DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax: (510) 337-6702 Industry Information: www.fda.gov/oc/industry	02/23/2012 - 03/28/2012* FEI NUMBER 3004182921

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Chungchiang Hsu, President & Chief Executive Officer

FIRM NAME	STREET ADDRESS
Impax Laboratories, Inc.	31153 San Antonio Street
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Hayward, CA 94544-7905	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:

OBSERVATION 1

Drug products failing to meet established standards and specifications are not rejected.

Specifically,

During my inspection of laboratory Quality Control raw data, I noted the following:

a) Multiple "trial" sample injections for Acarbose, USP 50 mg tablets (lot #(b) (4) bulk lot release) were performed for related substances (impurities) by HPLC

- Trial 1: 02/22/12 at (b) (4)
- Trial 2: 02/22/12 at (b) (4)
- Trial 3: 02/22/12 at (b) (4)

- Official: 02/22/12 at (b) (4)

An impurity peak (retention time (b) (4) minutes) was detected during the first "trial" sample injection for lot #(b) (4) at (b) (4) . This impurity peak was not detected during the subsequent two trial injections, and not detected during the "official" injection at (b) (4) .

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

b) Multiple "trial" sample injections for Acarbose, USP 25 mg tablets (lot #(b) (4) bulk lot release) were performed for related substances (impurities) by HPLC

- Trial 1: 10/06/11 at (b) (4)
- Trial 2: 10/06/11 at (b) (4)

- Official: 10/06/11 at (b) (4)

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The peak area for "Impurity(b) (4) dropped from (b) counts in the first "trial" injection for lot #(b) (4) at (b) (4) to (b) (4) counts in the "official" injection a(b) (4) (b) (4) drop).

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

c) Multiple "trial" sample injections for Acarbose, USP 50 mg tablets (lot #H0010111(b) (4) weeks a(b) (4)C/(b) (4)% RH stability) were performed for related substances (impurities) by HPLC

- Trial 1: 02/02/11 at (b) (4)
- Trial 2: 02/02/11 at (b) (4)
- Trial 3: 02/02/11 at (b) (4)

- Official: 02/02/11 a(b) (4)

I noted a difference in the impurities peak profile for lot # H0010111 corresponding to the retention time for "Impurity(b) (4) between each of the four sample injections listed above, including the "official" results.

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

d) Multiple injections for Buproprion HCl Extended Release 150 mg tablets (lot #(b) (4) bulk lot release) were performed on 11/21/11 for related substances (impurities) by HPLC

- Official 1: 11/21/11 at (b) (4) - analyst manually aborted sample set due to "split" peak at retention time (b) (4) minutes
- Trial: 11/21/11 a(b) (4)

- Official 2: 11/21/11 at (b) (4)

The "split" impurity peak identified at retention time (b) (4) in the first "Official" analysis a(b) (4) for lot (b) (4) was not detected in any of the subsequent injections.

There is no documentation and/or investigation to provide assurance that the multiple injections were performed using the same samples/lots under analysis.

e) A second sample injection for Fludrocortisone Acetate 0.1 mg tablets lot #10000283 (b) (4) weeks at (b) (4)C(b) (4)% RH stability) related substances (impurities) analysis by HPLC was manually added to the running sample set on 03/05/12

- Original injection on 03/05/12 a(b) (4)
- duplicate injection on 03/05/12 at (b) (4)

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According to the QC analyst on 03/06/12, this duplicate injection was added due to an "unknown" impurity peak identified in the original injection at Retention Time (b) (4) minutes.

This duplicate injection performed at (b) (4) shows no impurity peak at Retention Time (b) (4) minutes.

There is no documentation and/or investigation to provide assurance that both injections were performed using the same samples/lots under analysis.

f) Multiple injections for Nadolol and Bendroflumethiazide 40/5 mg tablets, lot #10001287 (b) (4) weeks a (b) (4) C/ (b) (4) %RH stability) were performed on 02/06/12 for related substances (impurities) by HPLC

- Official 1: 02/06/12 a (b) (4) - analyst manually aborted sample set after first sample injection due to "unexpected" peak at retention time (b) (4) minutes
- Trial: 02/06/12 a (b) (4)
- Official 2: 02/06/12 at (b) (4)

The "unexpected" impurity peak identified at retention time (b) (4) minutes in the first "Official" analysis was not detected in any subsequent injections.

