the process of developing and implementing an automated quality system - Quality Management System- (QMS) within Caraco's Enterprise Resource Planning (ERP) system to further ensure that:

- outstanding incidents are addressed in a timely manner
- product is not released with an open investigation or any other issues
- trending of complaints and incidents will be tracked

This program will include core quality systems, such as incidents, corrective actions [redacted], market complaints, change control, and QA Hold and Release (integrated with our ERP system).

(b)(4)

The system is in the final stage of development, and will undergo primary user review in December. It is expected to be implemented and validated at Caraco by the end of February 2009.

Second, your response to observation 1A (from the FDA-483) states in part that the two cross-contamination investigations "[redacted] and "[redacted]" Our investigators were provided with a draft incident report for the Tramadol HCl investigation, which had not been reviewed by your Director of Quality (until approximately four months after the cross-contamination incident), and your firm had not started an incident report for the Metoprolol Tartrate investigation. Approved extensions to the investigations were not granted by your QCU.

(b)(4)

CARACO RESPONSE B

We agree that an extension was not provided in a timely manner. However as discussed above we have enhanced our "[redacted] and the process to assure compliance. The Quality Engineering Unit is responsible and accountable to assure compliance. Going forward this is an agenda item during the biweekly review by the Quality Review Board. Specific comments and action steps will be appended to any incident deemed critical at the review meeting. At this time, there are no incidents or corrective actions that fall outside of the SOP requirements for approved extensions.

(b)(4)

When the incidents were initiated by the lab for the two cross-contaminated lots, the manufacturing investigations were started concurrently with the lab investigations. The Tramadol Incident was generated on 2/18/08 and the Metoprolol Incident was initiated on 2/25/08 each within 24 hours of the laboratory report.

The preliminary investigations were assigned to the heads of the Dispensing and Manufacturing Departments in order to determine the source of cross contamination within each department. During this same timeframe, laboratory investigations were being conducted by identifying the exact contaminants in each product. The contaminant in the Metoprolol Tartrate lot took longer to identify since a product sample had to be sent to an outside testing facility for [redacted] evaluation. (b)(4)

For events that are first observed in the laboratory, such as the extraneous peaks observed for these two lots, the first step in the investigation process is to generate a Manual Observation Checklist in accordance with Caraco SOP [redacted], "[redacted]" If the event is not immediately determined to be an analytical error, then a formal laboratory investigation is initiated in accordance with Caraco SOP [redacted] If the Laboratory Investigation Report (LIR) confirms the out-of-specification results, then typically an Incident Tracking Sheet is initiated at that time. Due to the significant concentration of impurity found in the initial laboratory testing, an Investigation Report (IR) was initiated immediately by the QC laboratory. The sequence of events for each lot is as follows: (b)(4)

	Tramadol, lot [redacted]	Metoprolol, lot [redacted]
Date MOC Initiated	02-18-08 (MOC [redacted])	02-25-08 (MOC [redacted])
Date LIR Initiated	02-19-08 (LIR [redacted])	02-25-08 (LIR [redacted])
Date LIR Approved	05-02-08	05-02-08
Date Investigation (IR) Initiated	02-19-08 (IR [redacted])	02-25-08 (IR [redacted])
Date Investigation Completed	05-28-08	05-28-08
Date Investigation Approved	06-15-08	06-15-08

(b)(4)

(b)(4)

At each stage of the investigation, additional evidence was being gathered to support a root cause determination; however the draft had not yet begun on the actual investigation report, which is what the FDA Inspector requested at the time of the inspection. As discussed above, The SOP is revised to require an interim report of on-going activities prior to any extensions being granted.

We recognize the need to enhance our investigation procedure to facilitate prompt follow up and completion of investigations as specified within the investigation SOP. As such we have

restructured the QCU to have a dedicated group of personnel whose major responsibility is to lead and conduct investigations, monitor [redacted] progress and implementation. The head of this group is responsible for preparing the report on a [redacted] basis for management review. The manager of this group will attend the QRB meeting to clarify any significant issues. A note will be appended to the investigation file to document actions taken. One of the significant points that will be discussed at the meeting would be adherence to the SOP. The Quality Review Board will take action as deemed necessary if the procedure has not been consistently followed to correct our investigations. (b)(4)

In addition, your response regarding the failure to extend the investigation to other drug products is troublesome. When discussing the issue of extending the investigation to other drug products, your response states in part "[redacted] Your release test methods are not validated for the detection of every potential contaminant and have not been demonstrated to be suitable under actual conditions of use (e.g. detection of any low level contaminant); therefore, we do not agree with your statement and advise you to fully investigate discrepancies and OOS results with reliable test methods that are validated for their intended purpose. (b)(4)

CARACO RESPONSE C

Our analytical procedures are designed for the testing of the applicable product quality parameters. The methods are qualified and validated with this intent. It was never our intention to use release test methods to identify cross-contaminated product and we agree that our release testing methods are not validated for the detection of other active ingredients at low levels or for that matter at any level. However, we would like to note that when extraneous peaks are detected in our analysis we would take appropriate action as indicated in this instance. We also agree that there is no single validated method that can detect the contamination from all other drug products produced in our facility. However, for this investigation we used a combination of 5 different methods to confirm the absence of API contaminants in products that were manufactured during the timeframe of January 25 to January 29, 2008 (Attachment 6 pages 14, 15, and 16).

