

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

555 Winderley Place, Suite 200
Maitland, FL 32751
(407) 475-4700 Fax: (407) 475-4768

DATE(S) OF INSPECTION

03/06/2006 - 04/18/2006*

FEI NUMBER

3003194604

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Thomas P. Rice, Chief Executive Officer & Director

FIRM NAME

Andrx Pharmaceuticals, Inc.

STREET ADDRESS

4955 Orange Dr

CITY, STATE, ZIP CODE, COUNTRY

Fort Lauderdale, FL 33314-3902

TYPE ESTABLISHMENT INSPECTED

Pharmaceutical Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

QUALITY SYSTEM

OBSERVATION 1

The quality control unit lacks authority to review production records to assure that no errors have occurred and fully investigate errors that have occurred.

Specifically,

- a) The Quality Control Unit failed to adequately review Ketoprofen Validation Protocol and Report No. 002PV.005 and, as a result, it released and distributed between March and July 2005 six batches of Ketoprofen ER capsules (lot #'s: 520E017, 520F0368, 520E018, F520F0840, F520F1030, and F520F1031) that were manufactured with a process that showed significant variability and was not adequately validated.
- b) The Quality Control Unit failed to ensure that Phase I Laboratory Investigations were adequately investigated, documented, and trended after they were removed from the [REDACTED] system in September 2005 and transferred to a manual logbook.

PRODUCTION, LABORATORY AND EQUIPMENT/FACILITIES SYSTEMS

OBSERVATION 2

Control procedures are not established which 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.

Specifically,

On 2/25/05, the QCU approved Doc. No. 0002PV05 titled "Process Validation Protocol- Manufacture of Ketoprofen

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██████████ using ██████████ readings documented from the ██████████ to evaluate the accuracy of scale reading versus ██████████ reading for the sustained release coating process as the difference in the ██████████ readings was identified as the cause for the shift in dissolution performance at the 8th hr. Five (5) commercial batches of ██████████ (520E017, 520E018, 52050, 55797 and 57043) were manufactured under this validation protocol, which resulted in three batches (52050, 55797 & 520E018, subplot#4) that failed dissolution specifications at the 8th hr. and a batch (57043) that deviated from the target capsule fill weight specified in the manufacturing batch record in order to meet dissolution specification at the 8th hr. The remaining six (6) finished product batches (520E017, 520F0368, 520E018, F520F0840, F520F1030, and F520F1031) of Ketoprofen ER Capsules that had acceptable dissolution results were released by the Quality Control Unit and distributed between March and July 2005 despite the demonstrated variability and significant inconsistencies of the manufacturing process documented in interim reports 002PV05-01i, 002PV05-02i, 0002PV05-03i, and the final validation report 0002PV05 approved on 7/28/05.

OBSERVATION 3

The use of instruments and apparatus not meeting established specifications was observed.

Specifically,

- a) In December 2005, the Quality Control Unit (QCU) determined the need to replace the flow rate valves of ██████████ apparatuses as a result of frequent clogging, flow rate problems, and increased bubble formation that randomly caused "erratic" dissolution results. ██████████ valves were purchased and received in January 2006; however, the QCU failed to adequately monitor the implementation of this corrective action and, as a result, the valves were not installed and the use of these dissolution baths with potentially malfunctioning valves continued for dissolution testing of all Cartia, Diltia, Taztia, Metformin, Naproxen Sodium, and Ketoprofen drug products.
- b) Subsequent to the determination of performance problems with the ██████████ dissolution apparatuses, the Metrology Department, responsible for laboratory equipment maintenance and calibration, conducted an investigation (date not documented & investigation not tracked) to determine the root cause of the problems in the dissolution apparatuses. The investigation concluded that "due to a blockage on the pores caused by crystal deposits (salts interference), air bubbles may form cause false readings in the middle of the run that do not represent a true absorbance reading of the sample" and recommended more frequent maintenance schedules to prevent flow valve problems. However, the QCU reported that the problem had been fixed in January 2006 with the replacement of the valves (that didn't take place) and failed to implement the recommended corrective and preventive/maintenance actions in a timely manner.
- c) The set-up procedures used for the ██████████ apparatuses are not adequate in that according to dissolution records reviewed from May 2005 thru March 2006 and interviews with analysts, the flow rate of the "blank" line is checked prior to each dissolution run to determine if the flow valve is working properly (flow rate spec: ██████████). However, your firm lacked scientific evidence to demonstrate that an adequate flow rate of the blank is directly correlated to an adequate flow rate to all ██████████ dissolution vessels in order to conclude that the flow valve is working properly and the flow to each vessel is within specifications prior to the run.

