



**CARACO**  
PHARMACEUTICAL LABORATORIES, LTD

June 19, 2009

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

Dear Judith:

Caraco Pharmaceutical Laboratories, Ltd. (Caraco) has carefully reviewed the FDA Form 483 issued on May 12, 2009. We appreciate the opportunity to respond to the concerns relating to our inspection that was initiated on March 11, 2009. We believe that we have taken the appropriate steps in our effort of continual improvement for the betterment of compliance. In the following response we have shared what has already been corrected prior to the inspection, what we have corrected during the inspection and we have provided the target completion date of any remaining remedial actions.

We realize that our systems continually need to be supplemented and revised to improve how we monitor and control the quality system that they must be scalable for the future. In the pages that follow, you will find detailed explanations and corrective actions to support both past and current compliance efforts.

We completely understand the serious nature of the observations. Since our inspection in May, 2008 we have taken the corrective actions necessary to gain further compliance. Most importantly:

- We have changed leadership in various critical areas of the company.
- As you have come to know, we have replaced the Vice President of Manufacturing
- We have changed the Director of Quality in January 2009.
- We have also released the Senior Manager of Manufacturing who was responsible for our pharmacy dispensing operation

Management felt it necessary to make this change to better align the direction of these areas to be consistent with the goals and objectives of the corporate management.. We were compelled to make these changes as expeditiously as possible yet these positions required the right "hands on" management to make an immediate impact on our progress. We believe that we have the right talent at those positions today. These managers have great pharmaceutical industry background and come fueled with best practices that will augment and improve our performance. Subsequently due to their own network and work ethic they have attracted other personnel to fortify our team. I am hopeful that the interaction with the agency to date has been accommodating and expeditious

For our product variability concerns which resulted in past recalls and product complaints of certain products, we have taken a (b) (4) approach of matching up (b) (4) (b) (4) We have tightened our operational ranges by reviewing our historical critical product parameters in order to optimize our performance for a quality output within the regulatory guidelines. Certain product like:

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- Metoprolol which was representative of approximately (b) (4) of our variability issue has been validated on a new (b)(4) tableting machine prior to January and since then we have not had any issue or concerns with this product. In essence the product is married to the right machine. No changes were required based upon our original filing.
- Clonazepam which was approximately (b) (4) of variability concern has been produced with a tightened operational range and consistent particle size through consistent (b) (4) rates which has allowed us to eliminate any variability.
- Digoxin which represents (b) (4) of the variability problem of reoccurring products is under the same process and we anticipate we will have the same outcome, since results to date are encouraging.
- Metformin which was also part of our variability study (b) (4) but did not face any complaints in the review period was corrected earlier by tightening process parameters along with aligning this product with the appropriate machinery.

This corrective action, born out of our variability study, established in November 2008, effectively resolves our reoccurring variability product issues.

Our Quality Management System (QMS) that tracks all functional aspects of the quality system is in its final stage of validation. Personnel were being trained at the time of the FDA investigation and escalated communications critical to the workflow authorities have been finalized this past week. This program includes core quality systems, such as incidents, market complaints, change control, and QA Hold. 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. The system has the capability of linking OOS investigations, repetitive nature of OOS, CAPA monitoring and cross functional investigations. These additional capabilities will be implemented once the development and validation has been completed. We believe the system we have put in place will provide information to the executive management in a timely manner to routinely review critical issues effectively. We believe that the transparency we have created will help eliminate gaps and implement corrective actions when gaps are noted for any of our quality systems. As previously committed the scale integration and electronic drum wise reconciliation in pharmacy dispensing is being tested, trained and once validated will be implemented. Due to programming improvements that we found necessary we had faced a set back in our original time line that we previously conveyed to you for the second phase of bar code scanning, our new target date is June 30,2009. However in the interim manual drum-wise reconciliation is being performed for all Active Pharmaceutical Ingredients. This system, once fully deployed, will provide system inventory adjustment tracking, weight confirmation through the dispensing scale and drum wise reconciliation for all excipients and actives among other improvements. Currently only scanning is being done. Any adjustments issued are being tracked electronically through work flow messaging notification to the management team.

Our expansion project has allowed the consolidation and modernization of our manufacturing activities as well as allowing executive management to be a part of the core manufacturing facility. Its primary function is to improve the operation. To date we have only moved the administrative

# CARACO

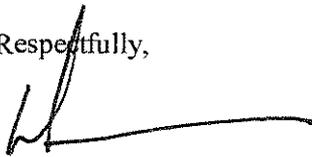
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office and pharmacy dispensing operations so that we are in one contiguous building with the appropriate space allocated for each function. We believe this will provide the cohesive structure required to positively reinforce our culture for continued improvement. The benefits of greater control, improved automation, and unidirectional process flow are just some of the instant benefits that will only contribute to improved compliance.

We believe that all products on the market have been tested for their efficacy and there are no safety concerns. We believe the additional testing that we have completed subsequent to the investigation reaffirms that position and that our release methodology is effective and is statistically sound..

We respectfully appreciate your concerns and will continue to work towards being a model of compliance in your district. It is important for our customers and the generic pharmaceutical industry as whole that we achieve that level of compliance. We would like the opportunity to discuss our action plan to convey our sense of urgency and address any relative concerns. We will reach out to you once you have had a chance to review our remediation response. Thanks again.

Respectfully,



Daniel H. Movens  
Chief Executive Officer

## MATERIALS SYSTEM

### OBSERVATION 1

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

#### Response:

Caraco has a procedure in place, SOP (b) (4) (b) (4) that clearly provides adequate information regarding an individual inventory record of each reconciliation of use. However, the procedure on isolated instances was not properly executed. It is also important to emphasize that batches manufactured using a particular lot of material are traceable through Lotwise Item Trace maintained by the (b) (4) system. In instances where the possibility of two receiving numbers of same component was improperly documented, notations, cross referencing these numbers has been placed for each receiving number in applicable record. Caraco's Quality Unit is committed to continuous improvements towards compliance within the Dispensing area and inventory controls.

#### Corrective and Preventive Actions:

We have implemented system and procedural enhancements such as (b) (4) reconciliation, control on material movement, and control on (b) (4) use, which will provide further assurance that required information is sufficiently documented. Prior to the closing of the FDA inspection, enhancements to the applicable procedure were made and dispensing operators have been re-trained for performing proper documentation. We have released the Senior Manager of Manufacturing responsible for our dispensing operation. The training was documented. Please refer to a copy of SOP (b) (4) (b) (4) Exhibit 1. Re-training Record is referred in Exhibit 2.

As a part of our long-term preventive action Caraco is in the process of validating (b) (4) (b) (4) system to (b) (4) (b) (4) This will provide (b) (4) This enhanced (b) (4) system has the capability to stop further activities in case the reconciliation is not performed or is not within the acceptable limits as defined in our SOP (b) (4) In addition, now QA will approve the material reconciliation if the material difference does not conform to the acceptable limits as defined in SOP (b) (4) Specific actions to be taken upon exceeding the acceptable limits are detailed in section (b) (4) (b) (4) of this SOP. The updating made in the enhanced (b) (4) system was discussed in detail with the investigators during the inspection.

Caraco has eliminated the use of virtual locations (FRSH and DISP) such as staging and in transit areas within the warehouse and all applicable areas. As per new procedure, (b) (4)

(b) (4)  
(b) (4)  
(b) (4)

(b) (4)

This change eliminates the

virtual warehouse location and the possibility of materials being "misplaced" or "overlooked" while sitting in a virtual location, awaiting further action from Material Handlers or Warehouse personnel. All trash or waste containers utilized within any operations areas were replaced with bright yellow-colored containers with lids. The containers are clearly marked for "trash-use only". Prior to using yellow trash containers, it was a common practice of using similar colored containers as those used for dispensed materials (white and grey) for waste / trash. It is possible, the use of similar colored containers could potentially cause confusion for an operator who might inadvertently discard material intended for return to the warehouse for storage. These changes will enhance our reconciliation process.

SOP (b) (4) (b) (4) was implemented during the FDA inspection for the manual (b) (4) reconciliation. The SOP will be revised and enhanced upon the implementation of our scale integration system by June 30, 2009. Please refer to a copy of System Requirement Specifications (SRS) Exhibit 3.

The above-referred preventive actions are applicable for each individual observations listed below.

A. (b) (4) Digoxin, USP, API Lot No. (b) (4) was dispensed from 1/09/09 to 1/12/09. On 1/13/09, 1.352 Kg of lot (b) (4) could not be located. To date, records do not indicate the disposition of the missing 1.352 Kg.

**Response:**

The missing of 1.352 Kg was treated as an incident as soon it became known to QA. The in-process incidence investigation was discussed with the investigators during the inspection, which includes the impact analysis and the scope of the investigation period. This small amount of material was stored in a large (b) (4) gallon drum container, which was similar to containers used for trash. More than (b) (4) production batches have been tested for the presence of digoxin drug substance and all batches were found free of digoxin. As per the conclusion in our investigation (b) (4) 1.352 kg digoxin was inadvertently discarded.

(b) (4) reconciliation of all Active Pharmaceutical Ingredients (API) has been implemented to alert the Management if the acceptable inventory reconciliation limit has been exceeded. The SOP (b) (4) Exhibit 1 of (b) (4) reconciliation and the applicable reporting form is presented in Exhibit 4 for (b) (4) Inventory History Record, Form No. (b) (4)

A number of Corrective and Preventive Action (CAPA) steps have been initiated.

- SOP (b) (4) (b) (4) was implemented during the FDA inspection for the manual (b) (4) reconciliation". The SOP will be revised and enhanced upon the implementation of our scale integration system for both API and excipients. This procedure will better track the usage of a receiving number and provide a running inventory, by each container as opposed to the previous procedure of reconciliation at the exhaustion of the entire receiving number. The automated system of both scale integration and bar code scanning improvements was also in the process of validation during the inspection, the expected completion date is June 30, 2009.

- Further enhancement is being validated in the (b) (4) system for the scale integration to capture the weight during weighing which will assist “on line” reconciliation of material. (b) (4) bar code scanning improvements will provide the assurance that irrespective of receiving number, each drum has to be scanned otherwise the system will not allow progress. This was also in the process of being validated during the inspection process and will be completed by June 30, 2009. Once implemented this system will automatically reconcile each drum in our system and an automatic adjustment is made if required at the time of reconciliation. Any adjustment beyond our acceptable limits will be investigated as part of this process and the operation will cease until assignable/ potential assignable root cause is determined and a product quality impact assessment have been completed.
- At any given time, an accurate inventory is currently available. With (b)(4) drum reconciliation discrepancies or trends will be highlighted in real time without waiting for the entire receiving number to be exhausted. As indicated in earlier response, the SOP (b) (4) will be updated upon implementation of our scale integration into the system by June 30, 2009.
- Previously, (b) (4) materials such as Digoxin were not assigned to specific locations since they were considered “in-process” and were located in a virtual location, which was a designated area of the warehouse. Currently, as a part of our corrective action plan, (b) (4) (b) (4) SOP was revised to include these requirements and concerned persons are trained on this aspect and training is documented. Refer to Re-Training Record, Exhibit 2.
- Digoxin due to its high potency and the small amount required for each batch has been stored in a secured warehouse location under an actual locator number in our warehouse. This product and other high potency products require a chain of custody by signature to be issued for dispensing to the dispensing room and return to secured warehouse location. Also this material is stored in unique colored containers, as additional visual aid to alert the operators of the type of material contained. This will help to eliminate the incidence of "misplaced" materials. Please refer to a copy of Chain of Custody Form (b) (4) Exhibit 5
- Based on the incident of missing material it became apparent that there was a possibility that smaller amounts of material at the bottom of a large container could be overlooked. SOP (b) (4) was revised to incorporate instructions that following dispensing, all empty vendor source containers and Caraco source containers, are turned upside down and labels defaced to ensure that no material remains in the container prior to it being discarded or sent for cleaning (Caraco container).
- A Kit which includes all actives and excipients for a particular batch of the product is prepared once all the materials for a batch are dispensed from applicable dispensing rooms. Once kitting is completed and checked by the Dispensing Supervisor, the material is transferred to manufacturing. No dispensed lots are stored within the Dispensing Department since we have moved to one contiguous building.
- All employees in dispensing have been retrained on the storage and handling of our raw materials relative to the dispensing process as referred in SOP (b) (4) Training has been documented.

- The material flow process chart from receipt to dispensing to a specified manufacturing batch is provided as referred in Exhibit 6, Flow Chart. Critical control points are identified on the flow chart.

**B. Metformin HCl, API Lot No. (b) (4) on 8/25/08, 15 Kg could not be located in the warehouse. The investigation (IR 08-793) was closed on 9/22/08 with the conclusion that operators combined different receiving numbers of the same product To date, records fail to account for the 15 Kg of Metformin Lot No (b) (4)**

**Response**

We have re-verified the rationale leading to the original conclusion of the referenced investigation. The shortage in the receiving number (b) (4) was evaluated as excess amount because finally we found excess in receiving number (b) (4). The data presented below provides clearer calculation of the material accountability in support of our original conclusion. Upon further investigation of (IR08-793), it was discovered that the receiving number, (b) (4) of Metformin Hydrochloride which had 15 kg less quantity was involved in another investigation (IR08-915) related to excess amount of 31.067 kg in addition to (b) (4). Upon further review of IR08-793, it is determined that the below receiving numbers were used in dispensing of Metformin batches. In summary, the total shortage was 4.382 kg by combining receiving numbers dispensed during that time instead of 15 kg as determined in original investigation. This quantity is shown in column 5 of the table below. Refer to a copy of IR08-793. Upon further review of IR 08-915, it is determined that the below receiving numbers were used in dispensing of Metformin batches. The total excess quantity found was 31.067 kg. This quantity is shown in column 5 of the table below. Refer to a copy of IR08-915.

Receiving no. as mentioned in Summary pickup list	DATA from receiving # (b) (4)				Qty used (in Kg)	Net qty shortage (-)/excess(+) as per (b) (4) in Kg	Supplier excess
	Lot no. as mentioned in (b) (4)	Quantity as per (b) (4) in (Kg)	QA	Quantity given to Dispensing (in Kg)			
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	1.77	2.2
						1.731	
							2.9
							1.4
							2.3
							0.37
						27.556	
							2
						0	2.95
						31.057	14.12

DATA from receiving # [REDACTED]							
Receiving no. as mentioned in Summary pickup list	Lot no. as mentioned in [REDACTED]	Quantity as per [REDACTED] in (Kg)	QA	Quantity given to Dispensing( in Kg)	Qty used(in Kg)	Net qty shortage (-)/excess(+) as per [REDACTED] in Kg)	Supplier excess
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	4.593	3.95
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	-14.981	2.95
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	4.369	0.35
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	2.672	1.55
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	-3.347	8.8

DATA from receiving # [REDACTED]							
Receiving no. as mentioned in Summary pickup list	Lot no. as mentioned in [REDACTED]	Quantity as per [REDACTED] in (Kg)	QA	Quantity given to Dispensing( in Kg)	Qty used(in Kg)	Net qty shortage (-)/excess(+) as per [REDACTED] (in Kg)	Supplier excess
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.77	2.2
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	1.731	2.9
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		1.4
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		2.3
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		0.37
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	27.556	
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	0	2
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	4.593	3.95
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	-14.981	2.95
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	4.369	0.35
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	2.672	1.55
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	27.71	22.92

We have also verified gross weight of these receiving numbers at the time of receipt and found that a total of 22.92 kg was received more than the gross weight claimed by the vendor.

Based on above two investigations:

- The net excess quantity of Metformin Hydrochloride (b) (4) receiving numbers) is (b) (4) (b) (4)
- The net excess quantity of Metformin Hydrochloride (b) (4) receiving numbers) received from vendor is (b) (4)
- The difference between excess quantity remained in Caraco's inventory (b) (4) and excess quantity found at receipt (b) (4).
- This differential quantity (b) (4) is within (b) (4) acceptable limits specified in our SOP.

