

FDA

Inspection Report

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SUMMARY OF FINDINGS

Establishment Inspection Report EIR to Verify Corrective Actions

xxx indicates that product or compound names have been deleted by the FDA

The most recent inspection of this contract manufacturer of Rx and OTC drug products (non-sterile) was conducted May 29 - June 7, 2001 to evaluate cGMP compliance for four profiles: modified release tablets, prompt release capsules, crude bulks (granulations, blends, immediate release and sustained release beads), and control testing laboratory. The deficiencies observed during the inspection resulted in the issuance of a Warning Letter on 7/10/01 and the firm's profiles for prompt release capsules (CHG) and crude bulks (CRU) were deemed unacceptable.

The current inspection was conducted to verify the firm's corrective actions in response to the Warning Letter as per C.P. 7356,002, Drug Process Inspections. General cGMP coverage was also given to the prompt release tablet profile (TCM). Two pre-approval inspections were also performed for the following products as per C.P. 7;46,832:

xxx USP tablets, xxx mg; Applicant xxx is IPC is responsible for manufacturing the finished dosage form, release testing and stability testing. Profile sample 122039 was collected.

xxx mg; Applicant is xxx IPC is responsible, for the initial drug layering an the non-pareil seeds and for the seal coating after vacuum drying by xxx does the final manufacturing steps to produce the finished dosage form and they do all in-process and release testing. A profile sample was not collected for this product since this firm does not make the finished dosage form.

The inspection found that the firm has made the promised corrections as detailed in their response to the Warning Letter, No deficiencies were noted during cGMP coverage of the TCM profile and no deficiencies were noted during the PAI for xxx capsules. One deficiency was cited for xxx USP tablets: there is no particle size specification for the API, USP. xxx representatives verbally promised a correction prior to manufacture of the process validation/commercial batches. A written response was also promised.

Persons Interviewed and Individual Responsibility

We presented our credentials and issued the FDA-482, Notice of Inspection, to Mr. John J, Larkin, Director, Quality Assurance. Mr. Larkin facilitated the inspection on 10/18/01. Mr. James F, Horger, Director of Quality Systems, was present and facilitated the inspection on 10/23-25.

Mr. Horger continues to have overall responsibility for quality issues. Mr, George Tomaich, President. is the most responsible individual at this site. There has been a change in the corporate reporting structure since the previous inspection. Mr. Tomaich now reports to Mr. Richard Yarwood, President. Modified Release Technologies. Cardinal

Health Inc. See exhibit KC-I for organization chart. The FMD-145 copy of this inspection report should be sent to Mr. Tomaich at the firm's mailing address.

Several other IPC employees also provided information during this inspection:

Stephanie L. Clem, QA Senior GMP Compliance Auditor
Patrick Shields, DEA Compliance Manager
G. Keith Arvin, QC Manager
Beth Rhodes, Stability Supervisor

There were two representatives from xxx present for the PAI of xxx USP tablets:

Conduct of the Inspection

Review of corrective actions for the Warning Letter was conducted by both Investigators Culver and Parmon on 10/18/01. The preapproval inspections and cGMP coverage of the TCM profile were conducted by Investigator Culver on 10/23-25/01.

Review of Corrective Actions for Warning Letter

Corrective actions for issues cited in FDA-483 items 1-3, 7 were reviewed by Investigator Culver.

1. ***There was no documentation in the batch record that powder blend was reclaimed from the vacuum system of the xxx Encapsulator and added back into the virgin blend for process validation batches 9805819 and 0000498 of 3 mg xxx Capsules***

The firm did conduct training of manufacturing employees and quality auditors regarding appropriate documentation in batch records. Review of the master batch record for capsules also revealed that it now has clear instructions that reclaimed fines must be documented as waste and that they must not be added back into the virgin blend.

The firm is also revalidating the manufacturing process for xxx capsules. Only one batch has been made thus far (0105794) and testing is still in process. Results for the blender samples and drum samples were all within specification.

2. ***There is no documentation that manufacturing employees were trained NOT to reclaim powder blend from the vacuum system on the xxx Encapsulator after the OOS data for validation batch 0000498 of xxx Capsules was obtained and the practice of reclaiming the powder was reportedly stopped***

Any training that is conducted outside of the quality unit is now tracked by issuing controlled training documents that must be returned within specified timeframes as described in SOP xxx Employee Training Program.

- 3. The investigation of OOS data for validation batch 0000498 of Capsules was not extended to batch 9803819 of Capsules xxx that was also manufactured using powder blend reclaimed from the xxx Encapsulator vacuum system.***

SOP General Procedure for Investigating Non-Conformance Occurrences, was revised to emphasize that any investigation must be extended to all batches potentially affected and this extended investigation must be documented. Training on this SOP revision was conducted 7/20/01.

