FDA

Inspection Report

Some Information has been removed by the FDA,
indicated in the text by
xxx.

Summary of Findings

The most recent inspection of this contract manufacturer of Rx and OTC drug products (non-sterile) was conducted 10/2000 as a preapproval inspection for xxx (trade name xxx) prolonged release capsules, xxx and xxx mg. No deficiencies were noted and CIN-DO recommended approval of xxx.

The current inspection was conducted as a cGMP inspection for four of the firm´s profiles: modified release tablets, prompt release capsules, crudle bulks (granulations, blends, immediate release and sustained release beads), and control testing laboratory. The inspection was conducted as part of the FY-2001 CIN-DO workplan under C.P. 7356.002, Drug Process Inspections. Coverage was also given to a field alert report for xxx mg controlled release tables under C.P. 7356.21m DQRS Field Alert Reporting. Review of a formulation change for prolonged release capsules, xxx and xxx mg, was also conducted under C.P. 7346.843, Post-Approval Audit Inspections.

An FDA-483 was issued at the close of the inspection for deficiencies including

- Failure to validate the manufacturing process for xxx Acetaminophen direct compression blend with preservative (xxx) prior to shipment of numerous batches into interstate commerce
- Failure to have an adequate validation procedure for computerized spreadsheets and failure to use fully validated computer spreadsheets for calculation of analytical results for in-process finished product testing
- Failure to have appropriate controls for computerized laboratory system to prevent unauthorized changes to or deletions of data
- Failure to extend the OOS investigations for validation batch xxx of xxx Capsules to batch xxx which was also manufactured using powder blend reclaimed from the vacuum system of the encapsulator
- There was no documentation in the batch record regarding the firm´s practice of reclaiming powder from the vacuum system of the encapsulator and adding it back into the virgin blend for validation batches xxx and xxx of capsules
- There was no documentation that employees were instructed/trained not to reclaim powder blend from the encapsulator when the firm reportedly stopped this practice

DOC sample 122034 was collected to document the shipment of batches of xxx into interstate commerce prior to a successful process validation study. Mr. James Horger, Director Quality Systems, refused to review the affidavit as per corporate policy.

Mr. Horger stated the firm would send a written response to the district (target NLT 6/29/01)

Personals Interviewed And Individual Responsibility

Investigator Culver presented credentials and issued the FDA-482, Notice of Inspection, to Mr. George R. Tomaich, President on 5/29/01. Investigator Parmon presented credential and issued a second Notice on 5/30/01 when he joined the inspection. Mr. Tomaich is the most responsible individual at this site. He was presented for the opening and closing meetings of the inspection.

Mr. James F. Horger, Director of Quality Systems, facilitated the inspection as did Mr. John J Larkin, Director QA. Mr. Horger has overall responsibility for quality issues. Mr. Larkin is responsible for quality assurance and has primary responsibility for release of products. Mr. Larkin reports to Mr. Horger. Mr. Horger reports to Mr. Tomaich and he also reports to Joseph White. Senior VP of Quality at Cardinal Health in Basking Ridge, NJ.

Several other IPC employees also provided information during this inspection

Stephanie L. Clem, QA Senior GMP Compliance Auditor
Robert Trupp, QC Validation Supervisor
G. Keith Arvin, QC Manager
Michael J. Camp, Director Manufacturing
Karen S. Mayer, Assistant Production Manager
Beth A Rhodes, QC Stability Supervisor
David Miller, QC Group Leader
Jack Hale, QC Chemist
Jeremy Nash, QC Chemist

Their responsibilities are generally indicated by their titles

History of Business

This firm has been purchased by R.P. Sherer Corporation, a subsidiary of Cardinal Health, Inc., since the previous inspection. IPC is now a subsidiary of R.P. Scherer. Cardinal Health corporate offices are located in Dublin, OH. Mr. Robert D. Walter is Chairman and CEO of Cardinal Health and has ultimate responsibilty for IPC. Mr. Tomaich of IPC reports to Mr. George Fotiades, Executive VP, Group President of Cardinal Health. See exhibit KC-1 for IPC organization chart, corporate reporting structure and names/addresses for key corporate officials.