Considering the excess material received at the time of receipt and variability of the weighing scales used at the point of receipt and at the time of dispensing, tare weight differences as claimed by vendor as against actual tare weight, the root cause for the excess material is attributed to combining of multiple receiving numbers during dispensing and excess material received from the vendor. The variances associated with the combined receiving numbers involved in the discrepancy of the material were within approved tolerances.

### **Corrective and Preventive Actions**

As a result of our investigations conclusion, all records and inventory history records involved, which are associated with the finished product lots, have been updated to reflect the incident and cross-reference the lots.

Since November 2008, we have revised SOP (b) (4) the revised procedure allows dispensing of only one receiving number of either an excipient or API in the dispensing room at a time for any particular lot. This revised procedure allowed us to reconcile without involving another receiver number and eliminate any possible discrepancy between receiver numbers for a particular lot.

As explained earlier in the response, the (b) (4) reconciliation, control on material movement, control on drum use will provide further assurance of material reconciliation at any given time. A review of the related investigation shows that these events do not have any adverse impact on product quality, as a result of previous practices. The implementation of revised SOP (b) (4) effective from May 26, 2009, in addition to the training of all personnel involved, replacement of supervision gives us a high level of assurance that this type of incident will be prevented.

## OBSERVATION 2

Written procedures are not followed for the storage and handling of components. SOP (b) (4) (b) (4) was not followed to assure sufficient quantities of raw materials were available, as designated by your inventory tracking system (b) (4) and the return of any excess.

**Response:** SOP (b) (4) requires that (b) (4) (b) (4) The (b) (4) system does not confirm and release a work order if there is no sufficient approved quantity available for use. Material Pick Up List (MPUL) does not generate to pick the material unless there is sufficient quantity in stock. The reference cited in the observation relates to our Summary Pick List (SPL). The use of summary pick list was out of scope of our SOP at the time of inspectional observation. The SPL is actually the collective needs for our entire material pick lists required for the day's production. The use of SPL should have been added to the SOP. The intention of our personnel using SPL was to improve operational efficiencies by reducing foot traffic. Operators and Supervisor's who did not follow our SOPs were reprimanded or terminated. All dispensing staff has been retrained under our revised SOP. Please refer to Exhibit 1 and 2 for Re-training Record

All necessary reconciliation for Active Pharmaceutical Ingredients (API) is now done on a (b) (4) (b) (4) basis. Prior to June 2009, our procedure was to (b) (4) (b) (4) As such, the material exact quantity could be somewhat different due to the differences in the container tare weight and unaccountable losses during the weighing process even though it shows in the stock. Given this scenario, occasionally sufficient amount of raw material may not be available for dispensing from that receiver number. It is very important to note that the accurate amount of material received for a receiving number is not known until the exhaustion of the specified receiving number since up to that time the weighed amount is only deducted from the vendor's labeled net weight and reconciliation was done at the end of the receiving number being exhausted.

**Corrective Action:** Gross weight of incoming API materials, prior to dispensing, is being captured and documented in (b) (4) reconciliation forms at the time of reconciliation. When material quantity differences occur that are outside acceptable limits as defined in our SOPs, an investigation is conducted along with product quality impact assessment. This investigation is approved by QA before further processing is allowed.

**Preventive Action:** As provided in detailed response to observation 1, Caraco has revised SOP (b) (4) (b) (4) to provide enhanced control and timely detection of material quantity differences in actual weight versus vendor's net weight.

In addition, virtual locations like "FRSH" (Fresh Goods) and "DISP" (Dispensing Location) will no longer be used. The actual location in which an item is stored is the location in which the material will appear in (b) (4) This commitment was discussed with the investigators during the inspection.

**A. For raw materials not in a specified warehouse location, the quantity given to Dispensing is not documented on the Summary Pickup list Examples include:**

- Tramadol (b) (4) "Not in LOC"
- Metformin (b) (4) "Not in location"
- Digoxin (b) (4) DISP"
- Digoxin (b) (4) "DISP"

**Response:** The Summary Pick List was used for picking materials from the warehouse locations and transferred to the staging area. At the completion of dispensing, the material was returned to the staging area (virtual location) and not the original warehouse locations. For Metformin HCl and Tramadol HCl the material was lying in the staging area and not located in its original locations.

The summary pick list is a document used as a transfer request of material from the warehouse to the dispensing rooms. This aids the warehouse personnel in getting the correct quantity from the correct warehouse locations. The actual documentation of the material dispensed is documented on the pick list where the dispensing operator and the supervisor sign for dispensing of the actual material. The pick list is attached to the BMR. This has been formalized in SOP (b) (4) (b) (4) which describes what steps and documentation are necessary to move material. Personnel have been trained to follow procedure as written. Deviation from procedure carries serious disciplinary action up to and including termination. Operators and Supervisor's who did not follow our SOPs were reprimanded or terminated. All dispensing staff has been retrained under our revised SOP.

DISP was a virtual location used for the staging of materials required for dispensing. When Active ingredients were (b) (4) they were transferred into DISP Location in the (b) (4) The use of a "virtual" staging area, DISP, has been discontinued. From the (b) (4) system, we have implemented (b) (4)

(b) (4) Our procedure has (b) (4) (b) (4) Any remaining material after dispensing is returned directly to the warehouse location from where it was taken. There will be no staging location, physical or virtual, utilized in the dispensing operations. This will cause the electronic (b) (4) tracking system to reflect the physical movement of the materials in the warehouse.

Also Effective, April 2009 all (b) (4) This improvement will help to eliminate the incidence of "misplaced" materials.

The use of "Chain-of-Custody" form to track the handling and/or use of very specific, small-usage, highly potent drug materials like Digoxin has been implemented. This procedure will document inventory usage and also track record of all individuals involved in the handling of the material as it is transferred between the warehouse and Dispensing Departments.

**B. Sufficient quantities of the following raw material were not given to Dispensing, as indicated on the Summary Pickup List generated by (b) (4)**

Examples include:

1. (b) (4) Receiving No. (b) (4) for Paroxetine (b) (4) Lot No. (b) (4) and (b) (4)
2. Citalopram Receiving # (b) (4) For Citalopram (b) (4) Lots (b) (4)

**Response:** The Summary Pick List is a summary of products needed for the day's dispensing production to save foot traffic in the material picking process. It does not have the detail that is part of the actual Material Pick List, which is a part of our batch record. When using the summary pick list if there was already material picked for the warehouse location and kept in the staging area for a previous lot, the quantity transferred in the next pick sheet will be less. This is due to the remaining material from the previous pick sheet was already available for use in the staging area, which is the remaining balance.

To avoid the type of incident cited in this observation, an enhancement to procedure "SOP (b) (4) (b) (4) has been made. This SOP

(b) (4) (b) (4) Because excipients can be used in multiple products on the same day, the supervisory staff and material handling staff will coordinate what rooms are using each material, and a single material should not be simultaneously used in multiple rooms. If a raw material quantity is found short and/or material can not be located, and/or if the differences are outside the acceptable limits an investigation is initiated as per SOP (b) (4)

As per current procedure (b) (4)

(b) (4) (b) (4) (b) (4)

**C. Failure to document the return of excess raw materials for the following batches. Examples include: Metoprolol (b) (4) batches (b) (4) Tramadol batches (b) (4) Metformin (b) (4) batch (b) (4) and Citalopram batches (b) (4)**

**Response:** As per our past procedure, raw materials after dispensing were transferred to a staging area. The use of the Summary Pickup List was not formalized in our SOP during the time of the FDA's visit. Also if the same raw material was required to be dispensed for another batch the material was transferred directly from one room to another. The Summary pick list was used to document the transfer of materials between the warehouse and dispensing areas. If materials were consumed during dispensing to another batch it was not generally documented for internal transfers.

**Preventive Action:** Currently, the use of the Summary Pickup List is formalized in SOP (b) (4) (b) (4) and all the operators have been trained on this SOP. The training is documented. Please refer to a copy of SOP Exhibit 8 and copy of Training Record.

### OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Investigation conducted under "NOE, Incident #09-005" dated 1/6/09 regarding (b) (4) individual raw material batches with OOS inventory reconciliations, was found to be incomplete in the following instances:

1. Metoprolol Tartrate USP, lot (b) (4) missing 2.61 Kg, thought to be incorrectly used in place of a different lot, but lacked evidence supporting this conclusion.
2. Carbamazepine USP, lot (b) (4) missing 1.27Kg, believed to be incorrectly used in place of a different lot, but lacked evidence supporting this conclusion.
3. Carvedilol, lot (b) (4) and (b) (4) found with excess 4.268Kg and 10.379 Kg, believed a third raw material batch was dispensed in their place and was inaccurately documented. Investigation lacked documented evidence that such a switch had occurred.
4. Tramadol HCl API, lot (b) (4) found with excess 2.405 Kg thought to be a result of rollover from previous lots dispensed and incorrectly documented but lacked documentation to support this conclusion
5. Metoprolol Tartrate USP, lot (b) (4) found to contain an excess of 2.756 Kg was not investigated.

#### Response:

It is Caraco's policy to fully and thoroughly investigate any discrepancies. SOP (b) (4) (b) (4) is the procedure followed to assure that unexplained discrepancies are thoroughly investigated. Prior to March 23, 2009, the discovery that a receiving number of a material is out of established acceptance limits during reconciliation is realized at the end of exhaustion of the entire receiving number. This could delay the discovery of any discrepancy to initiate the associated investigation; however our procedure SOP (b) (4) (b) (4) has been revised and updated to assure timely investigation of any receiving number that has been impacted by reconciliation issue. Caraco performs a (b) (4) inventory to ensure that the physical inventory is properly accounted for financially and on a GMP basis. It was discovered that certain discrepancies noted were in part due to the result of the physical inventory count during January 2009 (inventory period of December 2008) and not during the actual operation. The cited observations were found during the physical inventory count process. Applicable investigations were initiated once this became known and were in progress prior to the commencement of the FDA inspection.

For ease of review and to prevent repetitions, all investigations have been completed and are provided as an attachment to this response. Refer to Exhibit 9 The result of the investigation concluded that these events do not have an adverse impact on product quality. Corrective actions were taken as applicable and stated in detail in each response provided as an attachment

Due to similar nature of observations for variability regarding products identified in Observations are grouped together. A summary of the outcome of all related investigations regarding product quality assessment and global corrective and preventive actions are presented as follows:

**Preventive Actions:** From the (b) (4) system, we have implemented an electronic workflow messaging system where an Adjustments Issued Report is sent to all stakeholders including the upper management. Any out of established acceptance limits during reconciliation are investigated and the operations ceased until a root or contributing causes are determined and a quality impact assessment has been completed. The physical inventory that is taken (b) (4) will confirm our perpetual inventory. Any adjustments, which are outside acceptable limits specified in the SOP (b) (4) are investigated.

- As per revised SOP (b) (4) effective November 2008 (b) (4) (b) (4) This ensures accurate accountability of each receiving number and enabled us to reconcile each receiving number when the entire quantity of the receiving number is consumed. Also, (b) (4) (b) (4) (b) (4) since November 2008, we have no incidents of combined receiving numbers issued for any batch. As explained earlier in the response, the (b) (4) (b) (4) reconciliation, control on material movement, control on drum use will provide further assurance of material reconciliation at any given time.
- SOP (b) (4) was implemented during the FDA inspection for the manual (b) (4) reconciliation". In addition we are implementing a "(b) (4) reconciliation" procedure expected through the (b) (4) The SOP will be revised and enhanced upon the implementation of our (b) (4) for both API and excipient. This procedure will better track the usage of a receiving number and provide a running inventory, by each container as opposed to the previous procedure of reconciliation at the exhaustion of the entire receiving number. The automated system of both scale integration and scanning improvements was also in the process of validation during the inspection, the expected completion date is June 30, 2009.
- At any given time, an accurate inventory is currently available. With (b) (4) reconciliation discrepancies or trends will be highlighted in real time, without waiting for the entire receiving number to be exhausted. SOP (b) (4) was updated during the FDA inspection for the (b) (4) reconciliation of the particular lot and actionable in case of not meeting the requirement. As indicated in earlier response, the SOP (b) (4) will be updated upon implementation of our scale integration into the system by June 30, 2009. The container reconciliation is clearly explained in our SOP (b) (4)
- Digoxin due to its high potency and the small amount required for each batch, this material is being stored in a secured warehouse location under an actual locator number in our warehouse. This requires chain of custody for issuance to dispensing and return to secured warehouse location. Also this material is stored in unique colored containers, as additional visual aid to alert the operators of the type of material contained. This will help to reduce the incidence of "misplaced" materials. Please refer to a copy of Chain of Custody Form, Exhibit 5

- A Kit which includes all active and excipients for a particular batch of the product is prepared once all the materials for a batch are dispensed from applicable dispensing rooms. Once kitting is completed and checked by the Dispensing Supervisor, the material is transferred to manufacturing. No dispensed lots are stored within the Dispensing Department since we have moved to one contiguous building.
- SOP (b) (4) has been revised with specific instructions that do not permit two receivers to be brought to the room at the same time. In addition the barcode scanner has been implemented to verify that the correct materials are being weighed as per the Material Pick-up List. All operators have been trained on this SOP. The training is documented. Please refer to a copy of SOP Exhibit 1 and copy of Re-training Record Exhibit 2

**B. Citalopram Hydrobromide API assigned lot number (b) (4) was dispensed on 11/10/08 and again on 11/13/08 at which time 17.946 Kg could not be located. From 11/13/08 - 1/4/09 this missing quantity of 17.946 Kg was not investigated.**

**C. Meloxicam (Micronized) API assigned lot number (b) (4) was dispensed on or about 8/13/08. On 10/3/08 0.492 Kg could not be found and an entry into (b) (4) of "MATERIAL NOT IN LOCATION" was made. From 10/3/08 - 1/6/09 this missing quantity was not investigated.**

**D. (b) (4) Tizanidine Hydrochloride API lot 81161 was last dispensed 8/25/08 at which time an inventory of 0.868 Kg remained. On 9/14/08 it was noted that this remaining inventory could not be located, however investigation did not occur until 1/5/09.**

**E. Clozapine (b) (4) API lot (b) (4) was noted on 10/20/08 to have 2.821 Kg missing and an entry in (b) (4) of "UNABLE TO LOCATE MATERIAL" was made. This missing quantity was not investigated until 1/2009.**

**Response:** The cited observation is related to the discrepancy in the physical quantity of raw material supplied by the vendor and actual quantity found at the exhaustion of the entire receiving number. Considering the shortage material received at the time of receipt and variability of the weighing scales used at the point of receipt and at the time of dispensing, tare weight differences as claimed by vendor as against actual tare weight, the root cause for the less quantity of material is attributed to combing of multiple receiving numbers during dispensing and less or excess material received from the vendor. Corrective actions were taken as applicable and stated in detail as an attachment. Refer to Exhibit 9.

**Impact Assessment:** Based upon the review of the batch manufacturing records, weighing tickets, lot-wise item trace and pick lists it is confirmed that that the correct stock number, correct materials and accurate quantity of each material was dispensed for all lots identified in the observation. It is important to emphasize that all receiving numbers were tested and released prior to use. The finished product test results for identity, assay, content uniformity, dissolution and related substances as applicable were well within established specifications and trend. Therefore, the material discrepancy is not expected to have any adverse impact on product quality attributes.

**OBSERVATION 4**

Written procedures are lacking which describe in sufficient detail the receipt, identification, storage, and handling of components. Written procedures do not describe in sufficient detail the designation or employee responsibilities relating to drug components in the "FRSH" or "DISP" locations, which are not physical warehouse locations.

**Response:** The written procedures SOP (b) (4) (b) (4) and SOP (b) (4) are in place that describes in sufficient detail the employee responsibilities. However on a number of isolated instances procedures were not followed by the operators. Refer to Exhibit 10 and 1.