Subsequent to the receipt of the warning letter, the suitability of the methods for the intended purpose of detecting the contamination of [redacted] drug substances was verified by injecting low-level drug components (limit of detection study). The combination of [redacted] different HPLC methods was deemed to be suitable for this investigation to separate and detect the [redacted] drug components at low levels, up to [redacted] ppm ([redacted] (Attachment 7). The specificity of the methods in [redacted] different conditions was already established during the June 19th, 2008 investigation with a [redacted] ppm standard injection. (b)(4)

The cross contamination investigation was expanded to [redacted] suspected batches (including the [redacted] known contaminated lots) of [redacted] different types of products utilizing [redacted] different methods (please refer to pages 1 and 2 of Attachment 6). At the end of the completed study, only the two products were found to be cross contaminated; which were Metoprolol Tartrate lot # [redacted] (LI[redacted] Metformin as contaminant in Metoprolol tablets) and Tramadol HCl lot # [redacted] (LIP[redacted] Metoprolol contaminant in Tramadol tablets), while all other lots tested did not show any cross (b)(4)

contamination peaks. Also, no extraneous HPLC peaks were detected during QC release testing, which includes Assay and Related Substances, performed using the validated test procedures of the other lots that were dispensed /manufactured between 01-25-08 to 01-29-08. This demonstrates the integrity and quality of the products manufactured/dispensed during the investigated time period were not compromised.

Investigation was extended to other products to evaluate the possibility of any cross contamination that may have occurred due to any reason. Chromatographic conditions were selected which detect the compound of interest and sensitivity and selectivity were established. In case a criteria was not suitable for this condition then an alternate method was used that met the requirement for selectivity and sensitivity. Analysis was performed using the above approach and a total of ten experiments were run to select a proper method as per above criteria and to detect contamination of API dispensed during the suspected period. The result of the analysis with these methods was reviewed and no cross contamination was observed.

We have also expanded the scope of our investigation to analyze retained samples manufactured one month prior to and one month after the incident. There were no extraneous peak detected, Attachment 8 Experiment #2).
In addition to the testing, Caraco's Quality Control Department has already reviewed the assay chromatography and the impurity chromatograms for all lots dispensed three months prior to and three months following the cross contamination incidents in January, 2008. This review was to verify that none of the lots had out-of-trend impurity values or additional unknown peaks. . No extraneous peaks or out-of-trend impurity values were found Attachment 8 Experiment #1.

The response also states in part "[redacted] The scope of the products potentially impacted did not become known until approximately [redacted] months after the incident began and three months after confirming the OOS results. Failure to conduct investigations in a timely manner and to extend the investigations to other drug products that may have been impacted by the same failures while investigations of confirmed cross-contamination (without a probable root cause identified) were ongoing demonstrate the failure of your QCU to provide adequate oversight and ensure procedures are followed. Please note that as significant time elapses, investigations become more challenging. We note that your firm documented such a concern in another incident report: "[redacted]

(b)(4)

(b)(4)

CARACO RESPONSE D

We agree that the timeliness of investigations required improvement and we have taken specific action to invest in human and system resources to prevent reoccurrences. We want to emphasize that we realize that it is not in our organization's or the consumer's best interest to delay timely completion of these incidents. Over the past several years, Caraco has made many process improvements to the incident process in order to improve our quality system compliance.

Currently our Quality Engineering Unit is tracking all incidents and an electronic message is sent to the Quality Unit team for any incidents that are approaching the [redacted] day window as per our current SOP. The CEO and Regulatory Compliance also receive a copy of the message. (b)(4)

Following a Caraco Quality Review Board meeting in April 2008, Senior Management decided to make several changes to the organization of the Manufacturing and Quality Departments. Effective May 1, 2008 (the first day of the FDA inspection), the Technical Services Department, responsible for incident investigations at the time, moved from Manufacturing to the Quality Department, becoming the Quality Engineering Department.

As stated in the June 19, 2008 letter to the FDA and the July 10, 2008 response to the FDA-483, the number of personnel within this department increased from [redacted] including a new Quality Engineering Manager. This department is now fully staffed with [redacted] new senior level investigators (b)(4) (i.e. Sr. Quality Engineers), adding needed experience to the investigative group. The Quality Engineering Department is providing ownership of the incident process, relative to timeliness and follow-up on all outstanding investigations. In addition, the Quality Engineers are able to address incidents as they occur, ensuring consistent direction is provided for the subsequent investigation. Ownership and accountability with authority to perform this function is duly accorded to this department. The company will take disciplinary action up to and including termination for any non-compliance.

If an investigation exceeds [redacted] days, a justifiable reason will be documented in the extension (b)(4) request form and an interim impact report will be generated. The approval or denial by the Quality Engineering Manager will be based on the validity of the reason provided.

We have also observed improvement in the quality of the incident investigations based on the training that was provided internally, by the [redacted] and through external seminars. (b)(4) Although we are still in the early stages of implementing the changes, the number of incidents generated (i.e. incident rate has decreased based on the corrective actions to date and analysis of the trends that developed out of the day to day operation) have decreased significantly.

We are confident that we have created a process and organizational structure that will ensure that this quality system is expected to result in eliminating the discrepancies identified in previous FDA inspections.

