DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 Phone: 510-337-6700 Fax: 510-337-6702 Industry Information: www.fda.gov/oc/industry	06/16/2014-07/31/2014* FEI NUMBER 3004182921

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: George Frederick Wilkinson, President and Chief Executive Officer

FIRM NAME	STREET ADDRESS
Impax Laboratories, Inc.	31145 San Antonio Street
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Hayward, CA 94544-7905	Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

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

Specifically,

A.) On 07/09/2014, we reviewed Laboratory Investigation Report (LIR) PR218999, created on 10/11/2012, and observed that release testing for Pyridostigmine Bromide Tablets, 60mg (ANDA [redacted] bulk lot [redacted] had a reported assay value of [redacted] on 10/11/2012. The Quality Control Action Limit (QCAL) for the Pyridostigmine Bromide Tablets, 60mg assay is [redacted] as stated in written procedure 2QCC-001.02 titled, "Evaluation of Out-of-Specification (OOS), Quality Control Alert Limit (QCAL) and Aberrant Laboratory Results" Effective Date August 24, 2012. Confirmation testing was performed during the laboratory investigation (PR218999) on 10/11/2012 and the resulting assay values were out of specification, approximately [redacted] (specification range: [redacted] The firm concluded in PR218999 in part, "...there was no lab error found, the original below QCAL AS results for the Affected lot were true results...."

The investigation did not address the ramifications of generating out-of-specification confirmatory test results, nor did the investigation expand into manufacturing operations. Lot [redacted] has an expiration date of August 2015 and was approved by Quality Assurance and released to market on 11/13/2012.

B.) On 07/24/2014, we reviewed Laboratory Investigation Report (LIR) PR399755, created on 09/26/2013, for the release testing of Fludrocortisone Acetate Tablets, 0.1mg (ANDA [redacted]), bulk lot [redacted] We observed the result from one of the [redacted] (AS1) had a value of [redacted] performed on 09/17/2013, which is below the QCAL of [redacted] per written procedure 2QCC-001.02 titled, "Evaluation of Out-of-Specification (OOS), Quality Control Alert Limit (QCAL) and Aberrant Laboratory Results" Effective Date August 24, 2013. During the

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		Lance M. De Souza, Investigator Eric L. Dong, Chemist Stephanie A. Slater, Investigator	7/31/2014

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laboratory investigation (PR399755), the firm used standard and sample solutions that were [redacted] past expiry to perform confirmatory tests on 09/27/2013. The confirmatory re-vialed result was [redacted] for AS1, which was out of specification [redacted] The firm concluded in PR399755: "Since the results were consistent between the affected samples and the control samples, the original results were considered confirmed."

Based on test method 2TFDCAS.01 titled, "Fludrocortisone Acetate Tablets, USP Identification, Assay, Uniformity and Stability Test Method", the firm claimed that Fludrocortisone Acetate degrades [redacted] However, this investigation did not consider the [redacted] of the product as described in Report No.: SUM-AR-13-0057 Rev. 01, titled "Forced Degradation Studies for Fludrocortisone Acetate Tablets, USP Identification, Assay, Uniformity and Stability Test Method" dated 07/23/2013. Furthermore, the investigation and written procedure 2QCC-001.02 did not justify the use of these expired testing solutions.

OBSERVATION 2

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

Specifically,

A.) On 07/07/2014, we reviewed method validation report VTMSAS.03 titled, "Tamsulosin HCl Capsules Identification, Assay Uniformity, and Stability Test Method Validation" dated 01/14/2008. We observed that the [redacted] changed multiple conditions simultaneously. No justification was provided for this approach that may mask the opposing effects of multiple changes. Additionally, your written procedure 2LAB-054.00 titled, "Validation and Verification for Phase III and Commercial Test Methods", Effective Date 03/19/2014, does not specify to perform each [redacted] condition one at a time.

B.) On 07/14/2014, we reviewed the executed Method Transfer Protocol #MT-051 titled, "Tamsulosin HCl Capsules, 0.4mg" dated 12/01/2008. The absolute difference of the average results from each laboratory was [redacted] This significant deviation was not addressed by your firm and there was no documented justification for the continued use of the assay method 2TTMSAS titled, "Tamsulosin HCL Capsules Identification, Assay, Uniformity And Stability Test Method", Effective 06/15/2009.

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C.) A demonstration of equivalency has not been performed for all in-house test methods where an applicable USP test method is also available. For example, Document No. VP2TPYBAS.00 titled, "Supplemental Method Validation Report for The Assay Test Method (2TPYBAS) for Pyridostigmine Bromide Tablets, USP, 60mg", dated 06/27/2013 was based on USP, but was significantly modified and lacked a documented USP equivalency assessment. Additionally, other products, which lack an equivalency assessment includes: Bupropion HCl ER Tablets, 100mg, 150mg, and 200mg; Bupropion HCl ER (XL) Tablets, 150mg; Dantrolene Sodium Capsules, 25mg, 50mg, and 100mg; Dipyridamole Tablets 25mg, 50mg, and 75mg; Orphenadrine Citrate ER Tablets, 100mg; Oxybutynin Chloride ER Tablets 5mg, 10mg, and 15mg; and Rimantadine Hydrochloride Tablets, 100mg.

THIS IS A REPEAT OBSERVATION.

OBSERVATION 3

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used and instructions for protection of clean equipment from contamination prior to use.