The designation of "FRSH" and "DISP" were virtual locations that were used to stage product in between the actual designated warehouse location where it normally stored and prior to being physically moved to the actual process area for a particular work order. These locations were utilized to minimize foot traffic and were considered virtual locations to allow for the ebb and flow of material based on the effectiveness of daily production workflow of the particular batch scheduled that day. These locations were originally assigned an area in the warehouse for staging the product needed in the dispensing process rooms that were scheduled as the next batches to be dispensed for the current daily production. The material is not supposed to remain in these virtual locations for any time longer than it takes to complete the actual dispensing process for the day.

A rolling shut down of the Manufacturing facility to review and address the status of each of the manufacturing processing areas was implemented prior to the inspection. The plant shut down was conducted during the period of [redacted] During this period, re-training on SOPs and manufacturing and dispensing procedures were conducted. The documentation and cGMP training was provided by our Training Manager to all operators and supervisors for paying attention to the details and following batch record instructions.

**Preventive Action:** In order to eliminate potential errors in assigning raw material storage Caraco has eliminated the use of "FRSH" and "DISP" locations in the (b) (4) The applicable Standard Operating Procedure SOP [redacted] has been revised to specify that the material be taken from a specific location in the warehouse. Any remaining material that needs to be stored after dispensing is taken directly back to the actual storage location. The material is not allowed to be stored anywhere else other than its actual designated storage location in our warehouse racking system or its assigned dispensing room.

- A. [redacted] Digoxin, USP [redacted] Lot # [redacted] was documented in (b) (4) to be in the "FRSH" location between 10/13/08 to 1/26/09 and was dispensed during this time period.
- B. [redacted] Digoxin, USP ( [redacted] Lot (b) (4) was documented in (b) (4) to be in the "FRSH" location between 12/30/08 to 2/4/09 and was dispensed during this time period.
- C. [redacted] Digoxin, USP [redacted] Lot # [redacted] was documented in (b) (4) to be in the "FRSH" location between 9/15/08 to 9/26/08 and was dispensed during this time period.
- D. [redacted] Tizanidine Hydrochloride lot [redacted] was documented in (b) (4) to be in the "DISP"

**location 7/18-18/08 and was dispensed during this time period.**

**Response:** As noted above FRSH and DISP was a designated transit location for material about to be used in the dispensing process. It was errantly being used as a storage location without an actual locator number being assigned to designate its actual location. All of our stored raw materials have designated location numbers for each pallet bay in our warehouse racking system. In these particular instances the (b) (4) highly potent materials were assigned an area for storage rather than a designated locator position number in our warehouse since it was to be dispensed. Rather than remaining in its designated area location it should have been moved to a proper designated location as per our SOP.

**Corrective and Preventive Action:** We have eliminated the use of FRSH and DISP as a storage area location. All employees in dispensing have been retrained on the storage and handling of our raw materials relative to the dispensing process. Refer to Exhibit 1, SOP (b) (4) (b) (4). In addition, (b) (4) active materials due to its potency and the small amount required for each batch, has been isolated in a restrictive location under an actual locator number in our warehouse racking system which requires chain of custody by signature to be issued to the dispensing rooms for dispensing and return to storage. Also all potent materials are now stored in a (b) (4) and (b) (4) to make these material standout in all processing areas.

## MANUFACTURING PROCESS

### OBSERVATION 5

**Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.**

**Response:**

Caraco's Validation Master Plan requires that all equipment, utilities, facilities, personnel, materials, processes and products, must be qualified and validated prior to use in the manufacturing of the drug products. Our batch manufacturing record instructions and Standard Operating Procedures (SOP) used for drug product manufacturing are carefully reviewed prior to implementation as these in-process specifications are designed consistent with drug product final specifications and to control any potential variability in a drug product. All deviations associated within a batch are documented in the batch record appropriately and duly verified by a supervisor and Quality Assurance before the batch is released; however in some isolated instances the procedure might not have been closely monitored to tabulate and analyze the various adjustments made specifically during the compression process to assist in predicting the outcome.

Caraco has designed and implemented procedures for the preparation and review of trends of the critical process parameters and quality attributes for ongoing assurance during routine production. We are improving the measurements or trends of graphical presentation and statistical analysis of these attributes from executed batch records to better analyze the data within a batch or if tests established shows signs of diverging away from target or approaching signs of moving away from target or heading towards an out of tolerance range. This will allow us to assess real time what we should look for from a quality perspective if the batch and a product is showing variability within the operational ranges allowed. These parameters are derived from process average and process variability estimates and determined by the application of suitable statistical procedures, as applicable. Once the product history is developed and trends are established, we are performing statistical analysis on products and processes with a view to controlling batch-to-batch variability to the maximum extent possible.

We have also established procedures, which provide guideline for handling routine variation in process control parameters, and defined levels of alerts and actions within manufacturing the batch itself. This will allow us to assess quality outcome of the batch even before performing our [REDACTED] review. Additionally, several in-process tests such as (b) (4) [REDACTED] for monitoring (b) (4) [REDACTED] properties have been added to detect any variability in the process. Physical characterization testing tablets equivalent to number of stations of the tablet press plus [REDACTED] units checks is performed immediately after set-up of the machine, at the [REDACTED]. Manufacturing is also performing representative sample tests that measure weight, thickness, and hardness to support our in-process tests being made every (b) (4) [REDACTED] during the compression process. As reflected below under preventive action and prior to the starting of the FDA inspection some specific procedures for testing of attributes and/or variable that impact on the quality of drug products had been developed based on the out come of the comprehensive analysis of the circumstances surrounding the variability issue.

A detailed report identifying areas of process enhancement, equipment, personnel and procedure is being reviewed and updated (b) (4). A significant amount of these actions have been implemented and the current trends are encouraging.

**Corrective Actions:** We have optimized processes and control parameters for all products. All products are being manufactured under the modified parameters with tightened controls. The trend of all products are now reviewed and evaluated (b) (4) for further optimization as deemed necessary for continuous improvement. Meanwhile, in the interim, Caraco decided to mitigate any weight variability issue by implementing the use of automated thickness sorting machines for sorting tablets as an immediate corrective action to provide additional assurances of satisfactory batches before it is released to market will comply with the expected product specification limits. This would allow confirming repeatability for certain products that have had their operational range tightened for various process parameters or confirm any products outcome from validation on ongoing basis. It should be emphasized that the employment of the thickness sorter is being used for certain products which have been previously identified for potential size variation is a temporary approach to measure what we believe are permanent in-process solutions that have been implemented as a corrective action, where applicable.

**Preventive Actions** Prior to the commencement of the FDA inspection on March 11, 2009, Caraco's Quality Unit in association with (b) (4) completed a comprehensive analysis relating to weight variability relative to certain products. The report originally issued on December 7, 2008 is being continuously updated as data from our studies become available. A copy of this report was provided to the FDA investigators during the inspection. The report also listed a number of corrective and preventive actions that has been identified to mitigate the weight variability issue.

Caraco would like to emphasize that prior to initiating FDA inspection, the Quality Unit has reviewed data generated on marketed product complaint batches as well as internal incidents raised from 2007, 2008 and 2009 in regards to tablet size variations in order to determine if there is a trend. We feel it is important to also note that upon identification of these issues, immediate corrective actions were taken by Caraco to address these issues. We identified potential contributing causes; and initiated comprehensive corrective actions encompassing from (b) (4) conditions to mitigate the extent of the problem. The holistic approach consisted of the review of the specific dynamics of the manufacturing process, performance of equipment, tooling, personnel and material involved during the manufacturing process. We have taken corrective actions where necessary and have not limited our investigations to just the observations cited, but have performed a comprehensive review and investigated the systems and procedures affected. Upon further review and as a part of our continuous improvement plan, it was decided to enhance monitoring and control of the process and the control parameters. A systematic approach was defined to review step-by-step processes and based on this review applicable corrective action plans were determined which are already in progress or completed. The evaluation of various drug products revealed that the maximum incidents and market complaints are associated with Metoprolol, Clonazepam, Metformin and Digoxin tablets. Our actions included various products identified in this observation and the first product that represented (b) (4) of our size variability concerns based on internal incidents and market complaint was Metoprolol 50 mg round and 25 mg strength tablets. These two products have not faced any market complaints since our corrective actions and change over to

automated tablet press has been implemented. Internal incidents for this product related to size variability have also been non-existent.

As part of Caraco's tablet weight variability improvement plan and based on our evaluations, the use of (b) (4) compression machines have been discontinued. We have switched over to (b) (4) machines. (b) (4) machines have been ordered. Remaining (b) (4) machines are being (b) (4) (b) (4) (b) (4) Currently, those machines are not showing a trend to identify them as a concern. If we determine a trend that is less than satisfactory, those machines will be replaced as well.

Due to similar nature of observations for variability regarding products identified in Observations 5A and 5B, these observations are grouped together.

**A. The following lots were sorted for tablet defects after in process controls and compression related issues were noted:**

- 1. Digoxin 0.125 mg Tablets, USP lot 81404 was compressed 9/19-22/08 and sorted under SPO (b) (4) for noted thick and soft tablets. The sort resulted in the rejection of (b) (4) Tablets.**
- 2. Digoxin 0.125 mg Tablets, USP lot 81401A was compressed 6/14-20/08 and sorted under SPO (b) (4) for thick and thin tablets observed during packaging.**
- 3. Clonazepam 0.5mg Tablets, USP lot 81529A was compressed 7/17-21/08 and sorted under SPO (b) (4) for thin, soft, broken, and imperfect appearance tablets following observation of the same during packaging.**
- 4. Clonazepam 0.5mg Tablets, USP lot 81534A was sorted under two Special Processing Operation orders [SPO (b) (4) (8/19/08) and SPO (b) (4) (11/11/08)] following the observation of thin tablets during packaging.**
- 5. Clonazepam 0.5 mg Tablets, USP lot 81597A was sorted under Special Processing Operation order [SPO (b) (4) (9/4/08)] following the observation of thin tablets during packaging.**
- 6. Clonazepam 0.5 mg Tablets, USP lot 81532 was sorted under Special Processing Operation order [SPO (b) (4) (8/8/08)] following the observation of thin tablets during packaging.**
- 7. Metoprolol Tartrate 50mg Tablets, USP lot 80345 was compressed 3/12-14/08 and sorted under SPO (b) (4) for noted thin and soft tablets.**
- 8. Metoprolol Tartrate 50 mg Tablets, USP lot 82496 was sorted under two Special Processing Operation orders [SPO (b) (4) (11/10/08) and SPO (b) (4) (11/18/09)] following the observation of broken tablets, thick tablets and black spots during compression and again during packaging.**

9. Metoprolol Tartrate 50 mg Tablets, USP lot 81786 was sorted under Special Processing Operation order [SPO (b) (4) (08/20/08)] following the observation of soft tablets and imperfect appearance during packaging.

10. Metoprolol 50 mg Tablets USP lot 81102A was sorted under Special Processing Operation order [SPO (b) (4) (6/18/08)] following the observation of thick tablets during packaging.

11. Metoprolol 25mg Tablets USP lot 80667A was sorted under Special Processing Operation order [SPO (b) (4) (5/14/08)] following the observation of thick tablets during packaging.

12. Mirtazapine 30 mg Tablets, USP, lot 81126 was compressed beginning 06/02-04/08 and sorted under SPO (b) (4) for tablets with imperfect appearance.

**B. The following un-sorted lots were the subjects of complaints relating to compressed tablet defects. The batch record for each of the following noted compression issues during production:**

1. Metoprolol Tartrate 50mg Tablets, USP Lot 80959 was compressed 4/23-30/08 and received complaint COM (b) (4) on 09/03/08 for tablet size variation.

2. Metoprolol Tartrate 25 mg Tablets, USP Lot 81739A was compressed 8/26-28/08 and received complaint COM (b) (4) on 1/29/09 for tablet size variation.

3. Metoprolol Tartrate 50 mg round Tablets USP Lot 82036A was compressed 9/8-9/08 and received COM (b) (4) on 1/28/09 for tablet size variation (thick).

4. Metoprolol Tartrate 25 mg Tablets, USP lot 80658A was compressed 4/11-14/08 and received COM 08-083 on 6/16/08 for tablet size variation (thick).

5. Metoprolol Tartrate 25 mg Tablets, USP lot 82695A was compressed 12/26-30/08 and received COM (b) (4) on 3/12/09 for tablet size variation (thick).

6. Digoxin 0.125 mg Tablets, USP lot 81020A compressed 5/24-6/2/08 and received COM (b) (4) on 11/10/08 for tablet size variation (thick).

7. Digoxin 0.125mg Tablets, USP lot 80771A compressed 5/1 - 6/08 and received COM (b) (4) on 7/2/08 for tablet size variation (thick).

**Response:** Caraco understands the product quality issues and is committed to eliminate any variation seen in its products. Caraco's quality unit is committed to constant improvement towards operational and cGMP compliance. To assure batch uniformity and integrity of the drug product, in-process controls and tests have been established for significant stages of processing. Manufacturing instructions, in-process controls, and operator's in-process checks are promptly documented in the batch record. Quality Assurance inspects and tests compressed tablets during manufacturing of the drug product. At various stages of compression the operator examines and test samples to assure that the drug product and in-process parameters conform to specifications. The critical process steps and variables that affect the quality have been identified and are set within their operating ranges. The batch

analysis results demonstrate that the drug product has an acceptable quality with respect to the finished product release specifications and prove that the manufacturing process is in a state of control.

We have taken a deeper look into the production issues and various corrective actions and preventative action plans (CAPA) have already been implemented to improve the process and minimize if not eliminate any variability. Trending of effectiveness is being monitored for these actions. Please refer to response below for detailed preventive actions.

## **Corrective and Preventive Actions**

### ***Compression Machine Set-Up Checklist Implementation***

Corrective action no. CAR (b) (4) was implemented for establishing a comprehensive checklist which is verified during the initial set-up, any machine adjustments, troubleshooting, start/stops of tablet press, and/or maintenance of the tablet press in the SOP (b) (4) (b) (4). The SOP was further enhanced for incorporating instructions for removing the (b) (4) unit and product container while performing set-up of tablet press. Please refer to a copy of SOP, Exhibit 11

Corrective action no. CAR (b) (4) was implemented for verifying machine set-up checklist after cleaning of compression machines. SOP (b) (4) was further enhanced to establish a daily monitoring compression machine-specific set-up checklist for each working shift as a part of our continuous improvement. The steps for critical compression machine set-up conditions and parameters such as (b) (4) have been incorporated in the equipment specific forms. Please refer to a copy of SOP, Exhibit 11

## **Controls on Compression Process**

- Implemented physical characterization in-process test for tablets for verifying tableting parameters such as (b) (4) utilizing tablets equivalent to number of stations of the tablet press plus (b) (4) units. This test is performed immediately after initial set up of the machine, at the middle of the run and at the end of the compression run. This test is in addition of the normal in-process checks taken every (b) (4) minutes. All affected operators have been trained in the new enhanced procedures.
- The compression instructions in the batch records have been enhanced to specify the adjustments to be performed on machine, monitor and analyze the data within a batch when certain units within a test moving away from a target value and are repetitively approaching towards alert and action level. Process drift is stabilized by taking corrective actions by process optimization and standardizing operating procedures. This continuous process verification, monitoring and trend evaluation of routine production batches with respect to the established in-house and/or regulatory specifications controls are established to demonstrate that the process is in control.

## Improvements through Controls on In-process and Process parameters

As a part of our continuous process improvement program, the in-process and process control parameters such as (b) (4) and (b) (4) have been tightened to improve the operational performance, to reduce any variability in the process and ultimately improve the quality of the drug product. We have updated the batch records for documenting machine parameters, which are used for the compression process of a specific product. We have also increased the frequency of in-process checks for (b) (4) (b) (4) of compressed tablets. Phase 1 of batch record updating was completed on March 20, 2009 and Phase 2 will be completed by June 30, 2009.