Regulatory correspondence should be addressed to Mr. Robert D Walter, Chairman and CEO, at the following address:

Cardinal Health, Inc.
7000 Cardinal Place
Dublin, OH 43107

FMD-145 correspondence should be sent to Mr. Tomaich at the firm´s mailing address.

There have been no changes to the firm´s operations due to the change in ownership. The firm continues to manufacture approximately 6000 batches of product annually. See exhibit KC-2 for

a list of products made by the firm. There are three shifts for manufacturing and the analytical laboratory Monday through Friday. There is some weekend work depending on demand. This firm only packages products in bulk, intermediate packaging. There is no finished product packaging at this facility.

Inspectional Coverage

Other areas of coverage not otherwise discussed in this report included cleaning validation for the tablet press for Eskalith tablets, installational and operational qualification of the xxx capsule checkweigher (IPC #2673), customer complaints, laboratory OOS investigations, and general laboratory operations. No significant deficiencies were noted regarding these items. Review of the cleaning validation for coated iron (a food supplement) was also conducted and no problems were noted. The coated iron is manufactured in the 32" unit that is also used to manufacture drug products.

Field Alert Report for Controlled Release Tablets

The field alert report was submitted by xxx to FDA´s PHI-DO office on 4/19/01 for manufacturing lot xxx packaging lot which had OOS (fast) dissolution results at the three hour timepoint for the 2 month 25C/60%RH stability sample. The lot was manufactured at IPC and packaged at xxx. Expiry for the lot is June 4, 2001. See attachment 2. xxx representatives Manager Technical Support, and xxx Regulatory Compliance Advisor, were present and provided information as requested.

Review of the field alert investigation and conclusions did not reveal any concerns. No other commercial lots have exhibited the fast dissolution characteristics to date.

xxx Reformulation of xxx Extended Release Capsules

xxx extended release capsules, 2 and 4 mg, are manufactured for xxx. This xxx for this product is xxx and it was approved by FDA on 12/22/00. All the bioequivalence and xxx submissions lots were present during the inspection to provide information as requested. xxx representatives were Senior Quality Professional xxx, Director Manufacturing and Technology Management xxx; Senior Research Scientists xxx, Senior Director Pharmaceutical Sciences, and xxx Group Leader Trace Analysis.

In September 2000 IPC successfully validated the process for this product using the original formulation. They also started making batches in anticipation of the product approval and market launch. On 12/19/00, bead batch xxx failed dissolution at the 3 hour point (slow dissolution). Twelve other bead batches also failed for slow dissolution at the 3 hour test point and an investigation was initiated. See exhibit KC-3 with a "pending" status have now been rejected as reported by Mr. Larkin during the inspection. The investigation indicated that the release controlling excipient xxx was the most likely cause of the dissolution rates. See exhibit KC-4 for an interim report by summarizing the investigation and reformulation efforts. The firm reformulated the product by decreasing the amount of xxx by a total of 5% w/w in the formulation. This is a level 1 change under xxx.

Process validation for the new formulation (5% less xxx) was successfully conducted in March 2001 for 3 lots of beads that were subsequently encapsulated into xxx mg and xxx mg capsules. The process validation summary reports are attached as exhibits KC-5 (beads), KC-6 (xxx mg capsules) and KC-7 (xxx mg capsules). Since the validation of the new formulation, the firm has manufactured xxx additional batches which met the dissolution specifications. However batch xxx, manufactured 5/18/01 with the new formulation, failed to meet the dissolution specifications (too slow) and is on hold. The firm´s investigation is ongoing and no final outcome has been determined. Batches made with the new formulation have not yet been released for distribution, but xxx QA review is in progress to release these batches.

Control Laboratory Inspection

(I refers to Mark E. Parrnon in this section.)

The QA and QC laboratories are split into two separate areas of the facility -- one an the ground floor that houses the QA lab with some equipment used by QC personnel and one an the second floor that is used mainly for QC and stability operations. The QC laboratory runs three shifts - one for in-process and finished products testing, one for raw materials and cleaning validation testing and one for miscellaneous, shut-down, and start-up operations.