- 7. Numerous batches of xxx Acetaminophen blend were made and shipped into interstate commerce prior to June 2000 when a successful process validation study was finally completed/approved Process validation attempts in 2/99 and 1/00 did not meet all the validation acceptance criteria.***

The firm has revalidated the process for xxx Processes for some other xxx products were also revalidated: xxx. The firm also plans to revalidate the process for APAP with xxx starch the next time they make this product. Review of the completed process validation studies found no problems. The Quality Agreement between this firm and xxx now also has much more detail than the previous one.

Corrective actions for issues cited in FDA-483 items 4-6 were reviewed by Investigator Parmon.

- 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 values that result in within specification findings, aberrant high findings, and aberrant low findings.***
- 5. Failure to use fully validated computer spreadsheets to calculate analytical results for in-process and finished product testing.***

Each xxx spreadsheet used in calculating analytical results had been put through a battery of tests to examine how the spreadsheet would react. These tests include the entry of the following types of data: aberrant high findings, aberrant low findings, in-specification findings, zeros, negative numbers, and alphanumeric combinations. Each spreadsheet is product specific and has a separate validation package. Each package contains the initial testing of the information as entered into the Spreadsheet, a blank spreadsheet, and a spreadsheet showing the calculation formulas used in the appropriate cells. The package contains a list of the tests conducted and the dates they were performed as well as hand calculations of some trial data for comparison. Revised SOP xxx "QA/QC Computer Spreadsheet Validation," contains directions for testing new and existing spreadsheets prior to use in analytical testing. The xxx spreadsheets are checked monthly by a familiar analyst with previously entered data. The check results are compared to the originals to make sure that corruption of the file has not occurred. Any change of the spreadsheet requires a formula check, including format changes, such as text additions.

The following spreadsheet validation packages were examined: mg Blend, mg capsule Content Uniformity, mg capsule Dissolution; Assay, Content Uniformity, Dissolution; and

mg capsules Assay. The spreadsheet was examined as one revision had already been performed. In the laboratory xxx, the Content Uniformity, Assay, and xxx mg Content Uniformity spreadsheets were examined on one of the laboratory computers. No apparent problems were observed. The firm now saves the spreadsheets in read-only form to compact discs, specific to product. Changes to spreadsheets cannot be saved in this format. Two sets of CDs were made, one Set for the daily laboratory use and one master copy containing all spreadsheets kept by Keith Arvin, Quality Control Manager. If one spreadsheet on a CD is changed, then a new CD is burned and the old one is archived. The spreadsheet when printed out bears a file path at the bottom to assure it came from the CD.

6. *Failure to have appropriate controls over computerized laboratory systems to assure the changes in or deletions of records are instituted only by authorized personnel*

The firm has purchased a xxx Client Server. HPLC and GC instrumentation will be integrated into the client server around November 2001. Several HPLC units have xxx Software installed. Both the Software and the client server are still being validated and are not in official use. Other instrumentation, such as the xxx and xxx will have software upgrades to ensure Part 11 compliance. The software upgrades on these instruments is slated for completion for November and December 2001. Currently, the firm still uses the Systems that were in place during the last inspection. A List of Major Analytical Equipment, their proposed upgrades and their projected dates of completion was provided (Exhibit MP-1).

The firm has implemented two new SOP's, "QC Laboratory Computer Security," and, "Electronic Data Integrity for Computer Systems for the Quality Control Department." SOP states that doors to the QC laboratory are to be locked at all times with keys given only to appropriate QC and lab personnel. In addition, security cameras monitor the doors at all times. All QC computers have screen saver passwords on them that are known only to QC lab personnel. Employees will have user names and passwords on these computers and software that have user account capabilities. The SOP addresses user access rights, including no password sharing, minimal password length, and user profiles for access to certain systems. A copy of SOP was provided (Exhibit MP-2).

SOP xxx addresses data integrity issues on laboratory Systems. It states that analytical data shall be archived on CD and maintained for five years. These systems will data audit trails will record data activities It also addresses training and accountability. A copy of SOP xxx was provided (Exhibit MP-3). Once the client server and applicable software upgrades are made on instrumentation, these SOP's will be revised to reflect current operations. Validation and qualification packages will be reviewed during a subsequent inspection.

PAI Coverage for xxx mg Tablets

The Submission batch for xxx is lot 0005528, a full-scale batch. The Submission contains stability data for this lot as it was hand-packed at IPC; it is referred to as packaging lot number 0005529. Nine-month stability data for packaging lot 0005529 was obtained

during the inspection (except for dissolution data that were not yet available). See exhibit KC-2 for the 9-month data.