## Initiated use of automated equipment

Implemented use of (b) (4) tableting machines for less reliance on human intervention. Compression operators and supervisors are being extensively trained for the past nine months to understand details of machine set-up and adjustments by compression machine suppliers. The program for verifying the effectiveness of training is being implemented. For example,

- Upon the latest product complaint in January 2009, all product Metoprolol 50 mg round and 25 mg as a precautionary measure were sorted on our automatic equipment for detecting and removing any potential tablet variability prior to release to market. This allowed us to validate products made on the (b) (4) tableting machine while confirming the quality of our output on current tableting equipment. No Metoprolol 25 mg and 50 mg round has been distributed since January 2009 without either being sorted through the sorting machine. (b) (4) (b) (4) (b) (4) tableting machine has been successfully qualified for Metoprolol tablets. Prospective Process Validation for 50 mg (Round) was initiated on 10-1-2008 and completed on 12-01-2008. Similarly, Prospective Process Validation 25 mg strength was initiated on 02-26-2009 and report was approved on 05-05-2009. These two Metoprolol tablet drug products represented approximately of our size variation concerns in year 2008. No incidents or product complaints have occurred since we introduced the product on tableting machine.
- As a precautionary measure, since February 2009, we decided to sort Clonazepam tablets through automatic equipment for removing any potential tablet variability prior to release to market. tableting machine has been qualified for Clonazepam tablets. Prospective Process Validation studies for Clonazepam Tablets, 1 mg, were initiated on 02-24-2009 and completed on 03-16-2009. Similarly, (b) (4) mg validation studies were initiated on 04-01-09 and completed on 05-20-09. These Clonazepam tablet drug products represented approximately of our size variation concerns in year 2008. No incidents of product complaints since we introduced the product on (b) (4) tableting machine.

- We have implemented the use of (b) (4) with a (b) (4) with (b) (4) features during (b) (4) process. The (b) (4) assists in controlling the feed rate for (b) (4) process and reduces potential for variability in manual loading and transfer of (b) (4). The controlled (b) (4) process and conditions provides better control on the particle size distribution; improves the granule properties with less reliance on operator's performance. All drug products currently manufactured using the (b) (4) will be transferred to (b) (4) with prospective validation studies. The actual demonstration of the operation and performance of the (b) (4) was shown to the investigators during the plant walk through.
- Monitoring of (b) (4) (b) (4) for all drug products has been initiated from 01-12-2009. The Quality Control unit is performing an evaluation of data and any excursions are notified to the Manufacturing and Quality Assurance for deciding appropriate actions.
- Improved blend uniformity processes by improving geometric loading sequences of materials. This activity was conducted within the required regulatory framework.
- Implemented the use of Auto Tablet Tester which performs automatic testing of a tablet unit for (b) (4) without human intervention. The data generated on this instrument is presented with statistical interpretations and graphical presentation. An example of the data output was presented to the investigators. Please refer to a copy of SOP (b) (4) (b) (4) in Exhibit 12

#### **Enhancement of Acceptable Quality Level (AQL) procedure**

SOP No. (b) (4) " has been revised to increase the sampling density by (b) (4) and the number of containers sampled have been increased to collect and represent entire population of the batch. This SOP was enhanced and became effective since February 11, 2009 as a part of our continuous improvement. Please refer to a copy of SOP (b) (4) in Exhibit 13.

#### **Training**

We continue to use Third Party planned audits to oversee quality and operations and to conduct a gap analysis of our systems. We are also conducting extensive training for all operating, laboratory, quality and management staff from (b) (4) equipment suppliers and internal training to continuously improve the skills in each area.

- Established scheduled training program with compression machine suppliers to conduct (b) (4) training. Both operators and supervisors are being extensively trained from past nine months to continuously improve the skill and understand the details of machine set-up and adjustments. These machines require qualified operator and skills to maintain tablet press set-up adjustments.

- We have contracted with (b) (4) to provide training, conduct audits and provide additional support in batch record review and other areas of their expertise. The most recent audit and trainings were conducted in April 2009 by three experienced auditors from (b) (4). The next audit is scheduled in end July 2009.

### **Additional Resources**

- Caraco Management has appropriate staff necessary to implement changes and improvements. Additional supervisors are already on board to support operating staff and increase skill for more controls. We continue to recruit skilled, talented and experienced laboratory and QA personnel.
- The position of Tooling Manager and (b) (4) dedicated technicians has been created in October 2008 for handling, storage, inspection and maintenance of tooling used in the compression of the drug products.

### **Key Actions Taken**

- In January 2009, we initiated re-organization of our Manufacturing and Quality units by releasing its leaders. New personnel have been hired to align these departments with the direction of the corporation. New positions have been created for providing strong managerial and operational leadership to enhance quality systems and improve manufacturing operations. We have staffed these positions with people who have the appropriate training, education and experience in the pharmaceutical industry.
- The Manufacturing Compliance Department has been created for oversight on routine manufacturing operations. A position is also created for trending and monitoring of in-process parameters and critical process parameters recorded in the batch record.
- Technical Services Department has been re-organized by hiring talent for active involvement in process validation and equipment qualification program. This department will also address routine technical and troubleshooting.
- With deliberate efforts, since December 15, 2009, we have slowed down new product development and technology transfer activities for continuous focus on cross-functional training and resolution of process and product related discrepancies. Our R&D team is actively participating in conducting in process reviews, investigations, providing additional support in process validations, technical training, conducting audits, revising batch records, and other areas of expertise to assure proper functioning of compliance and technical systems.

## **Implemented a Rolling Shut Down of Manufacturing facility and Systems**

A Rolling Shut Down of the Manufacturing facility to review and address the status of each of the manufacturing processing areas was implemented prior to the FDA inspection. The plant shut down was conducted during the period of (b) (4) During this period, re-training on SOPs and manufacturing procedures were conducted. Additionally a process review and a gap analysis was conducted with all manufacturing department personnel. During this shutdown, all equipment was evaluated by the facilities department and appropriate preventative maintenance and repairs were conducted and completed prior to the re-start up of the facility.

## **Logical Introduction in the Facility**

As described to the investigators, we are in the process of qualifying and validating the expanded facility. This facility will provide appropriate space for all operations well into the future. We are equipping this facility with additional new equipment designed for enhanced process control. New equipment, more space, new environment, better material flow is expected to provide enhanced control over the manufacturing process.

## **Corrective Actions Ready for Implementation**

- As defined in our Validation Master Plan, we recognize the need for the review of all critical process parameters of our drug products on an ongoing basis and will take actions for re-validation of drug products, as appropriate.
- SOP (b) (4) has been developed which provide guidelines for handling routine variation in parameters using pre-defined alert and action levels. The training will be completed prior to implementation Exhibit 14
- SOP have been designed to define the procedure for preparation and review of trend for critical process parameters (CPP) and critical quality attributes (CQA). This SOP also provide guidelines for handling out-of-trend process parameters and quality attributes, if found while reviewing of the batch manufacturing record for ongoing assurance during routine production. The training will be completed prior to implementation. Exhibit 15

The Life-Cycle Approach of Validation of collection and evaluation of data throughout the production is adopted to establish confidence that the process is capable of consistently delivering quality products. On ongoing basis, the source of variability is identified with process understanding and more knowledge is gained during commercialization and routine production providing assurance that process remains under control. Based on the corrective actions implemented to date and others that are to be implemented, the quality system and procedures will prevent the reoccurrence of potential variability issues on an ongoing basis. The process variation indicators such as batch records, process deviation reports, out of specifications findings, operator's comments, Defect complaints and adverse drug effects will be applied. We believe due to enhanced processes and rigorous process controls, the reduction of such incidents will continue to be reduced. The efforts to further eliminate such circumstances by investigating variability for root cause and corrective actions are ongoing.

## OBSERVATION 6

**Written production and process control procedures are not followed in the execution of production and process control functions.**

**Response:** Caraco recognizes the seriousness of the inspectional observation and have developed an aggressive action plan for ensuring substantial compliance with cGMP regulations. In this regard, we have implemented numerous changes and improvements to address deviations identified by investigators and we feel we are on target to accomplish action plan objectives within the time frames stated. We acknowledge that there were certain instances found in which all steps in the procedure were not properly documented.

We continue to use Third Party planned audits to oversee quality and operations and to conduct a gap analysis of our systems within the facility. We are conducting extensive training for all operating, laboratory, quality and management staff. The most recent audits and trainings were conducted by (b) (4) in April 2009 by three experienced auditors to provide additional support in batch record review and other areas of their expertise. The Operating staff and Supervisors have been re-trained for the following critical documents such as SOP, batch manufacturing records, and protocols. The similar training was also provided to QA inspectors and reviewers for attention to the details in the review process and identification of gaps. Another round of audit and training to assess current progress and provide further direction to our compliance program is scheduled in July 2009. We will also conduct cGMP training for manufacturing and quality personnel during this time.

The audits conducted internally and by (b) (4) have been designed to assure that not only specific individual incidences are corrected, but that the entire quality system is reviewed and the appropriate procedures for substantial cGMP compliance be instituted. To this end, numerous quality tools have been utilized to assure the systemic health of the Company.

**Corrective Actions:** The operating staff and Supervisors have been disciplined and trained to not deviate from testing and process procedures. Any deviations from procedures will result in disciplinary actions up to including termination. During the Rolling Shut Down of the Manufacturing operations from (b) (4) Quality, Regulatory Compliance, R&D and Technical Services departments conducted the re-training on SOPs and manufacturing procedures. Additionally, a process review and a gap analysis was conducted with all manufacturing department personnel. Furthermore, interactive training on technical aspects was performed for operating personnel for all aspects of our operations on the shop floor itself for continuous learning, self improvement and skill enhancement.

**Preventive Actions:** Caraco has established new procedures to ensure the compliance of our processes at various stages. For example, automated balance is being purchased in addition to the current balances in use. This will further help the operators to easily detect trend and variation during the compression process. The intention of the data is to be displayed in graphical format with identification of any results that are outside the action limits. QA personnel are pulling random samples and using an automated or suitable system, the weight, thickness and the hardness of a defined number of tablets are determined. The result of this random test will be part of the batch record review in conjunction with all other attributes to determine the batch release status. This data will also aid in case of any investigation. SOP (b) (4) (b) (4) has been implemented from April 4, 2009 to assure compliance.

**A. In process tablet weights as recorded in the Batch Record are not always reflective of actual in process weights obtained.**

For example, tablets weighing (b) (4) were obtained during in process checks of Metoprolol Tartrate, 50mg Tablets, USP, lot 80345, however these values are not recorded in the Batch Record. The tolerance range for Metoprolol Tartrate, 50mg, USP in process weights as specified in the Master Batch Record is (b) (4) to (b) (4)

**Response:** It is important to emphasize that there are a written procedure and also instructions in the batch manufacturing record for compression operator for documenting pertaining parameters from print out tickets taken during compression process. This observation relates to an individual operator's lack of documenting the obtained results according to the batch record instructions.

**Corrective Actions:** Appropriate disciplinary actions were taken against operators, Supervisor and Quality Assurance reviewer involved in the process. We feel it is important to observe that upon identification these issues were immediately corrected or addressed by Caraco. Prior to packaging, the batch cited in the observation was inspected for sorting of weight variability in the batch by Special Processing Operation (SPO (b) (4)) and upon meeting acceptance criteria it was released to market. The manufacturing process has been fully validated which demonstrated our ability to continually produce a safe, effective and potent product. Training has been provided for all operating staff for proper documentation and promptly reporting all deviations. Caraco has implemented specific actions and established procedures to ensure the compliance of our processes at various stages. Our manufacturing and Quality Assurance personnel are committed to proper documentation and verification of all in-process parameters and following procedures as written for documentation practices. Various batch records have been enhanced for better control on the process.

**Preventive Actions:** Caraco has implemented several steps to reduce any possible human intervention in physical characterization in-process testing.

- For the compression equipment set-up, Caraco has implemented the use of (b) (4) system (b) (4) tester), which automatically performs weight, thickness, and hardness tests. The supporting results obtained are printed with statistical analysis and graphical interpretation. SOP (b) (4) has been implemented from April 4, 2009.
- SOP (b) (4) have been created which describes the process by which the in-process tablet weight, hardness and thickness are tested and controlled during the compression process within batch manufacturing record specifications. The alert and action level steps for handling routine variation in parameters have been defined in the SOP when any values fall outside the specified ranges of batch record. The training will be completed prior to implementation. Please refer to a copy of SOP, Exhibit 14

- SOP (b) (4) have been created to define the procedure for (b) (4). This SOP also provide guidelines for (b) (4). The training will be completed prior to implementation. Please refer to a copy of SOP, Exhibit 15
- The position of Manufacturing Compliance has been created for oversight on routine manufacturing operations. A position is also created for trending and monitoring of in-process parameters and critical process parameters from the executed batch record.
- We have also developed a Batch Manufacturing Record checklist to capture documentation discrepancies and any oversight. This checklist is employed by Manufacturing Compliance auditor while performing batch record review to assure that all necessary documentations activities are promptly captured.

**B. SOP (b) (4) was not followed during the dispensing of inactive raw materials Lactose (b) (4) NF, (b) (4) with Lactose (b) (4) NF, (b) (4)**

**Response:** In this instance, the incorrect material and receiving number was brought to the dispensing room by the Dispensing Operator without verification of label on the drum container. Although both raw material drum containers involved in the incident had different colored vendor labels and proper identity, Operator involved in the dispensing did not check the labels. This dispensing human error led to combining of two different raw materials. The discrepancy was realized during internal review process and all the raw materials containers involved were discarded. Refer to IR08-972 Exhibit 16

**Corrective Actions:** Appropriate disciplinary actions were taken against the operator involved in the incident and terminated. As per the SOP in place at the time of the inspection, the material is required to be transferred to the dispensing room by the material handler to the dispensing operator in the room. As per revised SOP (b) (4) all items going into to dispensing rooms are checked by the material handler and are verified by the supervisor. The supervisor is signing the summary pick list to document the verification of the same. This additional check by the supervisor is to ensure that the correct materials are taken in to the dispensing room. All dispensing staff has been retrained under our revised SOP. Please refer to Exhibit 7 for Retraining Record

**Preventive Actions:** We are in the process of validating our scale integration with the (b) (4) system where each container is required to be bar code scanned prior to dispensing. The system will prevent wrong receiving number of material to be dispensed. The automated system of both scale integration and bar code scanning improvements was in the process of validation during the inspection, the expected completion date is June 30, 2009.

**2 Sufficient quantities of (b) (4) was not given to Dispensing**

**Response:** The reference cited in the observation relates to our Summary Pick List (SPL) for (b) (4). The SPL is actually the collective needs for entire material pick list required for the day's production and it is used by the material handler for transferring material to the dispensing area. The use of SPL was out of the scope of our SOP at the time of inspectional observation. As per our previous practice, the partial quantity of (b) (4) was supplied to the dispensing room and weighing of two batches of Paroxetine tablets was completed. Since sufficient amount of material was not available in the dispensing room, an additional quantity of material available in the adjacent staging area was brought into the room for completing dispensing of the batch. Upon further review of Maintenance Use and Cleaning Log of adjacent rooms as well as lot wise item trace for this receiving number, it was confirmed that dispensing of (b) (4) in two different rooms was in progress on the same day. We would like to emphasize that our review of weigh tickets and Material Pick Up List confirms that an accurate quantity of (b) (4) was dispensed for assigned batches of Paroxetine tablets, Batch no. (b) (4).

**Product Quality Impact Assessment:** The in-process blend uniformity analysis and the finished product attributes such as assay, content uniformity, and dissolution results were verified and found within established specifications. This deviation has no adverse impact on the quality of the drug product.