There is no documentation and/or investigation to provide assurance that each sample injection was performed using the same sample/lot under analysis.

g) "Trial" and "Official" sample injections for Dantrolene Sodium, 25 mg capsules (lot # (b) (4) bulk lot release) were performed for assay and content uniformity by HPLC

- CU #4 Trial: 03/26/11 at (b) (4)
- CU #4 Official: 03/26/11 at (b) (4)

According to the QC supervisor on 03/20/12, content uniformity #4 was chosen as the "trial" sample because it was the highest weight out of the (b) (4) capsules needed for content uniformity testing. This "trial" sample was performed to see "if it would cause us problems" due to a higher peak area. Integration and potency calculation for the CU #4 trial sample for lot (b) (4) shows a result of (b) (4) %, while the "official" result for CU #4 was reported a (b) (4) %

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

h) At least one "trial" injection for Divalporex Sodium, 500mg Extended Release Tablets (lot #8121651, (b) (4) weeks at (b) (4) C/ (b) (4) % RH stability) was performed for chromatographic purity by GC

- Trial: 04/18/11 a (b) (4)

- Official: 04/18/11 at (b) (4)

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

i) At least one "trial" injection for (b) (4) capsules, (b)(4) mg (lot (b) (4) (b)(4) weeks at (b)(4) C (b)(4)% RH stability) was performed for chromatographic purity by HPLC. (b) (4) (b) (4) .

- Trial: 12/02/10 at (b) (4)
- Official: 12/03/10 at (b) (4)

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

j) At least one "trial" injection for Doxycycline, 150 mg capsules (lot #R09056-30, (b)(4) weeks at (b)(4) C (b)(4)% RH stability) was performed for related substances (impurities) by HPLC. This batch was the "pivotal" batch, submitted in support of ANDA 200065.

- Trial: 10/19/09 at (b) (4)
- Official: 10/19/09 at (b) (4)

There is no documentation and/or investigation to provide assurance that "trial" and "official" samples were performed using the same sample/lot under analysis.

OBSERVATION 2

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product.

Specifically,

a) Laboratory Investigation Report (LIR) 211082 was initiated on 10/07/11 due to an out of specification (OOS) assay/potency lot release result by HPLC for Acarbose (ACB) Tablets, 25 mg, lot #'s (b) (4) and (b) (4) at (b) (4)% and (b) (4)%, respectively (specification = (b)(4) %). The laboratory investigation found "no lab determinate error", and "OOS results will be reported to QA for disposition". The LIR was closed on 10/14/11.

A QA/manufacturing investigation was then performed under Investigation Report (IR) 200001927, and the root cause was

identified as: "(b) (4) ". The IR was closed on 12/16/11.

However, review of QC raw data revealed multiple "studies" performed from 11/11 to 02/12, which according to the Quality Control Manager, were related to IR 200001927, and were being performed to evaluate the accuracy of the potency method. The Quality Control Manager stated that these studies were being directed by Quality Unit management, and that the current method was found to produce artificially high sample potency results.

There is no evidence that the "studies" mentioned above were documented in any Quality record, and were performed according to an executed protocol with defined parameters. There is no data available to provide assurance that Acarbose tablets (25mg, 50mg, 100mg) meet potency specifications, due to questionable method accuracy.

Since the ACB OOS potency results were documented under LIR 211082 on 10/07/11 and the studies were initiated, a total of (b) (4) batches of ACB have been release by the Quality Unit for distribution; the most recent of which was released on 02/15/2012 despite known method inaccuracy.

b) Review of QC HPLC raw data revealed multiple "studies" within the data folders for Tamsulosin (TMS) and Oxybutanene (OXE). The Quality Control Manager provided the following explanation:

- During the analysis of Tamsulosin HCl 0.4 mg capsules lot #(b) (4) and (b) (4) lot release assay/potency and content uniformity by HPLC on 01/03/12, unknown peaks were identified in at least one sample injection for each lot.

- During the analysis of Oxybutanene 10 mg tablets lot (b) (4) lot release assay/potency and content uniformity by HPLC on 01/10/12, unknown peaks were identified in at least one sample.

On 01/05/12, 01/06/12, 01/11/12 and 01/12/12, the laboratory performed additional sample injections for the abovementioned lots alongside multiple injections with various other "spiked" active pharmaceutical ingredients (API's) manufactured by the firm, including Chloroquine (CHQ) and Acarbose (ACB). The purpose of the spiked API's was to determine the identity of the unknown peaks.

There was no written investigation documenting this evaluation of unknown peaks identified during lot release finished drug product testing.

OBSERVATION 3

Written procedures for sampling and testing plans are not followed for each drug product.

Specifically,

Investigations documented in the Laboratory Investigation Records (LIRs) are not conducted according to the procedures described in SOP 2QUA-053.03, "Evaluation of Out-of-Specification Laboratory Results".