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OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been thoroughly distributed.

Specifically, your firm failed to perform adequate investigations with scientifically justifiable conclusions to incidents of out-of-specification results or production deviations and/or failed to implement appropriate corrective actions for the root cause determination. The deficiencies are evidenced in the following:

Laboratory Phase II Investigations:

(a) The investigation report TWR #1691 for finished product testing of Metformin HCl Extended-release Tablets, 500 mg Lot No. F571F0692 was specifically for content uniformity testing. During analytical testing, one of the ten capsules (73.5%) failed to meet the Stage 1 established specification of [REDACTED] of label claim and another tablet was toward the low end of the specification range (88.0%). The root cause analysis indicated analyst error and two additional capsules were extracted with the results replacing the original OOS capsules. The investigation revealed that the analyst observed a gelatin like mass of material at the bottom of one of the flasks and a piece of undissolved gel at the bottom of the other flask after adding diluting solvent A. As a result, these two flasks were stirred for an additional 60 minutes which is longer than the procedure or the eight other flasks. The analyst who performed the QC method transfer stressed the importance of full tablet disintegration before adding diluting solvent A or the material will clump. The firm concluded that based on the physical observation of the two stock solutions in question proper active extraction did not take place. The investigation is inadequate in that:

- The analysts were retrained on the analytical method itself but there was no documented training regarding continuing the analysis knowing that he or she made an extraction error or that there was a problem with the disintegration of these two capsules during the analysis.
- The investigation did not address the reason why these two capsules did not dissolve adequately. The analyst's interview did not determine if the capsules were taking longer than normal to disintegrate before adding diluting solvent A, or if the capsules took longer to dissolve because he/she added diluting solvent A without making sure the capsules had disintegrated. The first scenario (the capsules taking longer than normal to disintegrate) would not indicate analyst error, but a possible process related error that would have required the investigation to be extended outside of the laboratory e.g. investigation of the process and historical data to determine root cause.

(b) The investigation report TWR #1540 for finished product testing of Metformin HCl Extended-release (XT) Tablets, 1000 mg Lot No. F575F0620 Sublot C was specifically for related compounds testing. The unknown related compound in this sample was OOS. With-in specification results were obtained upon retest of the sample and the firm concluded that the OOS result was due to contaminated glassware. In an attachment to this investigation, the firm states, "As part of GLP, all analysts normally rinse flasks before using for RC test. Both analysts are very experienced chemists and did that during sample preparation. In spite of that all glassware was rinsed by mobile phase before sample preparation there was still some contamination from glassware or from sample handling. As a corrective action, the analysts recommended to [REDACTED] flasks with [REDACTED] additionally and to rinse by mobile phase before using them for Metformin XT RC test." This statement indicates that there is no definitive assignable cause for the OOS result since they state that the contamination could have come from glassware or sample handling. The investigation does not explain how glassware contamination or sample

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handling may have increased the unknown related compound for this sample. If in fact the contamination was due to sample handling then the proposed corrective action of additional glassware cleaning would not be appropriate. In this case, the investigation indicated that the current glassware cleaning procedure may not be adequate for this particular product but does not explain why. The corrective action does not address training for all analysts on the required glassware procedure nor does it state if this will be incorporated into the analytical procedure for this product. Furthermore, the investigation was inconclusive and the results were invalidated without extending the investigation into the manufacturing area.