**Corrective Action:** All operators involved in the incident who did not follow our SOP (b) (4) (b) (4) were terminated. All dispensing operators have been retrained under on procedures.

**Preventive Action:** Caraco has revised SOP (b) (4) to provide enhanced control and timely detection of material quantity differences in actual weight versus vendor's net weight. We have revised the procedure and now as per SOP no (b) (4) the material handler takes material from the respective location. The quantity of the material taken will not be less than the quantity required in the summary pick list. The quantity in the summary pick list is verified by the supervisor at the door of the dispensing room, just before taking the material into the dispensing room. The supervisor will sign the summary pick list to document the verification of the same. Similarly after the dispensing the supervisor will verify the quantity of raw material (source container) coming out of the dispensing room.

In May 2009, we have updated our procedure and initiated (b) (4) reconciliation for APIs. Also, we have implemented additional controls by having (b) (4)

(b) (4) This ensures that the correct receiving number and the correct quantity of the required material are taken to the dispensing room and the correct amount of remaining quantity is taken back to the warehouse location. This issue will also be addressed in next version with the inclusion of individual (b) (4) bar code scanning and reconciliation for each receiving number of API and excipients by 06-30-2009. With reconciliation in addition to only one receiving no. of raw material in the dispensing room will ensure that all containers are correctly reconciled and accounted for and no material is carried over from one receiving number to another.

### 3. Source containers were not scanned.

**Response:** The bar code scanning of containers is performed based on the requirement of the number of containers being dispensed to. Due to the limitation of the (b) (4) system at the time of this observation, all source containers present in the room for dispensing may or may not be scanned based on the number of containers required for dispensed materials. For example if five source containers of the same receiving number are in the dispensing room to be dispensed into three containers (part lots), only three source containers are scanned, however all five containers are required to be visually verified for material code and receiving number.

The capability for bar code scanning for each individual source containers of the same receiving number will be functional in the (b) (4) module along with (b) (4) reconciliation by 06-30-2009. Also as per revised SOP (b) (4) prior to transferring the source containers in the dispensing room, all containers are visually checked for correct receiving number by the material handler and are verified by the supervisor. This activity is signed on the Summary Pick List. This additional check enables us to ensure that only one receiving number is taken in the room at a time and all containers in the dispensing room are of the same receiving number.

Training has been provided as a result of the revised SOP (b) (4) to all personnel in the dispensing department. Please refer to Exhibit 2

**Product Quality Impact Assessment:** The in-process analysis results including blend uniformity and the finished product attributes such as assay, content uniformity, and dissolution results were verified and found within established specifications. This deviation has no adverse impact on the quality of the drug product.

**C. Clozapine Tablets, USP, 100mg, lot 80849 was dried for (b) (4) hours. Batch instructions require (b) (4) of drying and SOP (b) (4) and (b) (4) permits continued drying at (b) (4) increments until the desired (b) (4) is achieved. Drying in additional (b) (4) increments did not occur for this lot**

**Response:** This cited observation is relating to the drying time excursion occurred due to power failure event. This is an isolated event occurred due to activation of program designed in the drying controller which led to additional drying cycle upon return of power. In this instance, the drying was performed at target temperature of (b) (4) until drying cycle of (b) (4) programmed in the logic controller. At the completion of drying cycle, the temperature sensor shut OFF; circulation fan remained ON and dryer reached to an ambient temperature and the product remained under air drying for about (b) (4). Due to power outage (power failure) event at 1 am, the dryer operation and functions were completely stopped. Upon return of power, within (b) (4) as per the logic provided in the controller, the previously set dryer program in the dryer was automatically re-started. Since the shift operating personnel to shut off the dryer was not available, the drying cycle was automatically continued as per programmed temperature cycle. During this period drying cycle was functional at target temperature for (b) (4) out of new (b) (4) (total drying time of (b) (4)) without supervision. Subsequently, the dryer was shut OFF by shift operating personnel for performing the (b) (4) testing. In this instance, as specified in the SOP, the (b) (4) testing at the completion of (b) (4)

cycle did not occur, instead, drying was started for a total of (b) (4) hours due to power outage event. The (b) (4) results were found within batch record specifications illustrating that the drying end point was reached. The power failure event was investigated, additional loss on drying tests were conducted to verify effect of excess drying on the properties of (b) (4). All in-process and finished product specifications results were found within established specifications demonstrating that there is no impact on the product characteristics. Review of batch manufacturing record, QA in-process report and Batch Packaging Records revealed that all tests conducted during manufacturing and packaging was within established limits. The batch was released for distribution upon meeting all specifications.

**Corrective Actions:** Upon review of this event, the performance of the same dryer was investigated under simulating power failure conditions. The design of experiments was conducted according to approved Change Control no. CR (b) (4) on 03-25-2009. The findings of these studies confirmed that dryer RE-starts and drying cycle is activated to original set conditions, upon return of power. Upon further review of this event, we performed a global impact assessment and as such we have changed the electrical configuration of the all dryers to be consistent within our facility. With the new design controls installed, now (b) (4) dryers will not re-start upon return of power or dryer start-up after inadvertent stoppage. In the event of any such deviation in future, both Supervisor and Facility Engineer will investigate the cause before starting the dryer.

**Preventive Actions:** SOP (b) (4), (b) (4) and (b) (4) and SOP (b) (4), (b) (4) and (b) (4), SOP (b) (4) (b) (4), (b) (4), have been expanded to provide detailed instruction for Supervisor to RE-start drying cycle for residual drying time. Upon completion of drying the residual drying period (original drying time cycle - actual drying time cycle) is calculated from the drying chart by Supervisor and verified by Quality Assurance.

Clozapine Tablets, USP, batch records have been revised to include end limits for drying times. A revised batch record specifies alert and action levels established for drying process until the final range has been achieved. In the event of exceeding drying times specified in the batch record, the applicable corrective actions to be taken are defined in the batch record.

**D. Batch Manufacturing Record compression instructions, "(b) (4)"** was not followed during compression of Metoprolol Tartrate, Tablets, USP, 25 mg lots. Four of four lots reviewed lacked documentation that this check had been performed. Examples: (b) (4)

**Corrective Actions:** Re-training was provided to all compression operators, and supervisors for paying attention to the details and following the batch record instructions Refer to Exhibit 17. During training emphasis was given for ensuring documentation that the verification of punch tightness is performed by writing it in the batch record. A copy of training record was immediately shared with FDA Inspectors. Review of batch manufacturing records, QA in-process reports and packaging records revealed that all in-process tests were conducted during manufacturing and packaging of these batches were within established limits and the batch was released for distribution upon meeting all specifications.

**Preventive Actions:** The batch records of all affected products have been revised and letter (font) size of the instruction has been highlighted to capture the instructions. In addition to this, compression operation of Metoprolol Tartrate Tablets, USP, 25 mg, has been successfully validated on (b) (4) automatic weight control tableting machine which has capability to detect and alarm an error related to lower punch tightness while the machine is in operation.

In addition to existing batch record review by Quality Assurance auditor, the position of Manufacturing Compliance is created for oversight on routine manufacturing operations to assure that batch record review is properly conducted and documented.

We would like to reaffirm that, the manufacturing operations are performed in accordance with cGMP requirements and specified process control parameters. Caraco is continuously producing finished drug products for which there is an adequate level of assurance of quality, strength, potency and purity of drug products distributed to the consumer.

**E. Review of the Batch Manufacturing Record compression section for Clonazepam Tablets, USP, 0.5 mg lot 81534 revealed the in-process hardness tests conducted between containers (b) (4) and (b) (4) resulted in five consecutive OUT OF CONTROL and OUT OF TOLERANCE test results on 8/14/08. Review of the Compression Parameters Record Sheet finds neither documented adjustments nor indication of hardness problems.**

**Response:** The cited observation is related to lack of documentation of adjustments and notations in the batch record. Review of batch manufacturing record, QA in-process report and Batch Packaging Records revealed that all tests documented in the batch record during manufacturing were within established limits. The batch was released for distribution upon meeting all specifications.

**Corrective Actions:**

- From 01-15-2009, we have enhanced scope of instructions and have implemented the additional history sheets to the BMR. The purpose was to capture documentation discrepancies and instructions for recording in the batch record that a supervisor and QA review needed to assure proper documentation. *The note specified in the batch record is - "(b) (4)*

(b) (4)

(b) (4) .

- The compression instructions in the batch records have been enhanced to specify the adjustments to be performed on machine, monitor and analyze the data within a batch when certain units within a test moving away from a target value and are repetitively approaching towards alert and action level. This continuous process verification, monitoring and trend evaluation of routine production batches with respect to the established in-house and/or regulatory specifications controls are established to demonstrate that the process is in control.

- During rolling shut down of our facility in February 2009, the documentation and cGMP training was provided by our Training Manager to all compression operators and supervisors for paying attention to the details and following batch record instructions.
- From 04-04-2009, we have implemented use of Tablet Testing System ((b) (4) tester) which automatically performs weight, thickness and hardness tests. The supporting results obtained are printed with statistical analysis and graphical interpretation. This information would allow operating staff to capture any variation.

**Preventive Actions:**

- SOP (b) (4) have been created which provide guidelines for handling routine variation in parameters within batch record specifications. The procedure describes the process by which the in-process tablet weight, hardness and thickness are to be tested and controlled during the compression process within batch manufacturing record specifications. The alert and action level steps have been defined in the SOP. This procedure also defines actions to be taken when any values fall outside the specified ranges of batch record. The training will be completed prior to implementation.
- We have also developed a Batch Record checklist to capture documentation discrepancies and any oversight. This checklist is employed by Manufacturing Compliance auditor while performing batch record review to assure that all necessary documentations activities are promptly captured.
- SOP (b) (4) have been created to define the procedure for preparation, review and analysis of trend for critical process parameters (CPP) and critical quality attributes (CQA). This SOP also provides guideline for handling out-of-trend process parameters and quality attributes, if found while review of batch manufacturing record for ongoing assurance during routine production to demonstrate that the process is in a state of control. The training will be completed prior to implementation.

**F. SOP [REDACTED] was not followed in the handling of excess quantities of raw material. IR 08-793, Dated 8-25-08 was initiated after (b) (4) showed 15 kg of Metformin HCl active raw material, Lot No. [REDACTED], could not be located in the (b) (4) Warehouse. The root cause was reported to be operators combining small amounts of one receiving number with another receiving number, which caused the stock of Metformin HCl, in [REDACTED] to become out of acceptable limits.**

**Response:** At the time of the above incident multiple receiving numbers of the same raw material were allowed per our SOP to be taken into the dispensing room as per pick list. Due to this, there was a possibility of the operator using and/or documenting one receiving number instead of another, thus creating excess or shortage out of acceptable limits between each receiving number. However the SOP specifically stated that receiving numbers were not to be combined. Considering the excess material received at the time of receipt and variability of the weighing scales used at the point of receipt and at the time of dispensing, tare weight differences as claimed by vendor as against actual

tare weight, the root cause for the excess material is attributed to combing of multiple receiving numbers during dispensing and excess material received from the vendor.

### Corrective and Preventive Actions

As per revised SOP (b) (4), effective November 2008, only one receiving number of any raw material is to be taken into the dispensing room at the time. This ensures accurate accountability of each receiving number and enabled us to reconcile each receiving number when the entire quantity of the receiving number is consumed. Also, as only one receiving number is taken into the room at a time there is no possibility of combining one receiving number with another receiving number. Since November 2008, we have no incidents of combined receiving numbers issued for any batch.

In May 2009, we have updated our procedure and initiated (b) (4) reconciliation for APIs. Also, we have introduced additional controls by having the supervisor verify each receiving number before the material enters the dispensing room and after completion of the dispensing activity the supervisor verifies the material going back to the warehouse. This ensures that the correct receiving number and the correct quantity of the required material are taken to the dispensing room and the correct amount of remaining quantity is taken back to the warehouse location. This issue will also be addressed in (b) (4) next version with the inclusion of individual (b) (4) bar code scanning and (b) (4) reconciliation for each receiving number of API and excipients 06-30-2009 With (b) (4) reconciliation in addition to allowing only one receiving no. of raw material in the dispensing room will ensure that all containers are correctly reconciled and accounted for and no material is carried over from one receiving number to another.

The (b) (4) reconciliation, control on material movement, control on drum use will provide further assurance of material reconciliation at any given time. A review of the related investigation shows that this event do not have any adverse impact on product quality, as a result of previous practices. The implementation of revised SOP (b) (4) effective from May 26, 2009, in addition to the training of all personnel involved, replacement of supervision gives us a high level of assurance that this type of incident will be prevented.

Since November 2008, we have revised SOP (b) (4) the revised procedure allows dispensing of only one receiving number of either an excipient or API in the dispensing room at a time for any particular lot. This revised procedure allowed us to reconcile without involving another receiver number and eliminate any possible discrepancy between receiver numbers for a particular lot.

### G. According to SOP (b) (4)

(b) (4) the (b) (4) result printout ticket for this lot is to be recorded with product specific information including product name, lot number, part lot number, and number of hours of total drying at the time of the test The (b) (4) print out ticket for Clozapine Tablets, USP, 100mg, lot 80849 is recorded as “(b) (4) (b) (4)”, though it is reflective of drying after (b) (4) hours active drying and (b) (4) of air drying.

**Response:** The documentation of drying times in the batch record and chart recorder was accurate. The time indicated on the (b) (4) print out tickets that (b) (4) test was recorded as (b) (4) instead of

(b) (4) The documentation oversight of recording (b) (4) on (b) (4) tickets was not captured during review process. This was an isolated incident due to human error for proper documentation. Review of batch manufacturing record, QA in-process report and Batch Packaging Records revealed that all in-process tests conducted during manufacturing and packaging was within established limits. The batch was released for distribution upon meeting all specifications.

**Corrective Actions:** We have also completed re-training of our operating staff with emphasis on documentation practices. Training was completed on Refer to a copy of Training Record, Exhibit 17

**Preventive Actions:** We have also developed a Batch Record checklist to capture documentation discrepancies and any oversight. This checklist is employed by Manufacturing Compliance auditor while performing batch record review to assure that all necessary documentations activities are promptly captured. We anticipate this will eliminate much of the variability found during internal audits.

**H There is no documentation to support QA approval to proceed when temperatures in the compression room exceeded (b) (4) on 7 occasions during compression of Metoprolol Tartrate, 50mg Tablets, USP, lot 80345 as required per production Batch Record instructions.**

**Response:** During QA review of batch record, it was found that interim QA approval for temperature exceeding (b) (4) was not obtained at the time of manufacturing of the batch. The compression was performed without any product defects such as picking and sticking. The in-process visual inspection report of compressed tablets at the beginning, middle and end of process indicated that no product defects were observed.

**Corrective Action:** Both Manufacturing and supervisors were required to ensure on-line verification that all batch record parameters are within specifications. Training was provided to all compression operators and supervisors to pay attention to the details and follow batch record instructions. Refer to Exhibit 17. A copy of training record was shared with FDA Inspector. Review of the batch manufacturing record, QA in-process report and Batch Packaging Record revealed that all tests conducted during manufacturing and packaging was within established limits. The batch was released for distribution upon meeting all specifications.

**Preventive Action:** The CAPA was issued to update remaining strength of Metoprolol Tartrate Tablets batch records. In addition to existing batch record review by Quality Assurance auditor, the position of Manufacturing Compliance is created for oversight on routine manufacturing operations to assure that batch record review is properly conducted and documented.

## OBSERVATION 7

**Batch production and control records do not include the weights and measures of components used in the course of processing each batch of drug product produced.**

**Master Batch Records do not contain complete weight records of dispensed material for the following:**

**A. Digoxin Tablets, USP, 0.25mg, Lot No. 90018**

**B. Lactose Anhydrous, NF, (b) (4), Lot No. (b) (4) dispensed for Paroxetine Lot #82576**

**Response:** In this instance, the weighing tickets of weighed materials were not found as those were misplaced or lost. Review of batch manufacturing record, QA in-process report and packaging records revealed that all tests conducted during manufacturing and packaging was within established limits. The batch was released for distribution upon meeting all specifications. Extensive search was conducted and upon verification of lot-wise item trace, material pick up list, accurate quantity of Digoxin and (b) (4) were dispensed and used in the respective batches.