The laboratories have HPLC, GC, UV-Visible Spectrophotometer, Dissolution, FT-IR, Flame AA, and Graphite Furnace AA equipment used for analysis. The firm uses xxx and xxx HPLC, GC, xxx and UV equipment, xxx and xxx Dissolution Apparatus, one xxx AA Spectrophotometer with flame attachment, and xxx Graphite Furnace AA Spectrophotometer. A list of the laboratory equipment was obtained (exhibit MP-1).

The QC laboratory logs incoming samples for testing into an xxx database created by Jack Hale. Chemist According to Mr. Hale, the laboratory- logs in about 100 samples per week. Each sample is assigned a six-digit sample number consisting of two digits for the year and four digits for the sequential sample for that year. All analysts have access to this database for checking samples in and out. The database has the capability to generate canned reports also created by Mr. Hale for workload management.

The sample is assigned to an analyst for analysis. The appropriate method for the sample is used. The laboratory performs appropriate method transfer testing for their customers in-house methods. These tests include linearity studies and comparison of product analyses to those run by the customers quality control laboratory. Two methods transfers, one for the Acetaminophen assay of xxx Tablets and one for the dissolution assay for xxx and components of xxx Tablets, were reviewed No apparent problems with the method transfers were noted.

The appropriate instruments are used for the analysis of the prepared sample. Certain instruments are on calibration schedules. Recent calibrations for two dissolution apparatus, 12 calibrated 04/16/01 and #8 calibrated 12/20/00, were reviewed with no apparent problems. Both calibrations used the most current USP calibration tablet lots.

Balances are calibrated by contract sources, which daily recorded weighing standard checks by laboratory analysts. The firm has Service contracts on the majority of their analytical instrumentation, so only routine cleaning and maintenance is performed by lab staff.

Upon completion of the instrumental analysis, the raw data is saved to the Computer hard drive. The firm stated that the first printed record is the official data. However, on more than one occasion, a second printing from the electronic record was found in analytical notebooks and folders. The data is stored on these hard drives until memory fills and Computer performance is noticeably slowed. The staff then goes from instrument to instrument with a portable CD writer drive, and transfers the raw data to CD. The data is then deleted from the hard drive. According to Jeremy Nash and Keith Arvin, this is done monthly or sooner, depending an the amount of available memory on the hard drive in question. There are no controls present to protect the raw data on these hard drives from being changed or deleted, by accident or design. (See section "Part 11 - Electronic Records and Signatures"), These Computers are kept in a locked area with screen saver passwords known only by laboratory personnel.

The raw data, whether chromatographic peak width/height or UV absorbance values, is entered into locked xxx spreadsheets for analytical calculation. Each product has specific spreadsheets for result calculation. The analyst enters in the appropriate raw data values and the spreadsheet calculates the end result. These spreadsheets were created by Jack Hale and reviewed by Keith Arvin. Only Mr. Hale has the password authorization to make changes to spreadsheets. The analysts use them in a "read-only capacity. Mr. Arvin does not review and check individual results, but rather reviews the formulas used in the spreadsheet. making sure that the formula pulls information from the appropriate cells for the calculation. A copy of the dissolution results for xxx SR Pellets, Lot xxx IPC xxx calculated using one of these spreadsheets was obtained (exhibit MP-2). Mr. Arvin also provided a copy of the mathematical formulas that was checked for this product spreadsheet (exhibit MP-3). Although the validation of these spreadsheets is on-going, they are being used daily to calculate results. The one for xxx SR Pellets, for example, has yet to be validated.

According to Mr. Arvin and Ms. Rhodes, all spreadsheets are in the process of being validated. SOP xxx "QA/QC Computer Spreadsheet Validation", was reviewed. I told Mr. Arvin and Mr. Hale that the SOP was deficient in that only a small range of values was being used to challenge the spreadsheet's mathematical calculations. The range used for verification involves a set of test values within specifications, a set that generates aberrant high results, and a set that generates aberrant low results. 1 explained that such procedures should include entering values such as zero, negative numbers, and non-numerical characters, among others, to see how the spreadsheet reacts. Mr. Arvin stated that the spreadsheet validation SOP was currently being revised and that the testing criteria would be reviewed. A copy of the current spreadsheet validation SOP was obtained (exhibit MP-4). A copy of the validation for the xxx Dissolution Spreadsheet was supplied as an example of their validation process (exhibit MP-5).