) **Rather than following SOP [redacted], which requires the approval of any incident report (IR) before the batch can be released, your QCU:** (b)(4)

i. **released [redacted] bottles of Methimazole Tablets, USP, 10 mg, lot [redacted], which at the time had an open investigation for equipment failure, and**

ii. **released two products, Tramadol HCl tablets (lots [redacted] and [redacted]) and Tramadol/Acetaminophen tablets (lot [redacted]), which at the time had an open investigation for a shortage of [redacted] of Tramadol drug substance (the raw material reconciliation limit is [redacted].** (b)(4)

Your July 10, 2008 response regarding the lack of adequate investigation into instances of raw material reconciliation is inadequate and inconsistent. You state the intent of the investigation was "[redacted]" You also state that "[redacted]." Your firm did not follow your written procedure to grant an extension to the investigation. While the procedure states that the investigation will be forwarded to your QCU within [redacted] days unless an extension is granted, your incident report is dated April 1, 2008 and the extension you refer to occurred on July 9, 2008. Your firm does not provide adequate rationale to justify the decision of your QCU to disregard these procedures to ensure discrepancies are thoroughly investigated and investigations are completed before product release. (b)(4)

CARACO RESPONSE E

(b)(4) These [redacted] incidents, noted above by the FDA investigators, were isolated. One was the result of a human error (Methimazole) and the other was based on a review of the analytical results and manufacturing records of the Tramadol lots.

Some of the Methimazole product had inadvertently been missed when the product was being placed on hold. The lots of Methimazole were placed on hold as required by the QA Supervisor. We have reviewed the Supervisors file and found no such incidents relating to this type of omission. Caraco has revised SOP [redacted] (Attachment 9), to include the requirement that any QA Hold issued to a lot that had been previously released to the market, must include the *Lot wise Item Trace Report* for each lot placed on QA Hold. We will also confirm the number of units released to assure that the entire packed products are accounted for. The QA Supervisor will confirm the lots placed on hold, sign the report and attach it to the QA Hold Tracking Sheet. (b)(4)

This change will provide a secondary verification that does not currently exist for this specific and rare situation where commercially released lots are placed back into a QA Hold status. A copy of this signed Lot wise Item Trace Report will be sent to both the Distribution Department and the Sales Department as an additional control.

For Tramadol we determined that there was a shortage in inventory after the Tramadol lots were already released. These lots were already released with no incidents open at the time of release. We reconfirmed that the assay results were normal for these lots. The assay for lot number [redacted] (b)(4)

Caraco has a procedure, SOP [redacted] (Attachement 2) [redacted], which has been revised to include a checklist of requirements which must be signed prior to batch release. These requirements include the satisfactory closing of any open incidents.

In addition to the checklist verification, which requires that all documents necessary to release a batch including a copy of closed out incidents/investigations are verified, an electronic system will be functional by the end of March 2009. Presently Caraco is in the process of developing and implementing automated quality systems (Quality Management System- (QMS) within Caraco's

[redacted] system) to further ensure that outstanding incidents are addressed in a timely manner and that a product is not released with an open investigation or any other issues. This program will include core quality systems, such as incidents, corrective actions ([redacted], market complaints, change control, and QA Hold (integrated with our [redacted] system). Furthermore, the QMS will tie into the QA release function, thus ensuring more thorough oversight of critical quality aspects at the time of lot release. As discussed above, Caraco has taken several steps to prevent the reoccurrence of this type of incident.

b)(4)

We realize that it appears that we did not follow our SOP on release on Tramadol with Acetaminophen. The shortage on Tramadol was discovered during our quarterly inventory reconciliation process on April 1, 2008. Tramadol with acetaminophen was awaiting final release. The release decision for this product was based on the fact that the assay for this product would be increased by approximately [redacted] if the [redacted] had been added to the product, and it was determined that the lot was not affected by our discovery of the API shortage.

b)(4)

The risk assessment which included a review of our controls at various process steps in manufacturing and the testing of the product conveyed there was no impact to the quality of the product. The incident was related to the inventory of the API and was not an impact on the product that was already released or the Tramadol with Acetaminophen.

Also we have gone through a rigorous GMP training since this incident. During the training it was emphasized to the Quality Control Unit personnel that failing to follow the procedure is not acceptable (Attachment 10).

c) **Your QCU failed to fully investigate and close incident reports from March 2007, concerning content uniformity failures for Metoprolol Tartrate tablets (lots [redacted] and [redacted] listed as rejected), and from August 2007, concerning dissolution failures for Carbamazepine tablets USP (lots [redacted], and [redacted]). As of May 2008, the reports were incomplete with no information for the manufacturing investigations.**

b)(4)

CARACO RESPONSE F

We acknowledge the lack of timeliness in our investigations of these issues. Please refer to Caraco Response D for our actions in preventing these types of human errors in the future

The dispositions of the lots mentioned in the observation were rejected and awaiting destruction (Attachment 11).

d) **Your QCU failed to fully investigate IR [redacted] (dated September 12, 2007) concerning a shortage of [redacted] of Citalopram HBr raw material, lot [redacted] thus failing to meet the raw material reconciliation limit ([redacted]). Your investigation did not expand to other products dispensed on the same day, speculated without justification that "[redacted]" and concluded that there was no impact on product quality.**

b)(4)

CARACO RESPONSE G

In review of this particular incident file, we concur that the depth of analysis of this incident did not meet our current investigative standards. The investigator who had drawn this conclusion is no longer with the company. To assure a complete investigation as per our SOP, Caraco initiated an additional incident (reference [redacted] (Attachment 12) to repeat the investigation in a manner consistent with current methodologies, including the proper assessment of potentially impacted lots.

(b)(4)

The updated investigation concluded that three possible probable causes exist. The quantity of the missing Citalopram raw material is within the range [redacted]) of the container tare weight values seen for this material. The revised root cause analysis thus indicates that it is possible that the dispensing operator tared the material container twice during the dispensing operation, which caused an additional amount of Citalopram to be added to the lot. The quantity of Citalopram in the lot was [redacted] so the additional amount (equivalent to approximately [redacted]) would represent approximately [redacted] more active in this lot which would be in the acceptable range for the specification.