**Corrective Actions:** All personnel are re-trained for awareness of this event for verifying that all associated documents of the batch records are returned to the batch record packet. Please refer to a copy of Training Record in Exhibit 18.

**Preventive Actions:** We have also developed a Batch Manufacturing Record checklist to capture documentation discrepancies and any oversight. This checklist is employed by Manufacturing Compliance auditor while performing batch record review to assure that all necessary documentations activities are promptly captured. SOP (b) (4) was implemented during the FDA inspection for the manual "(b) (4) reconciliation". The SOP will be revised and enhanced upon the implementation of our scale integration system for both API and excipients. This procedure will better track the usage of a receiving number and provide a running inventory, by each container. The automated system of both scale integration and bar code scanning improvements was also in the process of validation during the inspection, the expected completion date is June 30, 2009. Further enhancement is being validated in the (b) (4) system for the scale integration to capture the weight during weighing which will assist "on line" reconciliation of material.

(b) (4) bar code scanning improvements will provide the assurance that irrespective of receiving number, each drum has to be scanned otherwise the system will not allow progress. This was also in the process of being validated during the inspection process and will be completed by June 30, 2009. Once implemented this system will automatically reconcile each drum in our system and an automatic adjustment is made if required at the time of reconciliation.

## OBSERVATION 8

**Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product**

### Response:

Caraco recognizes that an overall review of system and process performance is a valuable tool. We have completed comprehensive review of critical process parameters and quality attributes evaluations for all products manufactured at Caraco. The conclusions of the finding were documented in (b) (4) approved on January 14, 2009. Specific preventive actions were identified and it is being implemented on an ongoing basis as required.

**a- End limits on drying have not been established for the drying of Clozapine Tablets, USP, 100mg. For example, during (b) (4) of lot (b) (4) of active (b) (4) drying occurred, with an additional (b) (4) of (b) (4) inside the (b) (4). The Batch Manufacturing Record for Clozapine requires (b) (4) of drying, though no end limit is specified. There is no data to support the acceptability of this (b) (4) after (b) (4) of (b) (4) in addition to the (b) (4) experienced by this lot**

**Response:** Caraco's approved batch manufacturing record of Clozapine Tablets; 100 mg provide instructions for setting the time limit for performing the initial drying to check the (b) (4) (b) (4) test. It also detailed instructions for additional drying to be performed until desired (b) (4) results are obtained. The drying is performed with consideration of (b) (4) as the end point test. The contributing factor for the extended time in the above cited instance was primarily due to power failure to the drying equipment on a weekend. When the power was restored the dryer started automatically and the drying process was continued for additional time. The impact of additional drying time was assessed by verifying (b) (4) testing across the batch. All (b) (4) results were within batch record specifications and hence no product impact was determined. Clozapine Tablets, USP, batch records have been revised to include end limits for drying times. A revised batch record also specifies alert and action levels established for the drying process until the final (b) (4) range has been established. In the event of the drying time excursions corrective actions to be taken are defined. In certain instances, when the action levels as specified in the batch record are exceeded, an event is generated and a product quality impact assessment is performed.

**Corrective Actions:** All other dryers were verified to assure that similar incident of power failure will not produce the same result.

**Preventive Action:** The electrical configurations of all dryers within our facility have been changed. With the new design control installed, dryers will not re-start upon return of power or dryer start-up after inadvertent stoppage. These changes will prevent potential for over drying of the drug product. In the event of any deviation, both Supervisor and Facility Engineer will investigate the cause of alarm before starting the dryer. The dryer will be manually re-started by Supervisor for the remaining period of drying cycle at the specified temperature as required. This instruction has been enhanced in SOP. Refer to a copy of SOP (b) (4) (b) (4) and (b) (4) "Exhibit 19

b- Time limits have not been established for the rate of addition of (b) (4) material to the (b) (4) used in (b) (4) Digoxin (b) (4) (for 0.125mg tablets, USP) as observed in the completed batch record, lot 81404. (b) (4) are recorded by operators performing this operation in the batch record. Different rates of addition were stated to affect (b) (4) (b) (4) of the (b) (4) material.

**Response:**

Review of batch manufacturing record, QA in-process report and Batch Packaging Records revealed that all tests conducted during manufacturing and packaging was within established limits. The batch was released for distribution upon meeting all specifications.

The (b) (4) in current use are (b) (4) equipment and the loading of material for (b) (4) varies based on the material that is being (b) (4) as such different operators may load the equipment at slightly different rates. Prior to the commencement of this inspection Caraco has introduced several steps to reduce human intervention in the (b) (4) operation process.

**Corrective Actions:** The (b) (4) used in the (b) (4) process has been reviewed and guideline on controlling the manual feeding process by revising instructions in the batch records. In addition to this, SOP, (b) (4) has been updated to include the instructions for performing (b) (4) process

**Preventive Action:** We are establishing the use of the (b) (4) with (b) (4) feeder. This is a similar (b) (4) except it has controlled feed rate features for continuous process enhancement and establishing better control on the particle size distribution of (b) (4) blend and improves quality of (b) (4). The (b) (4) feeder features assists in controlling the feed rate for (b) (4) process and reduces potential for variability in (b) (4) loading and transfer of (b) (4) during the (b) (4) process. The actual performance of (b) (4) and controls installed for (b) (4) operation were shown to the FDA Inspectors during the facility walk-through. For trending purposes Caraco has initiated the (b) (4) size distribution by (b) (4) and as (b) (4) of final blend for routine production batches from 01-12-2009. This testing and monitoring is performed by the Quality Control unit.

## BSERVATION 9

Deviations from written production and process control procedures are not justified.

Specifically,

Performance Qualification of the (b) (4) asset # (b) (4) observed in use in metal detecting CMT lot 90131 was found inconsistent with routine metal detection use in that the challenge pucks used to determine proper functioning of the unit prior to use, and consistent with current practice as observed on 3/16/09, are not the same sizes as those used in the Performance Qualification of this same asset

During the compression of CMT lot 90131 on 3/16/09 the (b) (4) in use were (b) (4)

**Response:** Caraco Validation Master Plan (VMP) requires that all system are validated/ qualified in accordance to the intended use.

The (b) (4) Asset no (b) (4) was qualified according to the protocol no. QP (b) (4) The IQ and OQ were performed. As per suppliers recommendations, equipment is required to calibrated prior to each use with the following pucks, (b) (4) (b) (4) the qualification and calibration was performed as stated by the vendor. Caraco has implemented the change in SOP in which the routine calibration was required to be performed by using the following pucks, (b) (4) (b) (4)

The calibration pucks referred in the approved SOP has smaller diameter of metal particle than suppliers recommendation, thus, has higher level of sensitivity and capability to detect with high efficiency. Therefore, this change had no impact on the equipment qualification or calibration status of any product passed using this detector.

**Corrective Action:** The performance qualification of (b) (4) Asset no (b) (4) was successfully executed using the following metal calibration pucks (b) (4) (b) (4) Caraco will continue to use same calibration pucks for each use as used in the qualification. All affected personnel have being retrained on the requirements of the protocol.

**Preventive action:** SOP (b) (4) has been revised for enhancement for documenting thorough impact analysis of any change and subsequent product quality impact assessment. Refer to Exhibit 20

## QUALITY SYSTEM

### OBSERVATION 10

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

The responsibilities and procedures applicable to the quality control unit are defined in our approved SOP (b) (4), Rev. (b) (4) effective from 05-25-2007. This SOP defines the functions and responsibilities of the Quality Unit which includes the Quality Assurance department, the Quality Control department, and in certain circumstances, the Regulatory Affairs department. Refer to Exhibit 21. It is the responsibility of Quality Assurance for management of the Change Control Program for all cGMP documentation, facilities, utilities, control systems, and equipment. Each change control is always reviewed and final approved by Quality Assurance.

**Specifically,**

**A. Change control record, CR 08-317, a permanent change reflecting the batch charge calculations of active and inactive materials, did not fully evaluate the batch impact of the change prior to implementation according to SOP (b) (4). (b) (4) Specifically, the dispensing of Digoxin, USP, active pharmaceutical ingredient, for Digoxin Tablets, USP, 0.125mg LOT 81404, under this Change Control resulted in (b) (4) (b) (4) dispensed containers of the material instead of the required (b) (4) dispensed containers per the Batch Master Record.**

**Response:** The role of the quality unit is as defined above, and as noted both OA and OC approved the change control referenced, however we have revised SOP (b) (4) to provide to clarify the role of individual department responsibilities. It is to be noted that the Quality Assurance is responsible for the product quality impact assessment with consideration of input from subject matter experts. The details of how this will be accomplished is provided in the Exhibit 20

**Corrective Action:** As part of further quality impact assessment due to change in procedure for dispensing activity all Digoxin Tablets manufactured following the instructions provided on change request CR # 08-317 was evaluated to determine if the batch manufactured meets the required quality and also that the API was dispensed in accordance with the Batch Master Record requirements.

**Preventive Action:** The Responsibility section of SOP (b) (4) has been enhanced to provide clarity for the responsibility and with structured evaluation process of any change. All applicable individuals and department representatives will be involved upfront in all the changes that impact the Chemistry, Manufacturing, Equipments, Development, and Regulatory Affairs submission. This will ensure that a scientific evaluation/discussion is made to determine the change request requirements and to ensure that the required approval process is performed.

Required check list for impact evaluation with recommendation is now included in the revised change control procedure. The detailed process flow and decision path is also included in the SOP. Impact assessment of change of bill of material from the batch manufacturing record and the need for change is addressed in the revised SOP. This improvement is designed to assure that the

required weight quantities of materials are displayed in the Material Pick Up list for dispensing the material according to the batch record.

B. SOP (b) (4) " was not followed in that training was not conducted "in a timely manner" and any documented extension was not requested until 3 months past the due date. CAR 08- 030 issued 5/15/08, CAR 08-043 issued 5/22/08, CAR 08-048 issued 6/12/08, and CAR 08-110 issued 8/27/08, were held until 11/7/08 when training for compression personnel on the proper tablet press setup, cleaning of tablet presses, and feeder platform set up deemed to prevent repeat issues of metal contamination, black spots and thick and thin tablet issues noted in manufactured Rx drug products. Likewise CAR08-074 issued 6/13/08 was held until 2/10/09 when training for compression personnel on the set up checklists after Type 1 and Type 2 cleaning were held. Examples include: Metoprolol Tartrate USP lot 81560, Clonazepam 0.5 mg lot 81597, Clonazepam 0.5 mg lot 81532

**Response:** This observation is related to the lag time to close the applicable CAPAs and documentation for timely completion of training. Our CAPA tracking system is enhanced for review of open CAPAs on a (b) (4) basis. QA personnel are responsible for tracking the open CAPA with an impact analysis. In case of CAPA is not closed within timeframe specified, QA is responsible to escalate to management representative in Quality Review Board (QRB) meeting for further action. The impact analysis of extending CAPA is performed prior to extending the timeframe. Furthermore, the Quality Management System (QMS) module is used to escalate CAPA. The work flow message is to be sent to each level of the quality management up to the CEO, if required to inform the predetermined implementation date has been or is approaching its deadline. The design of QMS has been successfully tested and the initial results are promising for successful implementation.

Event and investigation SOP (b) (4) is revised to include the completion of action before batch release. In case of short term action or training needs, QA ensures that such specific action is completed prior to release of a batch.

**Corrective Action:** SOP (b) (4) was revised in February 2009 to address this concern and training was provided. Refer to Exhibit 22 Caraco has discontinued opening CAPA where the training of personnel has been identified as a contributing factor in the cause of an investigation. The present requirement is that the training must be completed prior to closing of the investigation and that the individual who requires the re-training is not allowed to perform the same procedure until such re-training and evaluation has been successfully completed and documented.

Our SOP (b) (4) has been revised to include below:

- (b) (4)

• (b) (4)

**Preventive Actions:** SOP (b) (4) is revised to include (b) (4). In addition, new responsibilities have been added to the role of the Quality Unit which includes communication meetings to monitor CAPA progress and added time frame for closure. Refer to Exhibit 22 SOP (b) (4).

Trending of the CAPA is also initiated for studying the effectiveness and completion on time

C. SOP (b) (4), was not followed in that, per section (b) (4) an effectiveness check of CAPA record, CAR 08-038 (pertaining to the removal of the tablet (b) (4) during compression set-up and troubleshooting), dated 5/26/08 was not requested or performed though monitoring of the CAPA through incidents and complaints was possible.

Specifically Clonazepam 0.5mg Tablets, USP lot 81529 received a complaint and Metoprolol Tartrate 50mg, USP, lot 81102 was the subject of an incident after implementation of CAR 08-038. Both investigations reference the

**Response:** Event and investigation SOP always included the need for determination of the root cause or probable cause. Based on identified root cause or most probable cause applicable, a CAPA is generated. CAPAs are also trended for timeline implementation and effectiveness study. QA is responsible for review of CAPA its timely completion and effectiveness

Our current CAPA system does not have a systemic identifier for each incident which could occur, so our word search may not have always capture the CAPA in all cases. We have designed the QMS system which has pre-defined identifier. This word library will allow us to identify each incident and or CAPA by common description which will allow us to perform the CAPA effectiveness through database query during any investigation.

In case of non-effective the CAPA, discussion with technical team and management will take place for further enhancement and action which are deemed needed like stoppage of manufacturing, equipment, process change under regulatory purview, re-qualification, re-validation, if needed

**Corrective Actions:** All CAPA items have been reviewed to assure that they are being adequately tracked and that re-occurrence of similar incidents with similar CAPA is investigated for effectiveness. Appropriate actions will be taken at the completion of such event investigation

SOP (b) (4) and associated form no. (b) (4) have been revised. This procedure describes in detail the effectiveness check at the time of QA approval of CAPA record. Section (b) (4) states that (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

A copy

of revised SOP, form and training documents are included in this response as referred in SOP (b) (4) and Form (b) (4). Refer to Exhibit 22.

D. SOP, (b) (4), was not followed in that Approval by the Director of Technical (or designee) was not obtained for the compression of Metoprolol Tartrate, 50mg tablets, USP lot 80959 using the (b) (4) prior to actual batch compression.

Specifically, Change Control request, CR 08-219, to allow for the compression of Metoprolol Tartrate, 50mg tablets, USP using the (b) (4) was not approved prior to use in compression activities. This change control was originally initiated and approved for (b) (4) lots of Metoprolol Tartrate, 50mg tablets, USP (not including lot 80959).

**Response:** SOP (b) (4) always included the need for review of change control by QA and its impact on the various activities of manufacturing, quality, and regulatory impact. During this instance, an additional batch was included in the temporary change control for the compression purpose. The documentation of signature of Director of Quality (or Designee) was not obtained. This person is no longer working with Company.

QA document controller is responsible for issuing the Batch Master Record (BMR) with required correction in particular step with specific instruction in case of temporary change based on approved change control. Temporary change control will clearly specify the affected lots and will be maintained by Document Control to assure that further BMRs are not referred in the same change control.

All the concerned persons are trained to follow the written instructions in the BMR specifically emphasis on the batch record steps. Although, a temporary change control is generated but specific steps are not changed, the BMR steps must be followed. The enhancements in this SOP and the training of users will prevent such deviation in documentation practices.

The position of Manufacturing Compliance is created for oversight on routine manufacturing operations for batch record review and enhances the compliance.

