DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
Cincinnati District Office
Central Region
6751 Steger Drive
Cincinnati, OH 45237-3097
Telephone: (513) 679-2700
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July 10, 2001

WARNING LETTER
CIN-WL-8497-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Robert D. Walter
Chairman and CEO
Cardinal Health, Inc.
7000 Cardinal Place
Dublin, Ohio 43107

Dear Mr. Walter:

During a May 29 to June 7, 2001 inspection of your drug manufacturing facility, International Processing Corporation, located at 1100 Enterprise Drive, Winchester, Kentucky 40391, our investigators documented deviations from the Current Good Manufacturing Practices Regulations (Title 21 Code of Federal Regulations, Parts 210 & 211). These deviations cause your drug products [redacted] mg Capsules and Acetaminophen [redacted] granulation blend, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. The deviations included:

1. Batch records do not accurately reflect the actual manufacturing process. For example, there was no documentation in the batch record that powder blend was reclaimed from the vacuum system of the [redacted] Encapsulator and added back into the virgin blend for process validation batches 9805819 and 0000498 of [redacted] mg Capsules [21 CFR 211.110(a)].

2. There is no documentation that manufacturing employees are trained/instructed following significant changes in procedures [21 CFR 211.25(a)].

   For example, the Out of Specification (OOS) investigation for [redacted] Capsules, batch 0000498, indicates that the practice of using reclaimed powder during encapsulation will be discontinued, and the batch record will be revised to instruct the operators. However, batch 0002854, the next batch of [redacted] Capsules manufactured, does not indicate that the practice of using reclaimed powder was stopped, nor is there any documentation that operators were instructed or trained to discontinue this practice.

3. The investigation of OOS data for validation batch 0000498 of [redacted] Capsules was not extended to batch 9805819 of [redacted] Capsules that was also manufactured using powder blend reclaimed from the [redacted] Encapsulator vacuum system [21 CFR 211.165(a)].

[redacted] Capsules, batch 9805819, was manufactured immediately prior to [redacted] Capsules, batch 0000498, both using reclaimed powder in the manufacturing process. The use of reclaimed powder was identified as the cause of OOS content uniformity results for batch 0000498.

4. Failure to have an adequate validation procedure for computerized spreadsheets used for in-process and finished product analytical calculations. The current validation procedure uses only the values that result in within specification findings, aberrant high findings, and aberrant low findings [21 CFR 211.165(e)].

   For example, SOP 644.00, QA/QC Spreadsheet Validation, is deficient in that only a small range of values are being used to challenge computerized spreadsheet mathematical calculations.

5. Failure to use fully validated computer spreadsheets to calculate analytical results for in-process and finished product testing [21 CFR 211.165(e)]. For example, the computer spreadsheets used to calculate analytical results for [redacted] have not been validated.

6. Failure to have appropriate controls over computerized laboratory systems to assure that changes in or deletions of records are instituted only by authorized personnel [21 CFR 211.165(e)].

   For example, instrumentation where data is stored on the interfacing computer hard drive up to thirty days prior to being written on a compact disk for storage is available to all analysts. While the data exists on the hard drives, any analyst can access, print, or delete the data.

7. Products were manufactured and shipped in interstate commerce before process validation was successfully completed [21 CFR 211.110(a)].

   For example, approximately 115 batches of Acetaminophen [redacted] were made and shipped into interstate commerce prior to June 2000 when a successful process validation study was finally completed and approved. Process validation attempts in February, 1999 and January 2000 did not meet all of the validation acceptance criteria.

The above-described violations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations. Failure to achieve prompt correction may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

We acknowledge receipt of a written response to these observations, dated June 29, 2001, from James F. Horger, Director, Quality Systems, International Processing Corporation. However, a review indicates that Mr. Horger's response fails to address the following:

1. Regarding the use of powder blend reclaimed from the vacuum system for validation batches (FDA-483 #1), your response does not address the action that your firm plans to take to validate the manufacturing process of [redacted] capsules, to prevent future release of product prior to completion of validation.

2. Regarding the validation of computerized spreadsheets used for in process and finished product analytical calculations (FDA-483, #4), your response states that current spreadsheets were challenged using the proposed revisions to SOP 644, QA/QC Computer Spreadsheet Validation.

   However, your response does not indicate if computerized spreadsheets for all products which use the spreadsheets, were challenged using the proposed revisions to SOP 644. Also, your response does not indicate the reason why SOP-644 will not be revised until July 20, 2001, or the measures that your firm will take regarding in process and finished product calculations in the interim.

3. Regarding the failure to use fully validated computer spreadsheets to calculate analytical results for in process and finished product testing (FDA-483, item #5), your response states that old spreadsheets will be revalidated according to the proposed revisions to SOP 644 prior to being implemented into use. You identify that SOP 644 will not be revised until July 20, 2001.

   This response is not acceptable. Any validation studies performed must be performed using an approved revision to your SOP, validating using a proposed SOP revision is not an acceptable practice.

4. Regarding process validation for Acetaminophen [redacted] blend (FDA-483, #7), exhibit 8 of your response addresses accelerated stability for three validation lots 0008023, 0008024, and 0008122. However, process validation provided to our investigators during their inspection of your facility, identifies three different validation lots 0001503, 0001504, and 0001505. Please clarify this discrepancy.

   Furthermore, exhibit 8 of your response identifies that the validation lots were placed on accelerated stability on April 20, 2000. Our investigators documented that process validation was not completed and approved until June, 2000. Please address this issue.

You should notify this office in writing within fifteen (15) working days of receipt of this letter of the specific actions you are taking to address these issues, including an explanation of each step being taken to prevent recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your written reply and any supporting documentation should be addressed to the U.S. Food and Drug Administration, 6751 Steger Drive, Cincinnati, Ohio 45237-3097, to the attention of Michael P. Sheehan, Acting Compliance Officer. Any questions regarding this letter or other issues may be directed to Mr. Sheehan at telephone (513) 679-2700.

Sincerely,

Mary L. Womack for

Henry L. Fielden
District Director
Cincinnati District

cc: George R. Tomiach, President
International Processing Corporation
1100 Enterprise Drive
Winchester, Kentucky 40391