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a) LIR 212006 was initiated by the laboratory on 01/20/12 in order to investigate "suspect out of trend results" for Assay (AS) and Content Uniformity (CU) of Dipyridamole, 25 mg tablets, lot #'s (b) (4) and (b) (4).

- Suspect results for lot (b) (4) (CU sample (b) (4) = (b) (4)%) were collected on 01/18/12, and suspect results for lot (b) (4) (AS mean = (b) (4) %, CU mean = (b) (4) %) were collected on 01/19/12.
- A series of investigation and confirmation injections for each lot were performed on 01/19/12, including but not limited to:
    - Re-injection of original vials
    - Re-mixing of original vials
    - Re-stirring and re-dilution of original vials
    - Analysis of original vials on a different HPLC instrument

LIR 212006 was initiated retrospectively on 01/20/12 following the completion of multiple sample re-preparations and sample retests, in an attempt to summarize an investigation already performed. No LIR was initiated to document the investigation and multiple sample preparations, no IR was initiated by QA, and no sample resting was authorized, as required per sections 7-8 of SOP 2QUA-053.03.

b) Multiple injections, including "Trial" injections, for Nadolol and Bendroflumethiazide (NBZ) 80/5 mg tablets lot #10001642 (b) (4) weeks a (b) (4) C (b) (4) % RH stability) were performed from 01/11/12 to 01/12/12 for related substances (impurities) by HPLC.

- Official 1: 01/11/12 at (b) (4) - analyst manually aborted sample set due to "bump found at about (b) (4) minutes"
- Trial 1: 01/11/12 at (b) (4)
- Official 2: 01/11/12 at (b) (4)
- Trial 2: 01/12/12 a (b) (4)
- Trial 3: 01/12/12 a (b) (4)
- Official 3: 01/12/12 at (b) (4)

The QC Chemist stated that the original sample set performed on 01/11/12 was aborted due to a "bumb" (peak) identified in lot #10001642 at retention time (b) (4) minutes. Sample results were never processed/reported. LIR 212002 was retrospectively initiated on 01/12/12 following multiple same re-injections and re-preparations performed without prior authorization, as required per sections 7-8 of SOP 2QUA-053.03.

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OBSERVATION 4

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically,

a) During inspection of the non-dedicated fluid bed dryer located in manufacturing room (b) (4) on 02/23/12, the following conditions were observed:

i) (b) (4) unidentified stainless steel braided solvent processing hoses with unknown product residue buildup were found being stored in an open plastic bag. The operator on duty stated that these (b) (4) hoses with unknown product residue were not used in the manufacture of the current batch (Pseudoephedrine Sulfate 60 mg Lot #(b) (4)), and should have been removed from the room.

ii) (b) (4) stainless steel product scoop tools with unknown powder residue were each found as stored in plastic bags identified with a "major cleaned" green sticker.

b) Equipment failures requiring non-routine maintenance are not always investigated. For example:

- Out-of-Service Notification (OOSN) No. 2OOSN-11-337 was issued for the presence of water inside the electrical cabinet for Equipment No (b) (4) (b) (4) ; a non-dedicated in-process equipment used in the granulation process.
- OOSN No. 2OOSN-11-366 was issued for Equipment No. (b) (4), (b) (4) ; used to remove powder residue from tablets following compression, due to the equipment being not operational during the set-up of Doxycycline Capsules 150 mg, Lot (b) (4) .
- OOSN No. 2OOSN-11-1060 was issued for Equipment No (b) (4) , (b) (4) tablet compression machine, due to a hydraulic fluctuation during equipment set-up operations.

OBSERVATION 5

Written records are not made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.

Specifically,

There is a failure to document and investigate unexplained discrepancies that arise during the course of manufacturing and QC analytical testing, as detailed above in Observations 1 to 4:

a) QC "trial" sample raw data chromatograms appear to differ from official, reported results

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b) Unofficial and undocumented investigations are performed to evaluate suspect QC data, including but not limited to:
   i. Analytical method accuracy and reliability
   ii. Potential drug product cross-contamination due to "unexpected" peaks
c) Laboratory investigations into suspect sample results are not conducted according to written procedures
d) Unexpected manufacturing discrepancies, including but not limited to critical equipment failures, are not investigated

*** DATES OF INSPECTION:**
02/23/2012(Thu), 02/24/2012(Fri), 02/27/2012(Mon), 02/28/2012(Tue), 03/01/2012(Thu), 03/02/2012(Fri), 03/06/2012(Tue), 03/07/2012(Wed), 03/09/2012(Fri), 03/13/2012(Tue), 03/14/2012(Wed), 03/20/2012(Tue), 03/23/2012(Fri), 03/28/2012(Wed)

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