E. A QA Hold was not placed on Citalopram HBr Tablets, 10mg, lot 80795A, subject to Special Processing Operation, SPO- 08-491 as required per SOP, (b) (4)

**Response:** In this particular situation, packaging of the batch was in progress under Special Packaging Operation (SPO No. 08-491) which was created for inspection of appearance of tablets. While packaging a Notice of Event occurred and documented directly on the SPO. The root cause for the event was attributed to vibration of tablets against the stainless steel plate of channel counter

which was not covered properly. The root cause for the event was immediately identified and corrective actions were implemented. Since The execution of the SPO 08-491 for the inspection of the batch was already in progress and this prevents the release of the batch until SPO have been successfully completed.

**Corrective and Preventive Action:** All Quality Assurance personnel are re-trained for following the written procedures. Refer to Exhibit 23 for Training Record

**Preventive Action:** SOP (b) (4) has been enhanced for providing more clarity that any product at any processing steps involved in an event must be placed on QA hold in the (b) (4) while the processing is allowed to continue, once the root cause has been identified and corrective action has been determined The QA hold in the (b) (4) will be maintained until an event has been resolved and closed. Refer to Exhibit 24

**F. SOP (b) (4) was not followed to ensure batches are not released for distribution prior to closure of an incident Specifically, IRO9-067, in which 1.352kg of (b) (4) Digoxin, USP, lot 82855, was missing from the (b) (4) Warehouse. The final Digoxin Investigation list provided on 4/7/09 contains (b) (4) lots associated in IR 09-067, of which, 102 lots were indicated to have been released into distribution.**

**Response:** The investigation of any discrepancy and a failure of any of our product require an impact analysis and from this analysis the scope of the investigation is determined at the preliminary stage. The extension to other batches is dependent on the root cause or probable root cause. This provision is clearly defined in our SOP (b) (4). Our SOP (b) (4) also requires that an interim report and product quality impact assessment must be completed before a batch is released while the other aspect of the investigation is ongoing. In this specific instance, an interim report was prepared and product quality impact assessment was also completed. In addition, all released lots were tested and confirmed that they were free of any foreign materials. A copy of the report was presented to the inspectors during the inspection.

The rationale for extension and selection of impacted batches is solely based on the inspection findings and judgment based on scientific rationale. As a result of the discussion we had with the FDA investigators during the inspection, and upon further evaluation, verification and identification of all materials, the bracketing of the affected drug products from January 9, 2009 to February 10, 2009 was extended by eleven more days as agreed with the Agency. December 30, 2008 was the date of (b) (4) of Digoxin material and is considered the starting bracket and February 10, 2009 was chosen and documented as the end bracketing date based on all the physical and thorough inspections that had been performed. The time period covered encompasses a total of (b) (4). This period was determined (b) (4) times of normal dispensing cycle for material processing. We believed the rational for selecting the date range for testing of all products within this period was appropriate and justified. This time period is a bracketed period during which completion of all critical activities for search and investigation was focused. A thorough review of activities conducted at both the manufacturing site and the dispensing storage facility was also conducted. During this period, additional sampling and testing plan was included to cover the affected time period. All drug products tested from this period were found to be free of Digoxin or any foreign materials.

We recognize that the product quality impact assessment with supporting data demonstrates the safety and quality attributes of the drug product must be completed before any batch is released. We have revised and enhanced our SOP (b) (4) to more clearly define the requirements that must be completed prior to the release of the batch that may have been associated with an event.

G. SOP (b) (4) does not describe the procedure for 100% inspection.

1. On 3/16/09, an operator was observed inspecting a large pile of Metformin HC1 Tablets, USP, 500mg, Lot No. 82742, in a scoop rather than a clear inspection tray.
2. On 3/16/09 we observed an operator inspecting Allopurinol Tablet lot 90260 using a scoop rather than the inspection tray reportedly called for.

**Response:**

SOP (b) (4) was revised on the same day of the FDA observation. Training was completed and was implemented to provide manufacturing operators the procedures for performing the 100% visual inspection of tablets, capsules, blend ingredients and raw materials using the appropriate tools such as flip-over plastic trays along with clean, lined, stainless steel trays or plastic trays.

H. SOP (b) (4) does not describe the procedure the QA specialist should follow when performing the visual AQL inspections. On 3/12/09, Digoxin 0.25mg tablets, Lot #90187, was being sorted according to (b) (4) for black specks.

The QA specialist was observed scooping tablets with gloved hands and inspecting the tablets in her palm for all possible critical, major and minor defects, including but not limited to, size variation and soft/low weight tablets.

SOP "SOP (b) (4) does not describe the procedure the QA specialist should follow when performing the visual AQL inspections. On 3/12/09, Digoxin 0.25mg tablets, Lot #90187, was being sorted according to SPO (b) (4) for black specs. The QA specialist was observed scooping tablets with gloved hands and inspecting the tablets in her palm for all possible critical, major and minor defects, including but not limited to, size variation and soft/low weights.

**Response:**

To provide simplicity and ease of use we have created specific new procedure SOP (b) (4) which provides instructions for performing inspection by using appropriate tools such as the plastic inspection trays and lined stainless steel trays. At the time of the inspection, the procedure in use at the time SOP (b) (4) did not specify the actual techniques used in performing the 100 % AQL inspections. The scoops are necessary for transferring the bulk products to the lined stainless steel inspections trays for inspection. However, scoops should not have been used as a platform to perform visual inspection of the drug product.

## OBSERVATION 11

**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 batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.**

**The investigation of 1.352kg of missing (b) (4) Digoxin, USP, Lot No (b) (4) IR 09-067, did not extend to all other drug products that may have been associated with the incident**

**Response:** The investigation of any discrepancy and a failure of any of our product require an impact analysis and from this analysis the scope of the investigation is determined at the preliminary stage. The extension to other batches is dependent on the root cause or probable root cause. This provision is clearly defined in our SOP (b) (4). Our SOP (b) (4) also requires that an interim report and product quality impact assessment must be completed before a batch is released while the other aspect of the investigation is ongoing. In this specific instance, an interim report was prepared and product quality impact assessment was also completed. In addition, all released lots were tested and confirmed that they were free of any foreign materials. A copy of the report was presented to the inspectors during the inspection.

The rationale for extension and selection of impacted batches is solely based on the inspection findings and judgment based on scientific rationale. As a result of the discussion we had with the FDA investigators during the inspection, and upon further evaluation, verification and identification of all materials, the bracketing of the affected drug products from January 9, 2009 to February 10, 2009 was extended by eleven more days as agreed with the Agency. December 30, 2008 was the date of (b) (4) of Digoxin material and is considered the starting bracket and February 10, 2009 was chosen and documented as the end bracketing date based on all the physical and thorough inspections that had been performed. The time period covered encompasses a total of (b) (4). This period was determined (b) (4) of normal dispensing cycle for material processing. We believed the rationale for selecting the date range for testing of all products within this period was appropriate and justified. This time period is a bracketed period during which completion of all critical activities for search and investigation was focused. A thorough review of activities conducted at both the manufacturing site and the dispensing storage facility was also conducted. During this period, additional sampling and testing plan was included to cover the affected time period. All drug products tested to date from this period were found to be free of Digoxin or any foreign materials.

## OBSERVATION 12

**Individuals responsible for supervising the processing of a drug product lack the training and experience to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.**

**Response:** Caraco has taken steps to ensure that all personnel obtain adequate training prior to performing assigned job responsibilities. Where an incident has occurred due to human error, corrective action is taken in the form of coaching, retraining, discipline including suspension and termination. It is important to note that personnel involved in an incident are documented during the

course of an investigation. The investigation database is checked to determine if the same individual had been involved in similar incidents in the past one year. The nature and circumstances around the incident is evaluated to determine, if the procedure is clear, and if the individual clearly understands the procedure to determine what kind of action is required. Caraco also performed a rolling shut down for each process area in February 2009 whereas training and testing of all SOPs were performed. It routinely trains its staff on ongoing basis.

**Corrective Action:** Personnel are re-trained, or other actions are taken dependent on the nature of the incident and the historical performance of the individual.

**Preventive Action:** The applicable training SOP's are routinely reviewed and personnel trained accordingly. Generally, training and SOPs are revised to provide clarity and specific requirement for demonstrating comprehension of our procedures. In addition to Supervisor's or their designee must attest the individuals are qualified to perform the assigned responsibility.

**Citalopram HBr Tablet 40 mg lot 81940A was released and distributed after a newly trained QA Supervisor reportedly was confused and released this lot based on the in-process (b) (4) (b) (4) results, dated 9/16/08, and not based on the final product analysis report dated 12/5/08 which reported failed dissolution results.**

**Response:** The root cause of this incident was the inadequate training of the involved QA specialist at the time when the specialist was assigned to this function. She was new to the process paper work which led to the verification error pertaining to the product meeting QC release specifications for dissolution. The QA specialist is a long time valued employee with a previous experience in releasing raw materials. She has been with the Company for over six years. All products released by her prior to the incident were reviewed and no issues were discovered.

All QA personnel involved in the release of product for distribution have been re-trained on SOP [redacted] and its associated Form (b) (4) [redacted]. According to the SOP, any person new to the QA release function, regardless of tenure are trained in this SOP (b) (4) and effectiveness of that training is verified over the [redacted] of performing this function. Effectiveness (b) (4) is ensured by having a second person review the batch information and release check list (Form (b) (4) prior to actual release for distribution. SOP [redacted] has been updated and now requires a QA Hold to be issued at the onset of any Incident Tracking Sheet within Caraco's [redacted] system.

**OBSERVATION 13**

**Written records of investigation of a drug complaint do not include the findings of the investigation and the follow-up.**

**Specifically,**

**Complaint investigations into the following were not completely evaluated. For example:**

**A. Digoxin 0.125mg Tablets, USP, lot 81404 was the subject of both a complaint and an ADE as follows:**

**1. Complaint 08-176 was received on 12-04-08 for size and appearance variation. Retain samples (R1, R2, and R3) were evaluated noting: 19, 13, and 26 tablets from each bottle respectively with "Size Variation". There is no record that the 58 isolated tablets with size variation were further weighed or analyzed before the complaint file was closed 1-15-09.**

**2. ADE 08-184 was received on 11 -10-08, and involved hospitalization, with both labeled and unlabeled events reported. QC Testing of retained samples revealed the potency of selected individual tablets ranged from (b) (4) to (b) (4) of the labeled claim of the Digoxin 0.125mg tablets, USP.**

**No Health Hazard Evaluation on the effect of consuming tablets with individual assay values of (b) (4) to (b) (4) was performed on this marketed lot prior to the closing of this ADE investigation file on 1-23-09 with QA/RA confirmation on 3/02/09.**

**B. Digoxin 0.125mg Tablets, USP, lot 80771A was the subject of both a complaint and an ADE as follows: Adverse Drug Event #08-101 was received on 7/1/08 from a patient who experienced increased seizures, lips tingling, lightheadedness, and difficulties concentrating 2-3 weeks after taking this drug. Complaint #08-094 was received on 7/2/08 due to large tablets. An investigation was conducted and (b) (4) of (b) (4) complaint sample tablets was out of tolerance for high weight No action was taken as a result of the OOT finding. The complaint file was originally closed on 9/4/08.**

**C. Complaint #08-149 was received on 9/30/08 for Clonazepam 0.5mg tablet Lot #81529A due to variation in tablet size.**

**Retain samples were evaluated (R1, R2, and R3) which noted one tablet in R3 was out of tolerance for low weight Complaint samples were evaluated: 3/9 tablets were OOT for low weight and [redacted] tablets were OOT for low thickness.' No further action was taken as a result of the OOT findings. The complaint file was originally closed on 11/10/08.**

**D. Complaint COM 08-095 was received 7-02-08 for oversized Mirtazapine 30mg tablets, USP from lot 72694A.**

**Specifically, the complainant indicated that "5 tablets in the bottle were larger and they jammed the equipment". An evaluation of the complaint sample revealed that 3 units were out of tolerance for weight as specified in the Batch Master Record. No further action was taken as a result of the findings as listed above.**

**E. Clozapine Tablets, 100mg USP, lot 80849 was the subject of 3 complaints (08-079, 08-080,08-120) within 2 months (6- 7/2008) for broken tablets in this finished product The complaint investigations resulted in a review of the retained samples for this lot, and the isolation of a broken tablet and 3 chipped tablets. A batch record review was also performed indicating that [redacted] of excess drying was incurred during drying of this lot as a result of a power failure. The written investigation into each of the 3 complaints fails to address the excess drying, and any further analysis of the retained samples as a result of the chipped and broken tablet**

findings.

F. Complaint COM 08-083 dated 6/16/08 for Metoprolol Tartrate 25 mg Tablets lot 80658A for oversized tablets was the 11th of 14 events associated with tablet press # (b) (4). A problem with the scraper was documented at the beginning of the run. Returned samples were found to exceed Caraco's weight and thickness tolerances by over (b) (4). Retain samples were pulled on 7/24/08 (80658A) and again on 8/6/08 (80658B). Addendums were added to the investigation on 12/16/08 and on 2/12/09.

G. Complaint COM 08-169 dated 11/20/08 for Metoprolol Tartrate 50 mg Tablets lot 81786A for oversized tablets was the 5th Metoprolol complaint, the 15th overall complaint and the 8th incident for press # (b) (4) related to size received in 2008. Five hardness adjustments were made during the compression of this lot and a portion of this lot was subject of a 100% visual inspection due to soft and imperfect tablets being present. A returned complaint tablet was documented as outside Caraco's thickness range.

H. Complaint COM 09-006 dated 1/29/09 for Metoprolol Tartrate 25 mg Tablets lot 81739A for oversized tablets was the 12th of 14 events associated with tablet press #28840128. Problems with the feed frame were documented at the beginning and the middle of the run. The complaint sample weighed well in excess of Caraco's upper tolerance.

**Response:**

Caraco has consistently investigated any complaint received and the data obtained is evaluated against internal control specifications and USP acceptance criteria for weight variation and/or content uniformity, as applicable. If Caraco finds any result out of acceptable internal control specification but within the USP limits, the investigation is generally closed, however if the result is out of the USP limit, a Health Hazard Assessment (HHA) is performed requiring field alert for the specific product distributed to market. The review of the complaints investigation and adverse drug effects investigation are cross referenced to determine any relationship. With the initiation of QMS, these will no longer be monitored in separated databases which will improve the analysis of the relationship.

With reference to Observation 13A, due to the misinterpretation of the written instruction of the specific test requirements, the QA Technician did not perform the weight variation on the (b) (4) isolated tablets. However, these tablets were separately retained in the container. During the discussion with the Agency, the omission of weight variability testing was discovered, hence, the complaint file was re-opened and required testing was performed. A total of (b) (4) tablets were found to be (b) (4) above the upper tolerance limit (b) (4). Upon analytical testing, the content uniformity results were found to be within the finished product specifications.

With reference to Observation 13D, the weight limit of the Mirtazapine tablets coated tablet is (b) (4). (b) (4) The complaint samples returned by the customer were found to be (b) (4) and (b) (4). The highest weight of the tablet returned by the customer was (b) (4) which is above the upper tolerance limit; however, it was considered within USP (b) (4). (b) (4)

**Corrective Action:** Since March 22, 2009, Caraco has performed HHA for any complaint in which Caraco tolerance limits have been exceeded. Initially the Health Hazard Assessment (HHA) for complaints was not performed when the weight of the tablet was found within the USP weight variation limit. Going forward, Caraco will perform HHA. The action to be

(b) (4)

(b) (4) All actions are documented.

**Preventive Action:** Caraco has revised procedure SOP (b) (4)

(b) (4) Refer to Exhibit 25 for defining testing protocol based on the nature and type of a complaint. Any dosage unit found outside Caraco's approved specifications is evaluated for laboratory testing and Health Hazard Assessment as defined in the procedure. Any batch of the specific product that has been distributed to market and is found outside the USP or regulatory specifications requires a Field Alert.