Once the notebook and results are complete, Mr. Arvin reviews and signs the work. If the values are outside the specifications for the product, an OOS investigation is initiated per SOP "Investigation of Out of Specification and Aberrant Laboratory Test Results". The

investigation has three levels. Level I is a laboratory review of the analyst's work, looking for possible sources of technique or instrument error to invalidate aberrant results. Level II follows a Level I if no assignable cause is found. Level II involves further testing and resampling, if necessary. A Level III investigation involves a review of the manufacturing process to check for possible causes, and follows an inconclusive Level I or II investigation. Investigations are targeted for completion within 30 days and customers are notified usually the day an investigation is started. A copy of SOP was obtained (exhibit MP-6).

A copy of the OOS log from 10/02/98 to 05/22/01 was presented (exhibit MP-7). Several batches of xxx SR Pellets and Capsules (Lots xxx and xxx as OOS # and xxx respectively) for dissolution had failed at one hour and four hour intervals. Laboratory notebooks for these analyses were reviewed. Per customer request, the laboratory runs 12 trials at once for this product. According to Ms Rhodes and Mr. Miller, the coating polymer xxx was the suspect ingredient, allowing more of the active to dissolve in solution. After receiving new lots of xxx for manufacturing, the dissolution problems ceased. The Final investigation report is still pending.

Part 11 - Electronic Records and Signatures

(I refers to Mark E. Parmon in this section.

Electronic data on the hard drives of the computers whose Software controls the laboratory instrumentation is left available to all analysts for up to 30 days. At the end of this time period, the data is transferred to CD via a portable CD writer, where it can be retrieved if necessary. Depending on the amount of memory available an a particular computer. the data may be written to a CD sooner. Once the data is written to CD, the data on the hard drive is deleted. While the data exists on these hard drives. any analyst can access, print, or delete this information.

The firm contends that the First printed copy is the official data. However, on more than one occasion, data was reprinted or pulled up from the hard drive for viewing. I informed them that the electronic record was the official data. I stressed to them that the data was not secured from accidental or purposeful deletion from these hard drives. The firm keeps these computers in a locked laboratory area with screen saver passwords to prevent non-laboratory personnel from accessing the systems. However. I noted that there are no controls to prevent changes in or deletions of this electronic information by anyone except authorized personnel during its temporary hard drive storage.

Keith Arvin stated that the firm was in the process of purchasing a client server that would store all electronic data after generation. I explained that this System would have to have some sort of security controls in place. Several times during the inspection, I overheard discussions of the purchase of the client server between Mr. Arvin and other laboratory personnel.

The laboratory does have several HPLC units in the downstairs laboratory that are run by xxx software that is supposed to be Part 11 compliant. Jeremy Nash and Mr. Arvin

demonstrated the software for me. The system requires analysts to login prior to use and has administrator capabilities that enable only certain users to make changes in methods or delete information. Currently, only Mr. Nash and Mr. Hale have administrative authority in these systems, according to Mr. Arvin.

The firm does not use electronic signatures for their electronic records at this time and have no current plans to incorporate them. Mr. Arvin supplied me with a copy of the firm's Part 11 implementation plan (exhibit MP-8). However, with the purchase of the company by Cardinal Health, this plan has been put on hold as Cardinal has a separate Part 11 implementation plan that will be used for all of their contract manufacturers.