(b)(4)

The second probable cause was the inadvertent use of a different receiving number of the same material when dispensed into a batch. This would provide a similar scenario resulting in a unaccountable shortage.

The third probable cause was lack of weight verification when material was received from the vendor. The quantity ordered from the vendor and stated on the packaging list is what was entered into the [redacted] inventory as received. There might have been a difference on what was received versus the quantity entered into the inventory system.

(b)(4)

Corrective actions as stated in the attached IR – [redacted] have been implemented for all the three probable scenarios.

In order to rule out contamination of other lots with Citalopram, a systematic review of the chromatograms for the lots that were dispensed on the two days when this lot of Citalopram was dispensed (i.e. [redacted] products, [redacted] product lots) was performed which demonstrated no extraneous peaks for any of the lots. Using the current analytical methods for the four products, the laboratory spiked the samples in each system to determine the [redacted] of Citalopram. This laboratory verification confirmed that Citalopram contamination would have been definitely identified in the chromatography for each lot.

(b)(4)

We agree that investigation was not extended to the lots dispensed during that period. Please note that retraining of concerned personnel and implementation of new incident investigation procedure will assure proper assessment and compliance. As mentioned previously, [redacted] software for adjustment of a lot will be implemented to assure that flags are raised immediately when the inventory limit is exceeded. Inventory adjustments by QA will not be performed until a closed investigation by the Quality Engineering Department have been completed. This process will cause to hold any batches that are potentially involved until the investigation is completed.

(b)(4)

In order to eliminate any possible error on incoming material weights we have initiated new procedures. Receipt of material SOP [redacted] (Attachment 13) has been revised to include weighing for gross weight checking of incoming active material. In case of any discrepancies, QA will be notified and appropriate action will be taken. Lot will not be sampled until discrepancies are resolved.
Vendor gross weight verification is on ongoing and become permanent receiving process for all incoming API.

(b)(4)

e) Your QCU failed to fully investigate metal scrapings and foreign matter in compressed Metformin HCl tablets, 1000 mg [redacted] (dated February 27, 2008). As of June 11, 2008, there had been no written investigation.

(b)(4)

Your July 10, 2008 response regarding the metal contamination in Metformin HCl tablets, states in part "[redacted] Your investigation was not adequate since the scope of the investigation did not evaluate whether the operator was involved in similar occurrences.

(b)(4)

This is a repeat violation of the 2005, 2006, and March 2008 inspections.

CARACO RESPONSE H

This batch of product was not released.

We concur that the investigation should have specifically noted the employee history relative to the event that caused this incident. Regarding the scope of the investigation, we have since reviewed our investigation records for the past two years 2007 and 2008 to ascertain if the operator involved in this incident has been involved with similar situation in the past. The record indicated that he has not. We have added this requirement as part of parameters to be verified in any of our investigations.

In addition, Caraco's Compression department has instituted a [redacted] to provide guidance to the Set-Up Operators and verification of proper set-up by the Compression Supervisor. Form [redacted] (Attachment 14), as part of SOP [redacted] (Attachment 15). The SOP was made effective on November 17, 2008. We will monitor and check for effectiveness of our actions based on reduction of these types of incidents through our regulatory compliance group

(b)(4)

The repeat violation of machine set up has been resolved. We have arranged with all compression machine manufacturers to conduct [redacted] training. We have also established a group of super users for ongoing training internally previously all training was done internally. [redacted] the machine manufacturer for the manual compression machines previously did not have US support to train in the US on a routine basis. We have been transitioning to more automated machines by [redacted] the training has been set up with that firm as we transitioned. We had determined outside training was required on a routine basis to continuously improve the skill of our operators.

(b)(4)

Caraco has implemented a process improvement project relative to the formal set-up process for compression machines. Critical set-up parameters, which are deemed product-specific, will be added to the [redacted]. Examples of such parameters include [redacted] settings. The change control has been created for this change and the [redacted] revisions are on-going and expected to be completed by the end of first quarter 2009.

(b)(4)

The Change Request and [redacted]29) associated with this improvement are attached to this response as Attachments 16 and 17 respectively. An example [redacted] that has this change incorporated into the compression machine set-up section (Page 5 of 39) is included in this response as Attachment 18.

(b)(4)

This specific product has been moved from the [redacted] to the [redacted] tablet press. The [redacted] press has automated systems in place to alarm and shut down when a tool touches the feed frame during operation.

(b)(4)

WARNING LETTER ITEM 2

Failure of the QCU to follow written procedures [21 CFR § 211.22(d)].

a) **Your QCU did not follow SOP [redacted] as drug product subject to an open investigation was released (e.g. Methimazole tablets, lot [redacted] Tramadol HCl tablets, lots [redacted] and [redacted]).**

(b)(4)

CARACO RESPONSE A

These two incidents, noted above by the FDA investigators, were isolated as a result of a human error for Methimazole and a risk assessment of the Tramadol lots.