c) The investigation report TWR #1484 for finished product testing of Diltiazem HCl Once-A-Day Extended-Release Capsules, 240 mg Lot No. F599F0577 was specifically for related compounds and impurities testing. The levels of [REDACTED] and two unknown impurities were not typical for this product. For impurities testing, the analysts are instructed to rinse glassware before use as part of their cGLP training. In this instance, the investigation states that the analyst omitted to rinse the glassware. Therefore, a new dilution from the original stock solution was made with the impurity levels dropping to below a detectable level upon reanalysis. The corrective action for this investigation as stated in the TWR report was the counseling of the analyst in regard to glassware rinsing. According to the attached training record, the analyst was re-trained on the analytical test method STM #599, "Diltiazem HCl Once-A-Day Extended-release Capsule, 240 mg". This test method does not address the rinsing of glassware for related compounds and impurities testing. There was no documented evidence of re-training the analyst on the proper procedure for glassware cleaning.

(d) The investigation report TWR #1523 was for the assay of [REDACTED] raw material Lot No. 11140. The sample was analyzed twice with one of the two assay results not meeting specification. A re-injection of the original vial was made which confirmed the original OOS result. A new aliquot from the original flask was taken and analyzed which gave a within specification result. The firm concluded analyst error in that the analyst did not mix the flask sufficiently or did not mix the flask at all. However, in this case the analyst stated the flasks were properly mixed. Furthermore, in an attached memorandum to the TWR, the analyst involved refused to sign an acknowledgement of analyst error. The firm could not provide scientific justification as to what sufficient mixing would be for this analysis or any documented evidence that the analyst did not follow procedure. There was no further investigation into this lot of raw material.

(e) The investigation report TWR #1654 was for intermediate product testing of [REDACTED] Lot No. 572256 Sublot 3. The Phase I investigation as described on form QC-0126 does not state why the original OOS result was invalidated, no details on how the samples were re-analyzed and there is no assignable cause mentioned, yet there was no Phase II investigation performed and the original [REDACTED] investigation record was voided with product being released as meeting specification.

(f) The investigation report TWR #1617 was for the assay of [REDACTED] raw material Lot No. 11325. This lot along with three other lots was tested for impurities by [REDACTED] with Lot 11325 failing to meet the specification of not more than [REDACTED] for [REDACTED] impurity. The assignable cause was determined to be equipment failure (bad injection of the sample most likely due to an air bubble). During the investigation, the laboratory reviewed the online [REDACTED] logbook which did not indicate any equipment problems or malfunctions. The laboratory also reviewed the chromatograms as part of the investigation and determined that this lot had a different baseline than the other three lots. However, there is no description of how the baseline was different and how that would impact on the results. Furthermore, the firm did not perform any type of verification of the injector system on the [REDACTED] before making the conclusion that the equipment did not inject properly and there was no corrective action implemented for the [REDACTED] system. Therefore, there is no scientific justification for invalidating the OOS results. The other three lots tested concurrently were not re-injected. Though [REDACTED] is not a currently marketed product, the laboratory practices shown in this investigation were inadequate. This is a repeat observation from the previous FDA

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483, #19(B)(1).

Phase II Investigations related to Equipment Cleaning:

g) SOP QC-0135, "Evaluation of Extraneous Peaks During the Analysis of Cleaning Validation Swab Samples", establishes the criteria to determine when an unknown peak in a cleaning swab should be investigated. According to the SOP, if any individual unknown peak is not more than [REDACTED] of the target analyte peak or if the sum of the unknown peaks per swab location is not more than [REDACTED] of the maximum allowable residue limit of the target analyte, no further action is required. A Technical Services Supervisor said that their rationale for the limits stated in their SOP is based on a Consultant's article. The article indicates that "it might be appropriate to allow an unknown peak provided it is no more than 5-10% of the height or area of the target residue (the active, for example) at its residue limit" and that "Some companies will then have an additional stipulation that the sum of all peak heights or areas of unknown peaks be no more than 20-40% of the height or area of the target residue at its limit." However, the article also states that "In this case, it is expected that an investigation has been done to identify the unknown peak, and that it still remains unknown." The article also indicates that the amount of the unknown peak cannot be accurately determined unless a detector such as [REDACTED] is used because the relative absorbance is not known.