OBJECTIONABLE CONDITIONS

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

IPC manufactures immediate release, xxx mg Capsules for xxx in xxx owns the xxx. Formerly, xxx (now xxx due to a merger) owned the xxx and their personnel were involved with transferring the manufacture of this product to IPC. Both Mr xxx and Mr. xxx provided information regarding this product and the manufacturing process. The manufacturing process for this product was transferred to this site from the xxx facility in xxx in1998

The process validation approach was a concurrent one and there were discussions between IPC and CIN-DO prior to the execution of this approach. The first validation batch xxx was manufactured in June 1998. See exhibit KC-8 for the validation protocol and KC-9 for the report for batch xxx. No failing results were obtained during the validation testing of batch xxx.

The second process validation batch, xxx was manufactured in January 2000. See exhibit KC-10 for the validation protocol, KC-1 1 for the report, and KC- 2 for the protocol amendment requiring additional validation sampling. Although the blend uniformity samples were all within specification (see p. 15, KC-1 1), two content uniformity samples were OOS [<85%] from drum xxx of finished capsules (see p. 22. KC-11). A level I OOS investigation was initiated in the laboratory (exhibit KC-13). No analyst error was identified. Twenty additional capsules from drum xxx were analyzed for content uniformity and 4 capsules had OOS values ranging from xxx % (p. 5. KC-13).

A level 3 investigation of the manufacturing process was initiated to identify the cause of the OOS capsule uniformity results. The results of the investigation are documented in. a memo dated 3/15/00 (exhibit KC-14). The firm determined that the OOS capsule uniformity results were due to the use of powder blend reclaimed from the vacuum system of the encapsulator when the capsules in drum 13 were encapsulated. The reclaimed powder was scooped into the hopper at the rate of scoop xxx reclaimed powder for every xxx scoops of virgin powder blend. Additional testing was done per the supplement to the protocol (see KC-12) and only drums xxx of capsules were released by IPC for customer

use. See page l of exhibit KC-15 for batch record release of drums xxx . There were no OOS or failing results for samples taken from drums xxx.

After reviewing the validation data, I (KC) reviewed the batch record for batch xxx to determine how the powder reclamation process was documented in the batch record Batch record review revealed that reclamation of the powder from the vacuum system and the addition of that reclaimed powder to virgin blend was not documented. See exhibit KC-15 for the encapsulation section of batch record xxx. The other sections of the batch record also failed to contain any documentation of powder reclamation, but they were not copied due to volume. The batch record for xxx (p. 2, KC-15) does refer the Operator to SOP xxx for the encapsulator, but SOP xxx does not have any instructions about reclaiming powder from the vacuum system. See exhibit KC-1 for SOP xxx, Powder Encapsulation and Processing.

Since neither the batch record nor SOP xxx has any instructions about reclaiming powder from the vacuum System, I asked how the manufacturing employees knew to reclaim the powder and add it back to virgin blend at a rate of scoop xxx of reclaimed powder to xxx scoops of virgin powder blend. Mr. Camp Said the powder reclaiming instructions are in a procedure and IPC employees were trained to reclaim the powder during the transfer process. Mr xxx. obtained the xxx procedure for xxx Powder Filling and Weight Control (exhibit KC-17) and it does contain instructions about recovery of the powder from the vacuum system.

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

See the discussion under item 1 for background Information related to this deficiency.

In the firm's level 3 investigation report for the OOS results in xxx batch xxx the overall recommendation is to release only drums xxx and to discontinue the practice of using reclaimed powder during encapsulation. See page 2 of exhibit KC-18 for the investigation report and recommendations. The investigation also states that the batch record will be revised to instruct the operators about this change. However, there had never been any instructions in the batch record or SOP xxx regarding the practice of reclaiming powder, so no changes were made to the batch record or SOP xxx. I asked if the firm had conducted a training session with operators to inform them that the powder should no longer be reclaimed, but there was no documentation of this training.

I expressed concern about determining whether the powder had been reclaimed when the third validation batch xxx of xxx Capsules was manufactured in June 2000. No OOS results were obtained during the validation testing of this batch. See exhibit KC-19 for validation report. The firm provided a written statement from the encapsulation supervisors (Reed and Patrick) that the operators were instructed not to reclaim the powder for batch xxx (exhibit KC-20), but there is no documentation of those instructions prior to the manufacture of batch xxx.