This Warning Letter Item refers to the same incident detailed in Warning Letter Item 1. Please refer to Caraco Response E for a detailed response.

b) **Your QCU did not follow SOP [redacted] Rev. 04. Rather than placing a QA Hold on several Methimazole lots (e.g. [redacted]) because of an equipment failure (i.e., air handling unit associated with the [redacted] failed its HEPA recertification), your QCU released the lots without the required QA Hold which is intended to quarantine material from further processing or from being released.**

(b)(4)

CARACO RESPONSE B

As provided in the revised SOP [redacted] (Attachment 8), the material which is placed on QA hold will be verified by two personnel. The individual who places the lot/product on QA hold and verified by the QA Supervisor signature on the [redacted] notification list. At the time of the incident (May 16, 2008), these lots and several additional lots potentially impacted (a total of 13

(b)(4)

lots of Methimazole Tablets), had previously been released much earlier than the time of the initiation of the incident.

When the incident was initiated on May 16, 2008, Caraco Quality Assurance personnel were supposed to place all remaining inventory on QA Hold. As explained in the response above product from lot [redacted] was inadvertently not placed on QA Hold by the QA Supervisor due to his own oversight.

(b)(4)

As in Caraco Response E in Item 1, we have revised our investigation and [redacted] SOPs to prevent the reoccurrence of this type of incident

(b)(4)

We also Revised our SOP [redacted] (Attachment 19) for Work order procedure to assure pertinent personnel are aware through work order form when a breakdown or calibration failure has occurred on HEPA filters.

(b)(4)

In addition Quality Management System software will be in place by December for testing purposes and implemented within [redacted] months of testing after validation which includes breakdown maintenance handling and reporting. This system will run parallel to our current automated system.

(b)(4)

This system will enhance our compliance by providing the following process flow:

[redacted]

(b)(4)

c) Your QCU did not follow SOP [redacted] " by failing to track incident reports to ensure that required actions are completed and implemented as per internal procedures and to grant extensions when investigations cannot be completed within [redacted] calendar days.

(b)(4)

This is a repeat violation of the 2006 and March 2008 inspections.

CARACO RESPONSE C

Caraco has made organizational changes, improved systems and added the appropriate resources to the Quality Engineering Department to ensure that incidents are completed as per our SOP [redacted] (Appendix 1) and also those corrective actions are implemented as per the investigation commitment. The investigative team of Quality Engineers, appropriately staffed has the authority and accountability to follow the procedure as written.

(b)(4)

Please refer to Caraco A Response in Item 1 for further details.

As stated earlier in this response, we are confident that with our improved systems used currently and the systems being added, Caraco Quality Unit and its Quality Engineering Department will be able to maintain compliance through the ownership of the incident and CAPA processes. The continued addition of process automation will further enhance the ability to ensure acceptable compliance.

WARNING LETTER ITEM 3

Failure of the QCU to approve or reject all procedures or specifications impacting the safety, identity, strength, quality, and purity of the drug product [21 CFR § 211.22(c)].

a) Your QCU has not established procedures to evaluate changes which may impact the validation status of your manufacturing processes and parameters (e.g. Tramadol granulation, Tramadol/Acetaminophen tablets).

CARACO RESPONSE

Caraco SOP [redacted] and the associated Change Control Form, (CCF), Form [redacted] provide a process of prospectively assessing changes [to many types of documents], including Batch Manufacturing Records (BMRs). (b)(4)

For every change made to the Tramadol granulation or Tramadol/Acetaminophen tablets, a Change Control Form was submitted and prospectively approved prior to implementation. To improve upon this current process we have established a December 15 time line to implement a Master Validation Plan, wherein criteria for validation and revalidation will be defined.

Prior to the initiation of any BMR change, CCF [redacted] is circulated by the person responsible for BMR changes. All the requirements specified in the change control form are reviewed and approved prior to implementation. (b)(4)

This is further defined in our validation master plan. The proposed change is described in the document (or a more detailed description is attached). Approvers of the change, which includes Technical Services, Manufacturing, Regulatory Affairs and Quality Assurance (at a minimum), complete the Approval Analysis portion of the Change Control Form. This section addresses the risk/impact pertaining to training, stability, validation and regulatory compliance of each change presented.

The referenced Quality Management System (QMS) provides for the complete, prospective evaluation of change requests through out the manufacturing process. The QMS will provide for the initiation of the request by the user department; the requirements evaluation from the reviewing personnel; their recommendations based upon the prospective impact assessment within the change control form; the review and approval by the user department head for the execution; the verification and review of recommendations by QA; the issuance of a [redacted]. The

(b)(4)

entire system is able to be monitored throughout the process until the change is implemented and the change request is closed. As stated earlier in this response, this system will be implemented and validated at Caraco by the end of February 2009.

b) Your QCU has not established procedures to assure that components are not contaminated during the dispensing procedure. For example, SOP [redacted] does not include provisions to prevent contamination from opened component containers.

(b)(4)

Your July 10, 2008 response to the failure of the QCU to follow procedures on preventing cross-contamination when multiple materials are in the same room is inadequate. The associated SOP [redacted] lacks adequate controls to prevent cross-contamination of materials during the dispensing procedure.

(b)(4)

CARACO RESPONSE

In addition to the revision to Caraco SOP [redacted]s," which clarified the situations when a Type 2 cleaning was required, Caraco also made a revision to SOP [redacted] (see Attachment 20). This revision, which was effective on June 10, 2008, states in section [redacted] that the "[redacted]" In our view this process eliminates of any chance of cross contamination from material being dispensed in the dispensing rooms. We agree that the response to observation 5d of the July 10, 2008 FDA-483 did not completely address the observation and convey all of the improvements to the dispensing process that were made or were in process.

(b)(4)

The following immediate actions have been taken to further avoid cross contamination and operator error in the dispensing department. The bar code identification number has been added to our quarantine label which is scanned one product at a time in our dispensing department. Bar code readers have been put in place to confirm that we are using the correct material. Only one product at a time is allowed in the dispensing room. Process flow in dispensing areas has been redefined to have rooms dedicated for excipients and active material dispensing.