SOP QC-0135 allows unknown peaks at percentages even higher than the ones recommended by the Consultant on a routine basis without first making a reasonable attempt at identifying the extraneous peaks. The firm manufactures a wide variety of products with different toxicities and allowable residue levels, and even uses the same equipment used for commercial manufacture to manufacture products that are still under development. Applying the limits stated in SOP QC-0135 without first investigating the source of the unknown could result in allowing higher levels of residue than would normally be allowed had the identity of the extraneous peak been known. In addition, since the absorptivity of the unknown peak is not known and the actual amount of residue cannot be determined with the detectors used by the firm, the actual amount of residue could be even higher than the amount estimated by using the target analyte peak.

h) At least 24 cleaning swab samples containing extraneous peaks above the limits specified in SOP QC-0135 were reported for ten different pieces of equipment from May of 2005 through February of 2006. The inspection disclosed the following deficiencies regarding the investigations conducted for these unknown peaks:

(1) TWRs 1374, 1580, 1591, 1594, 1744, 1868, 1895, 1896, and 1964 are all related to unknown peaks in swab samples and were investigated under TWR 1555. The conclusion of TWR 1555 states that "Based on indirect evidence, the sponge, a general purpose scour pad of cellulose and nylon fiber material composition is the probable cause of the unknown peak". This conclusion was reached for all swab samples involved in these TWRs even when the firm's experiments failed to demonstrate that the peak was the same in all cases and that the source of the peak was the same. The firm conducted experiments only with the swab samples involved in TWRs 1744, 1868, and 1896. None of the experiments demonstrated that the source of the peak was the sponge itself. Although the unknown peak found in swab samples from TWR 1744 was also found in the sponge, the source was apparently an oily residue picked up with the sponge when it was used to clean the equipment involved in the TWR. Nevertheless, the only corrective action performed was removal of the sponges from the manufacturing area. An e-mail attached to TWR 1555 stated: "At this time, we are addressing only the sponges as they build up the contaminants." The firm conducted their product impact assessment based on their conclusion that the unknown peak was from a by-product of the sponge and released all lots involved because all material used in the manufacture of the sponges is food grade.

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(2) According to TWR 1555, no extraneous peaks have been identified in subsequent cleaning studies after use of single-use cleaning cloths was implemented in September 30, 2005. However, the current inspection disclosed that three additional swab samples collected in February of 2006 showed unknown peaks above the limit specified by QC-0135. These instances were not reported to the FDA Investigator and were not investigated under a TWR. Only Phase I laboratory investigations were conducted in these cases (INV-06-0041 and INV-06-0633).

(3) The firm did not make a reasonable attempt at identifying the extraneous peaks in order to determine if the extraneous peaks could come from residues of products manufactured prior to the last (target) product. None of the investigations performed included spiking samples with previous products to determine if the source of the unknown peaks could have been previous products manufactured in the same equipment. Review of the cleaning SOPs involved showed that most are not specific regarding washing and rinsing methods; however, none of the cleaning SOPs have been revised to provide more specific instructions regarding washing method, rinsing times or volumes, disassembly of equipment, etc. The corrective action in all cases was to re-clean and re-swab the equipment.

i) TWR 2194 was opened on 2/3/06 to investigate a swab failure for Diltiazem HCl ER Capsules. The TWR lists rinsing with [REDACTED] as one of the steps used in cleaning the capsule filler as per SOP PD-0018, "Operating and Cleaning Procedure for the [REDACTED]". However, the firm does not use any [REDACTED] to rinse equipment. The investigation failed to uncover the fact that the cleaning procedure is not being followed in that no [REDACTED] is used for the final rinse.

j) No investigation was conducted for several swab samples that failed detergent or active limits; these swabs were collected under Swab Analysis IDs 05-11-080, 06-02-091, and 06-02-038.