I questioned the relevance of the stability data for lot 0005528 that had been hand-packed at IPC because the filed process indicates that commercial packaging will be done at an ICN facility in Puerto Rico. Therefore, the actual commercial process will be more rigorous: overnight shipping of bulk tablets to Puerto Rico, then package on commercial equipment. I asked if there is any stability data for product packaged at ICN in Puerto Rico. Stability data for lot 0005528, packaged using the commercial process in Puerto Rico is attached as exhibit KC-3. At this time there is 3 months of data at xxx and 3 months data for xxx.

Review of lot 0005528 also revealed a possible problem in controlling the tableting process. Some thin tablets were discovered during the packaging process in Puerto Rico. The investigation could not definitively determine the cause of the thin tablets, but it was suspected that they were made at the very end of the run when the hopper did not have sufficient granulation in it. See exhibit KC-4 for investigation memo. There was some speculation that the end of tableting was "pushed" as far as possible to use as much granulation as possible due to the cost (expensive) of the xxx. I told IPC and ICN representatives that they must address this issue during process validation and that the end of the tableting run must be clearly defined (level of granulation in the hopper) and that they should collect data to prove that the last tablets of the run meet all specifications. Mr. McLauchlan said he was confident they could address this issue during process validation.

Review of this product found one deficiency that was cited on the FDA-483 : "There is no particle size specification for the xxx active pharmaceutical ingredient." The lack of the particle size specification is clearly explained in the application (attachment KC-1). The firm is changing suppliers for the xxx (from to xxx). xxx has not yet set any particle size specifications for the bulk, but is in the process of doing so.

The firm did compare the particle size distribution of the xxx to the xxx particle size specification for xxx and found smaller particles in the tenth percentile (see data in attachment KC-1). Dissolution profile testing was done to compare the last batch of product made with xxx to product made with xxx and tablet dissolution was not affected.

I explained my concern is in using any future batches of xxx without evaluating particle size prior to manufacturing a commercial batch. The acceptance testing for the xxx is done by IPC, but an evaluation of the particle size distribution is not required to accept the xxx. This allows for the possibility that xxx with a different particle size distribution from that of the submission batch will be used to make commercial product.

I advised IPC and ICN representatives that a particle size specification should be put in place based upon particle size distribution data for lots of xxx used in the xxx submission batch and feasibility batches. This specification should be in place prior to manufacturing any commercial batches to assure that commercial batches will be similar to the xxx submission batch. In the closing discussion, Mr. McLauchlan stated that they would set a particle size specification and Mr. Homer promised a written response.

PAI Coverage for Itraconazole Capsules 100 mg, ANDA 76-104

The xxx submission lot is RD00121 (finished product). Lot RD00121 was comprised of IPC batch 9905614 of non-pareil seeds with the drug layer applied, sublots A, B and C. Batch 9905614 was sent to xxx for vacuum drying as lot 991001. The dried intermediate was then returned to IPC for seal coating as lots 0000 52, 0000354 and 0000355. A review of the IPC batch records associated with the submission batch did not reveal problems. Records for other batches of drug layering on the non pareil seeds were also reviewed [batches 9905631, 9506366 _X, B, C). No deficiencies were noted. A profile sample was not collected because the finished dosage form is not made at this site.

CGMP Coverage of TCM Profile

This firm makes only one prompt release tablet product: xxx (mg xxx mg xxx mg xxx) tablets for xxx. The product is made by this firm but xxx performs all the release and stability testing. A review of complaints, OOS investigations, the process validation study, change control, and rejected lots for this product did not reveal any deficiencies.

Closing Discussions

A closing discussion was held with Mr. Larkin, Mr. Arvin, Ms. Clem, and NU. Shields on 10/ 18/01 and we informed them of our findings related to their corrective actions for the Warning Letter. We found their corrections to be acceptable and we told them that we would update the status of the CRU and CHG profiles to "acceptable."

A closing discussion was held with xxx representatives and IPC officials on 10/24/01 regarding xxx tablets. The FDA-483 was issued to Mr. Horger who promised a written response. Xxx of xxx verbally indicated that they would set a particle size specification for the xxx prior to the manufacture of process validation/commercial batches.

A closing discussion was held with IPC and representatives an 10/25/01. 1 (KC) informed them that no deficiencies had been noted and that the district would recommend

Attachments

FDA 482
FDA-443 issued 10/24/01
KC-1: xxx pages 3 and 4; xxx particle size data

Exhibits

KC-1: Organizations chart for IPC
KC-2: 9-month stability data, lot 0005528 0005529
KC-3: Stability data lot 0005528; packaged in Puerto Rico
KC-4: Investigations of lot 0005528; thin tablets

MP-1: Major Analytical Equipment in QC Laboratory

MP-2: xxx, "QC Laboratory Computer Security"

MP-3: xxx, "Electronic Data Integrity for Computer Systems in the Quality Control Department"