The Dispensing SOP defines the sequence of dispensing (most lightweight material is dispensed last). After completion of dispensing of excipients a dry cleaning is performed and after active material dispensing wet cleaning and sanitation is done. Active material is dispensed in active material dispensing areas one material at a time for multiple batches followed by complete wet clean up and line clearance prior to dispensing other active materials. All above initiatives will help in preventing cross contamination

As described in the [redacted] letters to the FDA submitted on August 8, August 22 and September 19, 2008, Caraco has implemented a bar code scanning verification system in the Dispensing Department. This system requires the bar code scanning of each raw material container prior to the dispensing process in order to verify that the correct material is being brought into the dispensing suite. The scanned material labels are compared to the bill of material requirements for a specific lot being dispensed. Pertinent personnel have been trained on the system and it has

(b)(4)

been used in practice since September 22, 2008. The attached SOP [redacted] also includes the operating procedure for the bar code verification process. Additionally we are integrating the weighing scales into our [redacted] whereas the system will stop the dispensing process if the weight for the particular product is not correct

(b)(4)

As a holistic approach we are expanding the use of bar code readers through out the organization. Caraco plans to expand the use of the bar code scanning technology for confirmation of materials throughout the manufacturing process as an additional improvement. At each stage of the manufacturing process, labels for intermediate containers are printed from Caraco's ERP program with bar codes on them. The labels can be scanned and verified at the beginning of each subsequent operation to confirm that the correct material is present. This system is currently completing the design, development and evaluation phase this quarter and will be implemented and validated by the end of March 2009.

Finally, Caraco is developing RFID capabilities to be used in the overall operation. We are currently involved in mapping out where the RFID technology is most applicable within our internal supply chain. This is a natural progression that the industry is working towards as part of product pedigree traceability in the distribution supply chain. We believe that it will offer a myriad of solutions within our overall operation. A project timeline will be developed once this initial evaluation is complete this quarter.

WARNING LETTER ITEM 4

Failure to maintain component records that include reconciliation of the use of each component with sufficient information to allow determination of any batch or lot of drug product associated with the use of each component [21 CFR § 211.184(c)]. For example,

a) **Material inventories are adjusted to achieve a zero balance without determining the source or final disposition of the extra material (e.g. Metformin HCl, lot [redacted] Tramadol HCl, lot [redacted]**

(b)(4)

b) **Upon receipt from your component suppliers, starting quantities of raw materials are not verified, resulting in unreliable and inaccurate inventory controls.**

CARACO RESPONSE

Response number 6A in the July 10, 2008 FDA-483 response letter indicates that Caraco has made several changes to the processes associated with the ordering, receipt, issuance and ERP adjustment of raw materials; as well as to the manner that material discrepancies are addressed.

For ease of review we have attached version [redacted] (Attachment 21)
Additional improvements to the process have been made in the subsequent weeks following the response. In summary, the changes are as follows:

(b)(4)

We have subsequently updated SOP [redacted] originally sent to you on June 10, 2008 "[redacted]" to include the following changes pertinent to this subject:

a. The gross weight of incoming API's is now verified upon receipt of the material into the facility and prior to being received into Caraco's [redacted] system.

(b)(4) b. Following the dispensing process, the materials are reconciled and deducted from [redacted] inventory prior to issuing the dispensed material to manufacturing. Thus, discrepancies are identified before the material leaves the area.

c. The acceptable variance specifications for API's and excipients were tightened to ensure that proper investigations are initiated in situations where inventory reconciliation limits are exceeded.

(b)(4) d. Any adjustments that are required to inventory levels of raw materials must be supported by a copy of the approved investigation by Quality Assurance (QCU). In Caraco's [redacted] system, only the QCU has the ability to approve these adjustments. This final verification will ensure that incidents are generated for all variances that exceed the specifications within the SOP.

We had started weighing all active materials on April 7, 2008 as part of our investigation of cross-contamination. We have updated our SOP [redacted] that any variance outside of our specifications would be confirmed by Quality Assurance and incident created by Quality Engineering and an investigation would be completed to determine source or final disposition of any variance before the dispensing process can proceed. (b)(4)

Our inventory control system is being implemented through the use of Caraco's [redacted] system to automatically compare material variances to our internal variance specifications. If the specification is breached, then the [redacted] system will provide a notification and will not permit any adjustment within the system without QA approval. Furthermore, this process will be tied to Caraco's Quality Management System (QMS), and an incident will be automatically generated for this event. This process is currently under evaluation and will be implemented by end of February 2009. (b)(4)

Based on the corrective actions implemented so far and other that are being implemented will provide Caraco us the quality system and procedures that will prevent the reoccurrence of incomplete investigations when reconciliation limits are exceeded

WARNING LETTER ITEM 5

Failure of the appropriate organizational unit and the QCU to review and approve any changes to established written procedures [21 CFR § 211.100(a)].

a) Your manufacturing process has not been validated for repeated changes to the drying time parameter of the oven dryers in the Tramadol granulation. The changes were implemented in an attempt to ensure granulation is not too dry without establishing a minimum specification and without an assessment on product quality.

Your July 10, 2008 response regarding the failure to establish acceptable range for the LOD (loss on drying) states in part that "[redacted]. However, your response does not address statements made by the Vice President of Manufacturing and the Director of Quality regarding concerns of granulation becoming too dry which prompted the change in drying times to obtain acceptable product. Please clarify the conditions and specifications which may produce a granulation too dry for compression with supporting documentation and your firm's plan to prevent this from recurring.