k) CAPA 1556 was opened on 6/20/05 to investigate the source of unknown peaks identified in TWR's 1476 and 1504 as laboratory glassware contamination. This CAPA has not been closed; the Investigation Extension Request approved on 2/10/06 states that "Initial work has been processed under QCP-05-059-MTH and reported under QCR-05-056-MTH". However, none of these documents addresses laboratory glassware contamination; they are related to the investigation of the source of unknown peaks in manufacturing equipment. TWRs 1476 and 1504 were closed before completion of the required follow-up investigation to be conducted under CAPA 1556.

l) TWR 2059 was opened on 11/15/05 to investigate an incident where a foreign tablet (Metformin HCl ER Tablet, 500 mg) was found in a [REDACTED] during the [REDACTED] stage for Metformin HCl ER (XT) Tablets, 1000 mg, lot 62253. The investigation disclosed that both products ran back to back in compression in room A-19 (Building 4955) on the [REDACTED] (WP-0007). TWR 2059 indicates that the most probable cause was human error in that the SOP cleaning instructions were not properly executed. However, the investigation did not include an examination of the compression machine involved and other compression machines used in the facility to determine areas where tablets could remain after a major clean without being detected. The investigation did not include a review of the operation/cleaning procedure to clarify instructions in order to make sure that those areas are given special attention when cleaning and setting up the compressing machine. Since June of 2005, the firm has reported five additional instances of foreign tablets or capsules found in different pieces of equipment (most related to packaging line equipment) for building 4955 and two for building 4001. In addition, on 2/24/06 the firm submitted to FDA an NDA-Field Alert Report due to a complaint of a foreign capsule of Cartia XT in a sealed bottle of Taztia XT. This event is still under investigation.

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Laboratory Phase I Investigations (At least 31 out of a total of 99 Phase I investigations reviewed from May 2005-March 2006 were inadequate due to incomplete documentation, lack of scientific evidence to support conclusions and/or invalidate original results, or lack of adequate corrective/preventive actions. Some examples include, but are not limited to:

m) INV-06-0062 was conducted on 3/2/06 to investigate the dissolution failure of Metformin HCl Extended-Release Tablets, 500 mg, Lot # 571G0059, which showed results of 35% for Vessel #2 at 3 hrs. (spec: ██████████ in dissolution bath QC#0074. The next time point dissolution result at 10hrs. was within specifications for Vessel #2. The investigation documented that there was an air bubble observed in line 2 at the end of the run that decreased the flow rate for Vessel #2 to 3.8ml/min (spec: ██████████ and concluded that it affected the results of the 3hr. time point only. However, the investigation did not explain how the flow rate only affected the dissolution result at the 3hr. time point and not the subsequent time point at 10hrs. In addition, no preventive or corrective actions were documented in the investigation report.

n) INV 05-0492 was conducted on 12/22/05 to investigate the dissolution failure of Metformin HCl Extended Release Tabs, 500mg, which showed results of 15% in vessel #5 at 1hr. (spec: ██████████ The results were invalidated because the flow rate for that vessel at the end of the run was found out of specifications. The investigation lacked scientific justification to support how the flow rate only affected the first time point at 1hr. and not the subsequent time points at 3 & 10hrs.

o) INV-05-0457 was conducted on 11/21/05 to investigate the dissolution failure of Diltiazem HCl Extended-Release Caps, lot # F599F1189 which showed results of 8% in vessel #3 at 2hrs. (spec: ██████████ The data was invalidated because the flow rate for vessel #3 was found out of specification at the end of the run but the investigation lacked scientific evidence to explain how the flow rate only affected the 2hr. time point and not the subsequent time points at 12, 18 & 24 hrs.

p) INV-05-0489 was conducted on 12/16/05 to investigate the dissolution failure of Diltiazem HCl Extended-release tablets, 60mg, lot #63730, Pan 6, which showed results of 27% for vessel #5 and 35% for vessel #6 at 1 hr. time point (spec: ██████████ It also showed failing results of 9%, -1%, and -2% in vessels 4, 5, & 6, respectively for the 2hr. time point (spec: ██████████ The flow rates for all vessels were confirmed to be within specifications. Nevertheless, the dissolution data was invalidated without considering other possible root causes, i.e. ██████████ malfunction.