In conjunction with the review of xxx Capsules, l also reviewed the firm's practices for xxx mg immediate release Capsules. This is another xxx product and powder was also reclaimed during encapsulation until revision of the master batch record on 5/0l/00 which deleted the instructions regarding reclaiming the powder. The process validation report was approved in July 1999 and no OOS results were obtained during validation testing. The blend for this product is xxx. Two lots of Capsules made prior to discontinuing the practice of reclaiming the powder are still within expiry: lots xxx and xxx. Both expire on 7/31/01. There have been no complaints an either lot and both are meeting specifications on stability through the last test date of 3/14/01.

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

See the discussion under items 1 and 2 above for background Information.

Both Mr. xxx and Mr. xxx stated that the powder would have been reclaimed from the vacuum system and added back into the virgin blend during the manufacture of batch xxx because that was the practice at that time. However, there is no documentation in the batch record of reclaiming the powder just as with batch xxx

Since the reclamation of powder was identified as the cause of the OOS uniformity results in drum xxx of batch xxx the investigation should have been extended to all lots which were manufactured incorporating reclaimed powder blend. The firm did not do any additional evaluation of batch xxx.

I (KC) determined during the inspection that batch was rejected by the owner, because there was insufficient shelf life left for commercial distribution. The lot was not entered into commercial distribution and it expired 5/31/01. See exhibit KC-21 for the reject notice.

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.***

Mr. Arvin had already stated that the procedure was currently under revision and the testing criteria would be revised. See section "Control Laboratory Inspection".

5. ***Failure to use fully validated computer spreadsheets to calculate analytical results for in-process and finished product testing.***

It was explained that the spreadsheets used to calculate batch results needed to be fully validated before use since this data was being used to release or reject product. Mr. Arvin

stated that spreadsheet validation was currently on-going and would be completed with the new revised procedure. See section "Control Laboratory Inspection".

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.

This applies to only the instrumentation where data is stored on the interfacing computer hard drive for any length of time prior to being written an a Compact disk for storage. During this time the data is available to all laboratory employees and can be deleted at will. The new owners of the company are collecting information for a Part 11 implementation plan. The firm's laboratory management themselves are looking at purchasing a client server which would hold electronic data instead of the computer hard drives. It was explained that this new server would also need to have some security controls in place. See section "Part 11 - Electronic Records and Signatures".

7. ***Numerous batches of* xxx *Acetaminophen* xxx *blend were made and shipped into interstate commerce prior to June 2000 where 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.***

Acetaminophen xxx is made for xxx and is commonly referred to xxx. This is a xxx acetaminophen blend that also contains preservatives (xxx and xxx). The blend is suitable for direct compression (DC) and has 36 month expiry date.

The first process validation attempt was in February 1999 when the first commercial batches were made. The validation for the granulation process is exhibit KC-22 and the protocol for the blending process is KC-22. A final validation report was not written for either protocol. Mr. Larkin wrote a summary of the validation efforts during the inspection for our benefit (exhibit KC-24). In summary, granulation batch xxx failed to meet the moisture specification of xxx with a result of xxx %. The three blends were batches xxx, xxx, and xxx. Each blend met the specification for moisture when the lot composite sample was tested by IPC and xxx. However, the validation composite samples failed to meet specifications (xxx %) for moisture when tested by IPC. Results were as follows:

IPC Blend Batch #	IPC Val Sample	IPC Lot Composite	Lot Composite
xxx	xxx	xxx	xxx %
xxx	xxx	xxx	xxx %
xxx	xxx	xxx	xxx %

See the following exhibits for the moisture results above and note the correlation of the IPC batch number and the lot number below.