With reference to Observation 13E, all in-process analysis and finished product test results of Clozapine Tablets, 100 mg, batch were within established specifications. The in-process control parameter such as (b) (4) was within specifications, we believed, the excess drying time had no correlation with the chipped or broken tablets. We continue to monitor and evaluate the trend for this product and appropriate actions will be taken.

With reference to Observations 13B, C, F, G and H the following corrective and preventive actions have been implemented. Based on the corrective actions implemented to date and others that are to be implemented, the quality system and procedures will prevent the reoccurrence of an increase in size variation issues on an ongoing basis. We believe due to enhanced processes and rigorous process controls, the reduction of such incidents will continue to be reduced. Investigations and efforts to further eliminate such circumstances are ongoing.

- Since January 2009, both Metoprolol 50 mg round and 25 mg products as a precautionary measure were sorted on our automatic equipment for detecting and removing any potential tablet variability prior to distribution. This allowed us to validate products made on the new automatic tableting machine while confirming the quality of our output on current tableting equipment. (b) (4) tableting machine has been successfully qualified for Metoprolol tablets. These two Metoprolol tablet drug products represented approximately (b) (4) of our size variation concerns in year 2008. No incidents of product complaints since we introduced the product on (b) (4) tableting machine.
- As part of Caraco's tablet weight variability improvement plan and based on our evaluations, the use of (b) (4) compression machines including asset # (b) (4) as noted in observation has been discontinued. We have switched over to (b) (4) (b) (4) (b) (4) machines. (b) (4) machines have been ordered (b) (4) (b) (4) machines are being evaluated for future replacement. Replacement will be determined based on analysis of predictability to produce the products manufactured in repetitious manner without incident. If we determine a trend that is less than satisfactory, those machines will be replaced as well. Currently, those machines are not showing a trend to identify them as a concern.

- SOP (b) (4) has been developed which provide guideline for handling routine variation in parameters using pre-defined alert and action levels. The training will be completed prior to implementation.
- SOP (b) (4) have been designed to define the (b) (4)  
 (b) (4)  
 (b) (4) The training will be completed prior to implementation.
- Based on the corrective actions implemented to date and others that are to be implemented, the quality system and procedures will prevent the reoccurrence of an increase in size variation issues on an ongoing basis. We believe due to enhanced processes and rigorous process controls, the reduction of such incidents will continue to be reduced. Investigations and efforts to further eliminate such circumstances are ongoing.

#### OBSERVATION 14

**Procedures are not established which are designed to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of investigations conducted. Caraco acknowledges the observation and has corrected the situation, however the timely report of an incident is dependent on individual who first becomes aware of the incident**

**Response:** Caraco acknowledges the observation and has corrected the situation; however, the timely report of an incident is dependent on the individual (s) who first become aware of the incident. We believe we have appropriately addressed this with proper training and systems.

**Corrective Action:** Caraco personnel were re-trained during the rolling shut down that occurred in February 2009 for prompt notification of any event to the appropriate level of management. The training was conducted by Senior Management including the CEO in a joint session. Among other subjects covered timely reporting of an incident as soon as one is discovered. The training department conducted training on good documentation practices. All personnel have been trained and are being continually reminded of this responsibility.

**Preventive Action:** QA provides a daily incident and event report that is sent to concerned stakeholders. In addition to this, QMS system has been established to provide a daily electronic status update on all events. Appropriate actions are taken as deemed appropriate.

**Specifically,**

SOP (b) (4) did not assure the responsible officials were notified of investigations. JR. 09-067 in which 1.352 kg of (b) (4) Digoxin, USP, Lot No. (b) (4) was missing from the warehouse. An initial search was conducted on 1/13/09. An Incident Initiation Investigation Tracking Sheet was not generated until 1/30/09.

**Response:**

As per our current procedure, SOP (b) (4) all

(b) (4)

(b) (4) In this instance, dispensing department personnel did not report the finding of misplaced or lost digoxin when it occurred on 01-13-2009. The search for missing material was conducted at the (b) (4) facility without notification to all levels of management. On January 29, 2009, the senior management was notified and the investigation ensued according to IR09-067.

The Quality Management System (QMS), system is designed and will be implemented by June 30, 2009,. This will provide detailed reporting, tracking and timely notification of Events and Incidents which occur within manufacturing, to the appropriate levels of supervision and management. Currently, QMS is setup to send a notification by e-mail of any new event and/or incident that is placed into the system to the stakeholders of appropriate departments to ensure completion of investigation in a timely manner.

**OBSERVATION 15**

**Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.**

**Specifically, requests for annual product review for Digoxin Tablets USP, Metoprolol Tartrate Tablets USP and Carbamazepine Tablets USP revealed only the year 2007 reviews were available in March 2009.**

**Response:**

Caraco conducts its Annual Reviews on a [REDACTED] throughout the year. The schedule for Digoxin indicates that the cut off date was 2/28/09, for Metoprolol and Carbamazepine the date was 1/31/09. Allowing for [REDACTED] days compiling, reviewing and approving the reports the approval dates would have been for Digoxin 4/28/09, and for Metoprolol and Carbamazepine the date was 3/31/09.

At the time of the Investigator's request, the reports were being compiled and thus were not available for review. These reports are now completed and presently routing for approval. The target completion date is 06-30-2009.

We agree with the investigators comments that one year may be too long and so we have incorporated on-line compilation of batch data into our daily operations. We will be reviewing [REDACTED] reports in order to evaluate any potential trends.

**Preventive Action:**

The status of Annual Product Review has become part of (b) (4) review of quality systems. This will allow the management to be aware of the status of the Annual product Review time adherence to the schedule and completion of reports and take appropriate action where deemed necessary to stay on schedule.

**FACILITIES AND EQUIPMENT**

**OBSERVATION 16**

**The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components and in-process materials and to prevent contamination.**

Caraco recognized this as a potential future issue and has taken the corrective steps to relieve the space constraint. Prior to the corrective actions that had been taken Caraco had a procedure in place to keep the warehouse organized and to prevent any possible mix-ups. While at the (b) (4) facility there had not been a documented incident that relates to inadequate space of the warehouse facilities.

**Preventive Action:** Caraco has moved into its expanded facilities which are an extension of our current manufacturing facility located at 1150 Elijah McCoy Drive. The footprint for the process areas has grown from approximately 135,000 sq. ft. in one contiguous building. Additionally, a 137,000 sq. ft. facility for distribution of the finished goods was leased in Wixom, Michigan.

**Specifically, Raw material warehouse facility (b) (4) location) did not have adequate storage available for all of its raw materials and in-process (b) (4) materials.**

**Response:**

Caraco recognized the potential space limitation at the (b) (4) facility, hence, several steps were taken to address any constraint to address adequate storage for raw materials. The entire facility was roughly 35,000 sq ft. and was across the street from our main manufacturing facility. Caraco opened a 137,000 sq ft distribution facility in order to primarily distribute its finished goods from this new distribution center. The finished goods part of the (b) (4) warehouse facility which held 18,000 sq. feet of the building was moved in June 2008. To give perspective manufacturing facility itself is approximately 80,000 sq ft. The dispensing department and raw material storage, (Pharmacy), assumed the space vacated by finished goods at that time. In July 2008 we retrofitted the space for what is considered the Dispensing Pharmacy. This adequately provides for the storage necessary to run an effective compliant facility. In order to increase efficiency with the rest of the operation the storage and dispensing has now been moved to our main building which we have recently expanded. The dispensing and warehouse storage became functional in May 2009. The area that is being used by the Dispensing Pharmacy and the warehouse itself is over 50,000 sq. ft. It is the company's belief that we could have utilized the space more efficiently whereas virtual locations which had space allocated to it should have been made actual locations so as to identify even "in process or in transit" where a particular product was actually located. The company has abandoned such practices as virtual locations.

**For example:**

- A. (b) (4) Digoxin lot (b) (4) was in location "FRSH" (Fresh) without a specific location designated for the warehouse from 10/13/08 to 1/26/09
- B. (b) (4) Digoxin lot (b) (4) was in location "FRSH" (Fresh) without a specific location designated for the warehouse from 12/30/08 until it was reported missing.
- C. (b) (4) Digoxin lot (b) (4) was in location "FRSH" (Fresh) without a specific location designation for the warehouse from 9/15/08 to 9/26/08.
- D. Baclofen, USP - (b) (4) lot (b) (4) was in location "DISP" (Dispensing) without a specific location designated for the warehouse from 4/22/08 through 7/25/08.
- E. Metoprolol Tartrate, USP lot (b) (4) was in location "DISP" (Dispensing) without a specific location designated for the warehouse from 5/15/08 through 9/25/08.

**Response:**

All items are required to be received into the specific location as defined in the ERP.

- Digoxin due to its high potency and the small amount required for each batch has been stored in a secured warehouse location under an actual locator number in our warehouse. This product and other high potency products require a chain of custody by signature to be issued for dispensing to the dispensing room and return to secured warehouse location. Also this material is stored in unique colored containers, as additional visual aid to alert the operators of the type of material contained. This will help to eliminate the potential incidence of "misplaced" materials. Please refer to a copy of Chain of Custody Form, Exhibit 5
- Caraco has eliminated the use of virtual locations FRSH (Fresh Goods) and DISP (Dispensing Location) such as staging and in transit areas within the warehouse and all applicable areas. As per new procedure, materials requested for dispensing are transferred directly from the warehouse specific storage location to the assigned dispensing room. Upon completion of the dispensing of that particular material, the material is returned to the specific warehouse location from which it was obtained. This change eliminates the virtual warehouse location and the possibility of materials being "misplaced" or "overlooked" while sitting in a virtual location, awaiting further action from Material Handlers or Warehouse personnel. The actual location in which an item is stored is the location in which the material will appear in (b) (4) This commitment was discussed with the investigators during the inspection.
- Previously, (b) (4) materials such as Digoxin were not assigned to specific locations since they were considered "in-process" and were located in a virtual location, which was a designated area of the warehouse. Currently, as a part of our corrective action plan, all products being dispensed regardless of whether they are (b) (4) or not are required to be in an actual warehouse location. SOP (b) (4) was revised to include these requirements and concerned persons are trained on this aspect and training is documented. Refer to Training Record, Exhibit 2.

## OBSERVATION 17

**Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.**

Caraco has taken corrective action and preventive action as stated below under the specific observation. The applicable SOP has been revised to clearly specify what type of study and date that must be collected to approve a change. A copy of this SOP is presented as referred in Exhibit 20.

Specifically, temporary change control no. 08-1009 dated 9/19/08 was approved to allow for the compression of (b) (4) lots of Digoxin Tablets using the (b) (4) tablet press as an alternate tablet press for Digoxin Tablets USP, 0.25 mg without a process verification to determine whether such a change would have an adverse effect on the finished tableted product. For example (b) (4) of the (b) (4) lots, 81819A was subject of a (b) (4) after finding soft and thick tablets

**Corrective Actions:** Revalidation activities for all strengths of Digoxin are being conducted and will show a successful prospective validation on a qualified suitable tablet press.

- We have performed evaluations of various contributing factors associated with size variation with specific reference to man (training), machine conditions (set-up parameters), material (control on granule properties) and process (tightened control parameters), and enhanced quality control procedures to provide high degree of assurance that the drug product manufactured at Caraco Pharmaceuticals meets desired quality attributes. Various applicable corrective actions for addressing size variation have already been implemented and are listed below:
- SOP [REDACTED] was enhanced by implementing corrective action no. CAR08-144 for establishing a comprehensive checklist which is verified during the initial compression machine set-up, any machine adjustments, troubleshooting, start/stops of tablet press, and/or maintenance of the tablet press. SOP was further enhanced for including instruction for removing the (b) (4) unit and primary product container while performing set-up of tablet press.
- Corrective action no. CAR08-149 was implemented for verifying machine set-up checklist after cleaning of compression machines. SOP [REDACTED] was further enhanced to establish a daily monitoring compression machine-specific set-up checklist for each working shift as a part of our continuous improvement. The steps for critical compression machine set-up conditions and parameters such as feed frame gap, lubrication levels, pre-compression and main compression settings have been incorporated in the equipment specific forms
- Implemented an additional physical characterization in-process test for tablets for verifying tableting parameters such as tablet weight, thickness, hardness, and friability utilizing tablets equivalent to number of stations of the tablet press plus (b) (4) units. This test is performed immediately after initial set up of the machine, at the middle of the run and at the end of the compression run.

- The compression instructions in the batch records have been enhanced to specify the adjustments to be performed on machine, monitor and analyze the data within a batch when certain units within a test moving away from a target value and are repetitively approaching towards alert and action level. Process Drift can be stabilized by taking corrective actions by process optimization and standardizing operating procedures.
- As a part of our continuous process improvement program, the in-process and process control parameters such as (b) (4) (b) (4) have been tightened to improve the operational performance, to reduce any variability in the process and ultimately improve the quality of the drug product.
- Updated the batch records for documenting machine parameters which are used for compression process of a specific product. Increased the frequency of in-process checks for weight variation thickness, hardness and friability of compressed tablets.
- Enhanced the compression instructions in the batch records for machine adjustment to maintain the tableting parameters at target parameters. SOP (b) (4) (b) (4) has been created which also provides a guideline for handling variations in parameters if pre-defined alert and action levels are exceeded.
- SOP No. (b) (4) has been revised to increase the sampling density by (b) (4) and the number of containers sampled have been increased to collect and represent entire population of the batch. The SOP has been further enhanced as a part of our continuous improvement to provide high degree of assurance to capture any variability in tablets.
- Established scheduled training program with compression machine suppliers to conduct (b) (4) training. Both operators and supervisors are being extensively trained for over six months to continuously improve the skill and understand the details of machine set-up and adjustments. These machines require qualified operator and skills to maintain tablet press set-up adjustments.
- We have contracted with (b) (4) to provide training, conduct audits and provide additional support in batch record review and other areas of their expertise. The most recent audits and trainings were conducted by three experience Auditors from (b) (4)
- A Rolling Shut Down of the Manufacturing facility was conducted in February 2009 to review and address the status of each of the manufacturing processing areas. During this period, re-training on SOPs and manufacturing procedures was conducted. Additionally a process review and gap analysis was conducted with all manufacturing department personnel. During this shutdown, all equipment was evaluated by the facilities department and appropriate preventative maintenance and repairs were conducted and completed prior to the re-start up of the facility.

**Preventive Action:** The Responsibility section of SOP (b) (4) has been revised to provide clarity for the responsibility and with structured evaluation process of the change. All applicable individuals and department representatives are involved in an upfront assessment of all the changes that impact the formulation, processes, methods, facilities, validation, equipment, procedures, and specifications that may affect the identity, strength, quality, purity, or safety of drug products. This will ensure that a scientific evaluation/discussion is made to determine the Change Request requirements and to ensure that the required approval process is appropriately followed.

**OBSERVATION 18**

**Written procedures for cleaning and maintenance fail to include parameters relevant to the operation. Specifically,**

**On 3/16/09, written procedures did not exist for the storage and labeling of cleaning solutions and agents used in cleaning production equipment and containers. For example,**

**A. A large drum of an unlabeled solution was observed in the (b) (4) wash rack area. This solution was stated to be for cleaning component container lids.**

**B. Two containers labeled "(b) (4)" were observed in the (b) (4) wash rack area; one container contained a clear, colorless solution and the second contained a blue solution. Confirmation of the identity of the blue solution was not provided.**

**Response:**

**Corrective Action** At the time of FDA observation the wash rack operator was immediately instructed to store cleaning agents used for cleaning of production equipment and containers with appropriate identification label.

**Preventive Action:** SOP (b) (4) was revised to provide clear instruction to wash rack and facility cleaning operator.

Section (b) (4) of this SOP now states that (b) (4)

(b) (4) (b) (4)

(b) (4)

b) (4)

A copy of training record is included in this response. Refer to Exhibit 26 SOP (b) (4) and Exhibit 27 for the Training Record.