(b)(4)

CARACO RESPONSE

Caraco's Change control system is described in our response to Item 3.

Acceptable tablets have been manufactured at the lower moisture levels; however, undue stress was placed on the compression machines to achieve target hardness values when lots below [redacted] were compressed (b)(4)

Caraco's R&D and Manufacturing Departments reviewed historical production data relative to the moisture content of the granulation, and compared it to the finished batch testing data. In all cases, the lots met the QC release specifications.

This review supports the LOD specification of NMT [redacted] since the range of moisture content among the lots reviewed was [redacted] LOD. When comparing this same data to incident trends for this product, it becomes evident that processing issues arise for lots dried to a moisture level below [redacted] LOD. For these lots, incidents were generated due to breakage of a punch tip during the compression process. (b)(4)

Supported by the result of this analysis Caraco has recently updated the Batch Manufacturing Record (BMR) to tighten the LOD specification from NMT [redacted] LOD ([redacted]) to reduce stress on the punches. As a part of our validation master plan, we will perform process validation of the product to reconfirm the range. (b)(4)

The Tramadol ANDA was filed and approved with the LOD limit of NMT [redacted]. We have been able to manufacture product meeting the approved quality specification. Caraco has manufactured [redacted] batches within last [redacted] without any significant quality issue. (b)(4)

The changes what we have made are all within the filed specification of LOD in the ANDA.

As a proactive approach Caraco R&D will perform an assessment of all commercial products where the LOD specification indicates a "[redacted] value. For these products and strengths, R&D will evaluate at least [redacted] lots to determine a minimum moisture value. The BMR's for these products are being updated with revised LOD specifications and targets. The BMR changes will be completed by January 1, 2009. We will perform process validation, where required. (b)(4)

The changes will not be implemented until a change control has been approved by the Validation Advisory Board who is also tasked with reviewing the data in support of the change, as defined in our validation master plan.

In reference to the comment made paragraph 3 of Warning Letter Item 5 regarding granulation becoming too dry, the Vice President of Manufacturing acknowledged making this comment. However there might have been some misunderstanding, his comment is in relation to the loss of efficiency due to the stress the very dry granulation asserts on the compression punches and not on product quality.

(b)(4)

b) For Tramadol/Acetaminophen tablets, lot [redacted], nine process change requests were implemented without evaluating the impact of the changes to product quality.

CARACO RESPONSE

For the subject lot, upon the review of the executed Batch Manufacturing Record (BMR) for Tramadol HCl Tablets, 50mg, lot [redacted] there were only two change requests that were issued to this specific batch. (b)(4)

The first change request, request CR [redacted], issued on December 5, 2006 to all product BMRs, includes a statement indicating that all granulation solutions must be used within [redacted] hours and all coating suspensions must be used within [redacted] hours based upon the validation results for these components. This change has since been made to the Master BMR for this product. (b)(4)

The second change request for this lot, and [redacted] additional lots manufactured sequentially during this timeframe (lots [redacted] through [redacted], was a temporary change (approved on February 20, 2008) adjusting the initial drying time from [redacted] hours to [redacted] hours, with subsequent [redacted] hour drying intervals until the required LOD results are obtained. (b)(4)

This change request was reviewed by two Manufacturing Managers, the Manager of Technical Services, the Associate Director of Regulatory Affairs and the Quality Director prior to initiating the change. This temporary change was deemed to have no impact on Quality since it entailed the testing of the granulation moisture at earlier intervals, thus avoiding additional drying time if the LOD endpoint is already reached. The results of this change indicated that the product achieved optimum compression results; therefore the BMR was changed permanently to include this process instruction change via Change Request CR [redacted], issued on May 1 and closed on May 19, 2008. (b)(4)

There were no other changes made to the Batch Manufacturing Record for Tramadol/Acetaminophen Tablets, lot [redacted] (b)(4)

To further enhance our Change Control System, a Validation Advisory Board has been established. Starting immediately changes will not be implemented until a change control has been approved by Validation Advisory Board who are also tasked with reviewing the data in support of the change. To improve upon this current process we have initiated a Validation Master

Plan (Attachment 22) wherein it defines the criteria for validation and revalidation following changes. This plan will be implemented by December 15, 2008

WARNING LETTER ITEM 6

Failure to establish valid in-process specifications derived from previous acceptable process average and process variability estimates where possible [21 CFR § 211.110(b)]. Your firm does not have information to support in-process hardness specifications for Mirtazapine tablets, USP, 15mg.

CARACO RESPONSE

Since 2006, Caraco Research & Development has implemented more strict evaluation methodologies for physical specifications such as tablet hardness. These studies include evaluations of extreme hardness ranges and their effect on tablet friability and dissolution values early in the product development process prior to production of the exhibit lot. As an additional verification, R & D, Manufacturing and Quality reviewed the process validation reports for all Caraco products that were validated prior to 2006 to ensure that a similar situation as this has not occurred for any other product. Revisions were made to all impacted product BMRs.

As a comprehensive approach we are extending our review to all other critical in-process data (b)(4) [redacted] for each Caraco product to assure that these specification limits have development or validation data that supports the specification limits. Anomalies, if any, will be addressed as a result. This evaluation will be completed by the end of November 2008. All recommended changes to specification values completed within the Batch Manufacturing Records for the affected products by the end of December 2008. All changes will go through the change control process and submitted to the Validation Advisory Board for review and approval prior to implementation.