IPC Batch xxx = lot xxx
IPC Validation sample result = K-25
IPC Lot composite result = KC-26
xxx Lot composite result = KC-27

IPC Batch xxx = lot xxx
IPC Validation sample result = KC-28
IPC Lot composite result = KC-29
xxx Lot composite result = KC-30

IPC Batch xxx = lot xxx
IPC Validation sample result = KC-31
IPC Lot composite result = KC-32
xxx lot composite result = KC-33

Note that xxx testing is performed in xxx, where xxx has a laboratory within the xxx facility. Mr. Larkin also explained that xxx test results overrule IPC results. For example, if the results are OOS at IPC but meet specification at xxx the batch is acceptable. The reverse is also true; OOS results at xxx fail a batch despite passing results by IPC. This is addressed in the Agreement between IPC and xxx (former name for xxx). See exhibit KC-34, article 6, which states that if xxx approves a lot based an the results of their testing, "such lot shall then be transferred to shippable PRODUCT." Note also under article 2 of the Agreement that xxx will accept retrospective process validation. I told IPC that retrospective process validation is not acceptable.

Regarding validation batches xxx there are no validation sample results for moisture that were tested by xxx. It appears that xxx released the batches based upon the lot composite results. However, xxx was aware that these batches were process validation batches because Mr. QC Manager for signed the validation protocols. Neither Mr. Horger nor Mr. Larkin could explain why a final validation report had not been written for this validation study, nor was there any written rationale why the batches should be released in spite of the OOS moisture results for the validation composite samples.

Batches xxx and xxx were shipped to xxx in xxx on 3/15/99 under bill of lading number 3548. DOC sample 122034 was collected to document this interstate shipment. Mr. Horger refused to review the affidavit because it is not allowed per corporate policy. Although these validation batches were shipped directly to a customer, most batches are shipped to facilities in xxx or xxx (see exhibit KC-35 for addresses).

The second process validation study was conducted in January 2000. See exhibit KC-36 for the validation protocol for the granulation and KC-37 for the blend protocol. There are no final reports for these validation protocols. Mr. Larkin summarized the outcome in a memo (KC-38). In summary granulation batch xxx failed to meet the particle size specification of xxx cumulative minimum an CR-80. Raw data was not obtained for this failure. Three blends were made from various granulations (xxx to xxx granulations go

into a blend): IPC batches xxx, xxx and batch xxx met the moisture specification at both IPC and IPC and moisture results for blends and were OOS (low) and both were rejected by xxx. See results below .

IPC Blend Batch #	IPC Moisture	Moisture
xxx	xxx	xxx%
xxx	xxx (passing result)	xxx%

No IPC validation samples for moisture were taken during this study.

See the following exhibits for the moisture results above and note the correlation of the IPC batch number and the xxx lot number below:

IPC Batch xxx = lot xxx
IPC Lot composite result = KC-39 (pg 2)
xxx Lot composite result = KC-40

IPC Batch xxx = lot xxx
IPC Lot composite result = KC-41 (pg 2)
xxx Lot composite result = KC-42

The xxx rejection of batches xxx and xxx is documented an exhibits KC 40 and 42 where there is a checkmark next to "Rejected" in the section for xxx lot release. These blends with OOS moisture results are normally reworked back into another blend at a specified rate and not destroyed, but no additional information regarding the reworking of there two batches was obtained.

Validation batch xxx did meet all specifications and was released. but shipment data was not obtained. xxx release of IPC batch xxx (batch xxx xxx) is documented on exhibit KC-43

The firm's third attempt at process validation was in March 2000. The validation protocol for granulation is exhibit KC-44 and the validation summary report is KC-45. The validation protocol for the blends is exhibit KC-46 and the summary report is KC-47. This process validation study was successful. Note that the last signature of approval on the validation summary report for the blends was June 1, 2000. According to Mr. Larkin, the validation summary reports were written by Mr. xxx of xxx even though they are printed on IPC letterhead.

Prior to the completion and approval of the successful process validation study (final approval 6i 1/00), the firm shipped approximately xxx batches of xxx into interstate commerce. xxx batches were made and released in 1999 -see exhibit KC-18. xxx blend batches were made and released in 2000 - see exhibit KC-49.

CLOSING DISCUSSION

The FDA-483 was issued to Mr. Tomaich, Mr. Larkin, Mr. Horger, Ms Clem, and Mr. Arvin also attended the closing meeting. Each deficiency was read aloud and discussed. There were no significant comments from firm officials for items 1-6. Regarding item 7, Mr. Tomaich commented that there will be some changes in their validation policy. Mr. Horger said they plan to have a written response to the district by 6/29/01, but he also noted that the response will undergo more review than in the past due to the new corporate structure. He was not certain if the additional review might prevent from meeting their target of 6/29/01 for the response. No further discussion was held and the inspection was concluded.