Specifically,

A.) On 07/22/2014, we observed Quality Assurance (QA) Inspectors perform cleaning verification procedures on your [redacted] (equipment number IP5025) and [redacted] (equipment number EQ6346). After the sampling of Fludrocortisone Acetate API residue and cleaning agent residue was completed, we observed residual rayon fibers on the inner surface of the [redacted]. The trace rayon fiber strands measured up to 1.2 cm in length. Your written procedure 2QUA-085.03 titled, "Equipment Swab, Rinse Preparation and Sampling" Effective Date 07/21/2014 does not instruct employees to perform a visual inspection check of the swab locations after swabbing, nor does it instruct the cleaning of the swab areas post-sampling.

B.) Written procedure 2QUA-085.03 titled, "Equipment Swab, Rinse Preparation and Sampling" Effective Date 07/21/2014 was not consistent with other cleaning validation test methods that are currently used by QA Inspectors. For example, on 07/22/2014, your QA Inspectors followed 2QUA-085.03 and test method 2TFDCCV.03 titled, "Fludrocortisone Acetate Tablets Cleaning Validation Test Method" Effective Date

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11/20/2003. Written procedure 2QUA-085.03, section 5.5.3 states in part, "Document the start time of the soaking [of rayon for sampling swabs] in SOP VAL-029 attachments" and section 5.5.5 states in part, "Document the End Time for soaking [of rayon for sampling swabs] in SOP 2VAL-029 attachments." However, according to cleaning validation test method 2TFDCCV.03, the sample preparation steps do not require documentation of the soak start and stop times.

OBSERVATION 4

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

Specifically,

The [redacted] spectrophotometer located in the GMP Analytical R&D Laboratory (equipment number IP8032, located in Building B8) and the [redacted] spectrophotometer in the QC Laboratory (equipment number IP4263 in Building B5) did not have validated data integrity acquisition systems to ensure that analysts cannot re-write or delete analytical data during analyses. Both systems were used in GMP activities, such as release testing, raw material testing, stability testing, method validation, and cleaning verification.
THIS IS A REPEAT OBSERVATION.

OBSERVATION 5

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

Specifically,

A.) On 6/16/2014, we found a plastic bag containing thirteen (13) auto sampler vials next to an Instrument Ion Chromatography System (equipment number IC3). The plastic bag was labeled, "HPLC 236 B", which references a different type of laboratory instrument, HPLC (high performance liquid chromatography).

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Six of the thirteen vials lacked reference to the test method or notebook. A single vial labeled, "H2O" was not labeled consistent with instructions given by written procedure 2LAB-010.00 titled, "Control of Labeling of Chemicals, Reagents, and Solutions" Effective Date 03/04/2014, in that it was missing references to the test method, notebook, and date prepared. Written procedure 2LAB-010.00 section 5.3 Standard and Sample Solution Labeling, states in part, "Label standard solution with the name of the standard, date of preparation, analyst initials, method and reference…Label sample solution with the sample name, date of preparation, analyst initials, method and reference."

B.) On 07/28/2014, we reviewed laboratory notebook number WI24900, pages 22 to 27, which described the stability testing for dissolution of Fludrocortisone Acetate Tablets, 0.1mg lot number 10000283 ([redacted]= [redacted] weeks, [redacted]). We found that the standard accuracy check was outside of the acceptable range [redacted] with a value of [redacted]. The analyst did not follow written procedure 2QCC-008.03 titled, "General Chromatography" Effective Date 04/28/2014, section 5.4.6.1, which instructs analysts to "Re-inject the standard check solution to make sure the failure was not due to equipment malfunction." The analyst proceeded to step 5.4.6.3, and prepared another set of two standard solutions and repeated the standard check.

C.) On 06/17/2014, we observed two small, unlabeled plastic bags containing tablets in the large waste bin in Building B2 Room 196. One bag contained 11 orange tablets. The second bag contained 12 purple tablets. The bags did not have the required waste label affixed to them and they were not entered in the waste bin logbook per written procedure 2MFG-149.01 titled, "Solid Non-Controlled Substance Waste Disposal" Effective Date 06/05/2014.

OBSERVATION 6

Buildings used in the manufacturing and holding of a drug product are not maintained in a good state of repair.

Specifically,

On 06/16/2014, during our inspection of the walk-in Stability Chamber (equipment number IP5166, 23-27oC, 55-65% RH) we observed the following:

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1.) Rust stains were on the metallic floor of the Stability Chamber underneath rubber floor mats.
2.) The copper piping elbow was covered in silicone-epoxy.
3.) One ceiling tile was sagging.
4.) Corrosion was on the condensate drain pan.

This walk-in Stability Chamber is used for the storage of GMP commercial products on stability studies, products for R&D Submission studies, and products on clinical stability studies.

OBSERVATION 7

Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit.

Specifically,

A.) Change Control No. 200005111 dated 04/30/2014 requested a change to written procedure 2QUA-092.03 titled, "Sampling Plans for Process Performance Qualification Lots" to remove references to "FDA Guidance for Industry, Powder Blends and Finished Dosage Units Stratified In Process Dosage Unit Sampling and Assessment, Draft October and November 2003" from the procedure. However, the most recent version of the procedure, 2QUA-092.04, section 6.1.2.1, was not changed according to this change control request.

B.) Written procedure 2QCC-016.04 titled, "Data Review Procedure for Quality Control Laboratory" Effective Date 05/12/2014 section 5.3.1.1 refers to "Attachment 1". Attachment 1 is a guideline that can be used by Quality Reviewers to review laboratory data. We observed that Attachment 1 was missing from 2QCC-016.04. According to section 5.3.1.1, "The reviewer is responsible for reviewing the material in both the guideline and topics covered in this SOP". Furthermore, on 7/15/2014, we observed QC Notebook Reviewer A.G.P. use an uncontrolled, Excel spreadsheet during a laboratory notebook review.

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