Production TWR Investigations:

q) On 3/6/06 while inspecting the production area, the batch production record for ██████████ lot #66461 was reviewed. It documented that during the preparation of the coating solution on 2/16/06, foreign particles coming from the bulk ██████████ system were observed and, as a result, the solution was discarded. On 3/7/06, the investigation report was requested at which time your firm provided TWR #2280 dated 3/6/06 (date opened). According to production personnel, at the time of this incident they were advised by QA that no investigation was needed because the solution was discarded and therefore there was no product quality impact. However, the draft investigation documents that the pump on the ██████████ system failed and this resulted in particles being released from the pump into the ██████████ stream. The determination of the impact to previous lots manufactured using the same ██████████ system was not investigated in a timely manner.

r) TWR #2169, dated 10/13/05 (occurrence date), was discovered on 1/25/06 and opened on 1/27/06 to document that during the processing of the second half of part 2 of the ██████████ stage of Lovastatin 60 mg, lot F630F1132 (60315), it was determined that the product temperature probe was reading seven degrees higher than actual which means that for 45 minutes of spray time the product temperature was running between 16-18°C instead of the specified range of ██████████ The

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investigation report documented that the temperature probe was adjusted on 10/12/05, one day before the occurrence of this incident and that the most probable cause for the product temperature probe reading 7° higher was actually attributed to a calibration error; however, the documentation for the calibration performed on 10/12/05 shows that the temperature probe was reading 9 °C and 12 °C low and was calibrated to the required parameters. The root cause and the determination of the impact to previously manufactured lots using the same temperature probe were not determined during this investigation.

OBSERVATION 5

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used.

Specifically,

a) Eight out of ten cleaning SOPs reviewed are not specific regarding the washing method (scrub, sponge, cloth, rinse) the number of rinses, or rinsing time or volume of the rinsing agent to be used for the rinsing step: PD-0012, "Operating/Cleaning Procedure for the [REDACTED]"; PD-0018, "Operating and Cleaning Procedure for the [REDACTED]"; PD-0043, "Operating and Cleaning Procedure for the [REDACTED]"; PD-0124, "Operating and Cleaning Procedure for the [REDACTED]"; PD-0182, "Cleaning Procedure"; PD-0103, "Operation/Cleaning Procedure for the [REDACTED]"; PD-0108, "Operation and Cleaning Procedure for the [REDACTED] with [REDACTED] and [REDACTED]"; and PD-0152, "Operation/Cleaning Procedure for [REDACTED]". In addition, the cleaning SOPs reviewed lack specificity in the following sections:

- (1) Section 7.3.2.3.7 of SOP PD-0012 indicates: "If necessary, brush the interiors and exteriors and walls with [REDACTED] detergent." When asked when brushing is necessary, one operator [REDACTED] said that he "thinks" it is always necessary to brush while another operator [REDACTED] said that it should be done for every major cleaning.
- (2) Several sections of SOP PD-0012 indicate spraying or rinsing parts with [REDACTED] (e.g., 7.3.2.3.5.1, 7.3.2.3.8.3, 7.3.2.3.9, 7.3.2.5.3, 7.3.2.6.5, and 7.3.2.6.6). Operator [REDACTED] said that he can either spray the part with [REDACTED] and wipe it with a cloth a "little bit" damp with [REDACTED] or just wipe it with the [REDACTED] damp cloth.
- (3) The current version of SOP PD-0124 (version 4 dated 6/23/05) is missing a rinse step; after washing parts with the detergent solution, step 8.3.20 indicates wiping with [REDACTED]. According to the firm's officials, this step was inadvertently left out when the current version was written.

b) Several investigations related to cleaning swab failures that included product, detergent or unknown residues stated that the root cause was the failure to thoroughly rinse or clean equipment or that the cleaning procedures were not specific enough. However, none of the SOPs involved in these investigations have been revised to make the rinsing and/or cleaning instructions more specific. For instance:

- (1) TWR 1545 was opened on 6/17/05 due to 3 swab samples ([REDACTED]) that failed the limit for [REDACTED] residues. The SOPs that describe the cleaning procedure for the [REDACTED] include SOP PD-0012, "Operating/Cleaning Procedure for the [REDACTED]"; SOP PD--0115, "Operating

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER 555 Winderley Place, Suite 200 Maitland, FL 32751 (407) 475-4700 Fax: (407) 475-4768		DATE(S) OF INSPECTION 03/06/2006 - 04/18/2006*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Thomas P. Rice, Chief Executive Officer & Director		FEI NUMBER 3003194604
FIRM NAME Andrx Pharmaceuticals, Inc.	STREET ADDRESS 4955 Orange Dr	
CITY, STATE, ZIP CODE, COUNTRY Fort Lauderdale, FL 33314-3902	TYPE ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer	

and Cleaning Procedure for the [REDACTED] with [REDACTED] and SOP PD-0090, "Operation/Cleaning Procedure for [REDACTED]". The TWR indicates that none of the rinse steps in the SOPs lists a length of time or volume of rinsing agent for the rinse, and that the SOPs do not specify the [REDACTED] concentration for the rinse steps. According to the TWR, the interviews of the manufacturing operators disclosed variations of the procedure in respect to the number of rinses and rinsing agent use and/or order, and rinsing times (between 5 minutes to one hour). The swab analysis forms showed inconsistency in the cleaning vehicle used; some forms indicated [REDACTED] whereas other forms showed [REDACTED] as the cleaning vehicle. However, the SOPs have not been revised to make the cleaning and rinsing procedures more specific.

(2) The interim report for TWR 1555 indicates that no specific rinse times or volumes are defined in SOP PD-0005 effective 3/9/05; this SOP had not been revised at the time of the inspection.

(3) TWR 2194 was opened on 2/3/06 to investigate a swab failure for Diltiazem HCl ER Capsules. The TWR indicates that "one possible root cause for the cleaning validation failure would be that the operator did not clean the equipment properly per SOP, although this could not be proven". The TWR also indicates that, "in light of the cleaning validation failure, validation personnel reviewed the cleaning procedure, and determined that no changes were warranted at this time." However, the cleaning procedure (PD-0018, "Operating and Cleaning Procedure for the [REDACTED] [REDACTED] is not specific regarding how parts should be washed (scrubbed with brush, sponge, cloth, or just rinsed) and rinsed (time or volume of rinsing agent). In addition, the procedure indicates that parts should be rinsed with [REDACTED] but the firm does not use any [REDACTED] to rinse equipment.

(4) TWR 2259 was opened on 2/24/06 for detergent swab failures on the [REDACTED]. The TWR states that "...considering the high results, it is most likely that the rinsing of the equipment was not thorough enough. Considering this most possible cause for the obtained results, emphasis on proper rinsing for equipment after any major cleaning will be discussed with the operators, as per PD-0043." However, neither the version that was in use at the time of the cleaning failure (version 2.0, effective 11/13/02) nor the current version (version 3.0, effective 2/24/06) of PD-0063, "Operating and Cleaning Procedure for the [REDACTED] (this is the correct SOP number, not PD-0043) are specific regarding how equipment parts should be washed (with brush, sponge, cloth, etc.) or regarding rinsing times or volume.

OBSERVATION 6

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

a) The firm's Equipment Cleaning Validation Policy, TSP-0001, indicates that [REDACTED] or other [REDACTED] used for final rinse shall be the same quality, or better, as that used for manufacturing or by regulation". According to this policy, [REDACTED] should be used for the final rinse of the equipment because it is the quality of [REDACTED] used for manufacturing. In addition, SOP PD-0018 indicates that [REDACTED] should be used for the final rinse of equipment. A tour of the manufacturing area disclosed the presence of [REDACTED] points of use; however, an interview with the Manufacturing Director [REDACTED] and an

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FOOD AND DRUG ADMINISTRATION

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Maitland, FL 32751
(407) 475-4700 Fax: (407) 475-4768

DATE(S) OF INSPECTION

03/06/2006 - 04/18/2006*

FEI NUMBER

3003194604

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Thomas P. Rice, Chief Executive Officer & Director

FIRM NAME

Andrx Pharmaceuticals, Inc.