WARNING LETTER ITEM 7

Failure to maintain equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality and purity of the drug product beyond the official or other established requirements [21 CFR § 211.67(a)]. Your firm did not perform any maintenance on the air supply unit (including the HEPA filter) associated with the FBD equipment ([redacted]), prior to its use n manufacturing operations. After use in production, the HEPA filter housed inside the unit failed the maintenance recertification. (b)(4)

This is a repeat observation to the 2005 inspection.

CARACO RESPONSE

As stated in the response to observation 8A in the July 10, 2008 response letter to the FDA-483, the certification of the HEPA filter on the fluid bed dryer was not put into Caraco's

calibration/certification program at the time that the equipment qualification was completed in April 26, 2005 due to an oversight by the Engineer who initially qualified the equipment.

The equipment qualification process SOP was revised at the time of the observation to include the secondary verification of calibrated and certified instruments and components prior to completion and approval of the qualification report. Caraco SOP [redacted] was updated to include this verification requirement (Attachment 23).

(b)(4)

Caraco performed an audit of every piece of cGMP equipment within the facility, including manufacturing and laboratory equipment, and ensured that each item has been placed in Caraco's calibration/certification program. In addition we have incorporated all calibration schedule into our current automated preventative maintenance system to enhance compliance.

Further action is being taken to enhance compliance of our internal procedure and as a corrective action; Caraco plans to integrate the calibration and preventative maintenance systems (i.e. Maintenance Module) into our current [redacted] program, thus automating the calibration initiation process and the notification process for calibrations, re-certifications, and preventative maintenance activities.

(b)(4)

An incident ([redacted]) was generated at the time of the FDA observation on May 16, 2008. Discussion of this incident in the sections above indicated that the investigation concluded that there was no impact on product quality for this marginal HEPA filter failure (i.e. [redacted] efficiency rating).

(b)(4)

Recently, the Technical Manager, who is responsible for maintaining Caraco's calibration/certification program, has moved from the Quality Department into the Facilities Department. This change properly aligns the calibration program to the preventative maintenance program within the company. Attachment 24

Warning Letter Comments

Your July 10, 2008 response to observation 7 of the FDA-483, regarding the failure to maintain complete batch records by excluding product discrepancies found during the inspection, is inadequate. Rather than allowing your operators to continue the in-process inspections of tablets (which appeared to be effectively detecting product defects), your response indicates that QCU will no longer allow the operators to perform these inspections in an effort to eliminate redundancies (inspections are performed by the QCU) and inspection discrepancies concerning the inadequate documentation of batch records. Please provide information to demonstrate that the inspection performed by your QCU are producing the same or better results than the ones performed by the manufacturing operators. You should not eliminate a process that improves quality of your products without sound justification.

CARACO RESPONSE

We agree that no inspections should be arbitrarily eliminated. No changes will be made unless there is complete documentation to support any change. Historical data will be reviewed prior to any change request is granted.

The inspections referenced in Observation 7 of the July 10, 2008 response letter to the FDA-483 were implemented in March 2008 following the initiation of the Metformin HCl Tablets, 1000mg product recall for thin tablets. This short-term corrective action was implemented specifically for this product as a measure to ensure that the corrective actions made in the compression process were effective at eliminating the possibility of thin or thick tablets. We have not discouraged the operators from reporting any defects that are noted. All observations will continue to be reported and classified.

The compressions operators have always and currently perform an in process check every thirty minutes.

There is always a visual check performed by the coating and compression operators.

The in process check was changed specifically for Metformin. The failure or any observations are recorded in the batch record only identify if there is an observation or failure.

Our revised SOP provides that regardless of whether there is an observation or not, that it will be noted in the BMR as a pass or fail and if fail it will be noted what type of observation or defect was noted Attachment 25).

You state in your July 10, 2008 response that your firm continues to undergo annual external audits with the most recent audit conducted August 2007. Our last inspection conducted in June 2008 and your firm's compliance history raise concerns about the effectiveness of the audits. Most of the corrections to the inspectional observations were initiated after the FDA investigators discovered the failures in your CGMP systems. Please comment on how future audits will ensure that the Quality Management System will identify and correct deficiencies and prevent recurrences.

CARACO RESPONSE

We are in the process of further expanding the scope of our in house quality regulatory compliance group that will oversee the quality system and audit all quality systems.

This regulatory compliance group will manage and review all corrective actions that are in place based on previous inspections and audits. In addition, this group will be conducting periodic GMP audits and allows us to monitor our own quality system for cGMP compliance.

Relative to external audits of Caraco's quality systems conducted by outside consulting firms, for the near term Caraco will continue such audits on a routine basis; with a general GMP (i.e. quality system) audit, a laboratory audit, and a facility/process audit performed at least once each year. It is also our strategy to change the auditor and/or the consulting company used in order to avoid complacency and familiarity to the processes being audited.

In conclusion Caraco is properly staffed with people that have the appropriate level of training and skills to address compliance improvements identified through internal/external audits, incident trends, product complaint trends, corrective and preventative actions, historic FDA observations among. We have taken a holistic view in our corrective actions and have not limited our improvements to those noted by FDA.

Quality Review Board meetings held [redacted] that includes executive management will track the effectiveness of our Quality units performance by reviewing a culmination of audits performed in the last [redacted] weeks by the quality assurance auditors and will review Regulatory compliance reporting that manages the effectiveness of our audits of the quality system. We will continue to improve upon the culture of compliance by having additional training that supports our efforts along these lines. (b)(4)