Attachments

FDA-482
FDA-483
1. xxx mg tablet Field Alert Report dated 4/19/01
2. xxx mg tablets Field Alert investigation

Exhibits

KC-1: IPC organization charts
KC-2: List of products made by IPC
KC-3: List of xxx rejects due to dissolution
KC-4: 6/01 Interim Report – Release Rate Variation of xxx
KC-5: 4/19/01 Validation report xxx beads

KC-6: 5/3/01 Validation report xxx capsules xxx mg
KC-7: 5/4/01 Validation report for xxx capsules xxx mg
KC-8: 6/11/98 validation protocol,xxx capsules
KC-9: 12/9/99 validation report, xxx capsules
KC-10: 12/16/99 validation protocol, xxx capsules

KC-11: 3/24/00 Validation report xxx batch xxx
KC-12: 3/21/00 protocol amendment for xxx batch xxx
KC-13: Level 1 investigation OOS-0001073, xxx val. samples
KC-14: 3/15/00 memo from Larkin/Camp re Batch Review Investigation
KC-15: Selected pages xxx batch record, xxx

KC-16: SOP xxx Powder Encapsulation and Processing
KC-17: xxx manufacturing directions for xxx capsules
KC-18: Level 3 investigation, report OOS-0001073
KC-19: 8/16/00 process val. Report for xxx capsules
KC-20: 6/01/01 memo from Reed Re batch xxx

KC-21: Rejection of xxx lot xxx
KC-22: Validation Protocoll 2/10/99 – xxx granulation
KC-23: Validation Protocol 2/10/99 – blend v xxx
KC-24: 6/7/01 memo from Larkin to xxx Val. File re 2/99 study
KC-25: Validation test results batch xxx - moisture

KC-26: xxx Blend xxx record
KC-27: xxx lot analysis: IPC batch xxx lot xxx
KC-28: Validation test result batch xxx moisture
KC-29: xxx Blend xxx record
KC-30: xxx lot analysis: IPC batch xxx lot xxx

KC-31: Validation test result batch xxx – moisture
KC-32: xxx Blend xxx record
KC-33: xxx lot analysis: IPC batch xxx lot xxx
KC-34: xxx /IPC Tolling Agreement
KC-35: xxx Shipping addresses for xxx blend

KC-36: Validation Protocol 1/26/00 – xxx granulation
KC-37: Validation Protocol 1/26/00 – xxx blend
KC-38: 6/7/01 memo from Larkin to xxx Validation file
KC-39: Selected pages from batch record: xxx blend xxx
KC-40: xxx reject lot xxx (lot analysis results)

KC-41: Selected pages from batch record: xxx blend xxx
LC-42: xxx reject lot xxx (lot analysis result)
KC-43: xxx lot release xxx batch xxx
KC-44: Validation Protocol 3/16/00 - xxx granulation
KC-45: Summary validation report – xxx granulation

KC-46: Validation Protocol 3/16/00 – xxx blend
KC-47: Summary validation report xxx blend
KC-48: List xxx blend batches xxx released in 1999
KC-49: List xxx blend batches xxx released in 2000 [before 6/0/00]

MP-1. List of IPC Analytical Equipment
MP-2. Copy of dissolution results for xxx SR Pellets, Lot xxx, IPC
MP-3. Analytical spreadsheet with mathematical formulas for xxx SR Pellets dissolution
MP-4. IPC SOP xxx "QA/QC Computer Spreadsheet Validation", dated MAR 09 2000
MP-5. Dissolution Spreadsheet Validation for xxx
MP-6. IPC SOP xxx "Investigation of Out of Specification and Aberrant Laboratory Test Results"
MP-7. IPC OOS Log from 10/02/98 to 05/22/01
MP-8. Projected Schedule and Responsibilities for Implementation of 21 CFR Part 11 Requirements.