STREET ADDRESS

4955 Orange Dr

CITY, STATE, ZIP CODE, COUNTRY

Fort Lauderdale, FL 33314-3902

TYPE ESTABLISHMENT INSPECTED

Pharmaceutical Manufacturer

operator [REDACTED] disclosed that [REDACTED] is never used to rinse equipment. The incoming city water is not treated and, although it is sampled once a week, the test performed (microbial) is for information only.

b) Operator [REDACTED] said that he executes the cleaning procedures by memory based on his experience; he said that he only reads the SOP when there are changes.

OBSERVATION 7

Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

a) Filters used in [REDACTED] and [REDACTED] are cleaned using [REDACTED] but are not included in the cleaning validation studies to confirm that the rinsing procedures are effective in removing [REDACTED] residues.

b) Report number QCR-05-051-MTH, "Analytical Test Method Report for the Determination of [REDACTED] on [REDACTED] Surfaces", shows that the recoveries obtained by Analyst [REDACTED] in [REDACTED] and [REDACTED] plates were significantly lower than the recoveries of the other two analysts. Since the test would not meet acceptance criteria using the recovery data obtained by Analyst [REDACTED] in these two surfaces, the firm changed the analyst and calculated the correction factor for residues using the data from the fourth analyst. No investigation of Analyst [REDACTED] swabbing technique was conducted to determine the reason of her low recoveries and no corrective actions were implemented to make sure her swabbing technique effectively recovers residues from equipment. However, Analyst [REDACTED] is still swabbing equipment for cleaning validation and verification purposes. The firm does not have any procedure to make sure that the analysts' swabbing techniques are adequate before the analysts are allowed to perform swabbing for validation and verification studies.

OBSERVATION 8

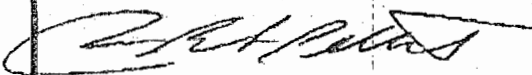
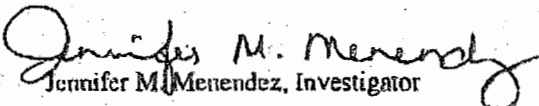
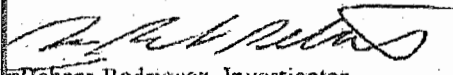

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.

Specifically, your firm failed to perform an adequate method validation for Taztia XT Capsules. The current approved analytical procedure for the analysis of [REDACTED] for drug release (STM 696, 697, 698, 699, 700) requires the use of [REDACTED] as the dissolution media. The method validation for this product was performed using [REDACTED] as the dissolution media.

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OBSERVATION 9	
Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up.	
Specifically,	
a) The cleaning swab failure investigations reported under TWRs 1545, 1555, 2194, 2259 disclosed that the root cause was the failure to thoroughly rinse or clean equipment or that the cleaning procedures were not specific enough. The QC Unit failed to follow up on these findings and none of the SOPs involved in these investigations have been revised to make the rinsing and/or cleaning instructions more specific.	
* DATES OF INSPECTION: 03/06/2006(Mon), 03/07/2006(Tue), 03/08/2006(Wed), 03/09/2006(Thu), 03/10/2006(Fri), 03/13/2006(Mon), 03/14/2006(Tue), 03/15/2006(Wed), 03/16/2006(Thu), 03/17/2006(Fri), 03/20/2006(Mon), 03/21/2006(Tue), 03/22/2006(Wed), 03/23/2006(Thu), 03/24/2006(Fri), 03/27/2006(Mon), 03/28/2006(Tue), 03/29/2006(Wed), 03/30/2006(Thu), 04/17/2006(Mon), 04/18/2006(Tue)	
FDA EMPLOYEES' NAMES, TITLES, AND SIGNATURES:	
 LCDR Heana Barreto-Petit, Investigator	 Jennifer M. Menendez, Investigator
 Rebeca Rodriguez, Investigator	 Jennifer D. Hollstrom, Analyst
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