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	01/08/2013 - 02/28/2013* 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.	31145 San Antonio Street
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Hayward, CA 94544-7905	Drug 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

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

Specifically,

Pertaining to NDA (b) (4) Levodopa/Carbidopa IPX066

A. The method validation performed for NDA (b) (4) (b) (4) (IPX066) (Levodopa/Carbidopa Capsule) finished drug products as specified in Test Method, T066RS.18: *Quantitation of Degradation Products in IPX066*, is inadequate. For example:

1) The firm failed to establish specifications (evaluate, identify, monitor, and test) for the two known impurities and/or degradants, (b) (4) and (b) (4) that are identified on the COA for API, levodopa, manufactured by (b) (4)

2) The impurity profile does not include these two (2) known impurities in the finished stability product.

3) The specificity of the test method is not established because the force degradation studies were not performed under acid, base and oxidations conditions.

4) The USP assay test method used for lot release and retesting of the carbidopa and levodopa API is not stability indicating.

5) Water determination using (b) (4) titrator for components I, II, III and IV was not validated.

6) The firm is not testing for the isomer d-Dopa in the levodopa API during release.

7) The study to determine the relative response factor (RRF) for impurity (b) (4) was inadequate. The firm's Relative Response Factor was not determined with a fully validated method because it lacked accuracy and linearity to cover the validation ranges. (b) (4) purity was based on (b) (4) of Levodopa. (b) (4) utilizing placebo samples (free of the active) was not studied and no comparison of (b) (4) area response to a solution of (b) (4) standard.

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Commercial Products

B. Non-suitable test methods are used to release finished drug products.

1) During the establishment inspection, we reviewed test methods for eighteen (18) products and found that 100% of the reviewed methods were not properly validated. For example, accuracy, sensitivity, linearity, LOD, LOQ, and/or specificity were not assessed in the method validations. There is no assurance of the reliability of the data and results generated with the use of the following test methods:

Inadequate Test Methods/Non-Validated Test Methods

Product	Loss on Drying	Chromatographic Purity/Related Substances	Dissolution	Content Uniformity	Assay
Acarbose Tablets	NV	IV	IV	IV	IV
Bethanechol Cl Tablets		IV	IV	IV	IV
Bupropion HCl/ ER (XL) Tablets	NV	IV	IV	IV	IV
Carbidopa/ Levodopa ER Tablets	NV	IV	IV	IV	IV
Fenofibrate Tablets		IV	IV	IV	IV
Nadolol/ Bendroflumethiaz ide Tablets	NV	IV	IV	IV	IV
Colestipol Tablets		IV		IV	IV
Carprofen Tablets	NV	IV	IV	IV	IV
Tamsulosin Hydrochloride Capsules		IV		IV	IV
Pyridostigmine Bromide Tablets		IV	IV	IV	IV
Terbutaline Sulfate Tablets	NV				

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Inadequate Test Methods/Non-Validated Test Methods

Product	Loss on Drying	Chromatographic Purity/Related Substances	Dissolution	Content Uniformity	Assay
Chloroquin Phosphate Tablets	NV				
Dipyridamole Tablets	NV				
Loratadine Tablets	NV				
Primidone Tablets	NV				
Orphenadrine Citrate Tablets	NV				
Oxybutynin HCl Tablets	NV				
Oxymorphone HCl Tablets	NV				

NV= No Validation Data IV= Inadequate Validation Data

2) The firm's consultant completed an assessment of one hundred and twenty seven (127) test methods for stability and product release and found them inadequate. The analytical methods include, but are not limited to, identification; assay; content uniformity; dissolution and related substance. As of 2/8/2013, QC and/or QA approved and concurred with eighteen of these assessments. The firm continues to analyze and release products with these methods regardless of the known deficiencies.

Lots Released with Deficient Test Methods

Product	Dosage	Lot #
Acarbose Tablets	25, 50, 100 mg	H0030371, 10000593, 10004381,10002860, 10002859, 10004380, 10000595, 10001534, H9071531
Bethanechol Cl Tablets	5,10, 25, 50 mg	H0091541, 10003129, 10001683, 10001801

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Lots Released with Deficient Test Methods		
Product	**Dosage**	**Lot #**
Bupropion HCl ER Tablet	100, 150, 200 mg	10000516, 10005195, 10003829
Carbidopa/Levodopa ER Tablets	25/100, 50/200 mg	10000700, 10000803, 10000804, H9101291, H9101551, H9101341, H9101351
Fenofibrate Capsules	54, 160 mg	10001036, 10001037, 10001294, 10001223, 10001293, 10002865
Nadolol/Bendroflumethiazide Tablet	40/5, 80/5 mg	10005261, 10003033, 10001642

3) The firm failed to determine the acceptability of test methods prior to using them in the QC laboratory through formal method transfer procedures. The test methods are currently used by the QC laboratory to release raw and in-process materials, finished drug products, and stability samples. SOP 2ALY-012.07, "Transfer of Analytical Test Method", effective on 8/15/12, states in Section 2.2: *This procedure applies to the transfer of validated, non-compendial, analytical test methods from the Originating Laboratory (OL) to the Receiving Laboratory (RL) (including transfers to and from an Impax laboratory to a contract laboratory).* Examples includes:

Inadequate Method Transfer	
Product	**Test Method**
Loratadine/Pseudoephedrine ER Tablets	Assay, Dissolution, Related Substances
Sotalol HCl Tablets	Assay, Content Uniformity, Dissolution, Related Substances
Terbutaline Sulfate Tablets	Assay, Content Uniformity, Dissolution, Related Substances

4) Impax uses test methods that are not stability indicating to re-test and release active pharmaceutical ingredients (API) used in the production of finished drug products. Examples include:

a. The firm uses USP assay test method (Titration Method) for Pyridostigmine Bromide API, for raw material retest. Titration is not a stability indicating method and cannot detect unknown degradants. For example, Pyridostigmine Bromide purchased from the API manufacturer (b) (4) on (b) (4) with retest dates (re-evaluation) of November 24, 2009, were retested by the firm using the USP titration method. This API lots were used in the manufacture of Pyridostigmine Bromide 60 mg tablets lots (b) (4) approved June 23, 2010.

b. The firm uses USP assay test method for Bendroflumethiazide API (a titration method) for raw material retest. Titration method is not a stability indicating method and cannot detect unknown degradants. For example, Bendroflumethiazide purchased from the API manufacturer (b) (4) lot (b) (4) with retest date (re-evaluation) of September 4, 2012, and was retested by the firm using the USP titration method. This API lot was used in the manufacture of Nadolol/Bendroflumethiazide 40/5 mg tablets lo (b) (4) approved November 30, 2012.

c. The firm uses USP assay test method for Pseudoephedrine Sulfate API (a titration method) for raw material retest. Titration is not a stability indicating method and cannot detect unknown degradants. For example, Pseudoephedrine Sulfate purchased from the API vendor (b) (4) lot (b) (4) with retest date (re-evaluation) of September 1, 2009, was retested by the firm using the USP titration method. This API lot was used in the manufacture of Loratadine/Pseudoephedrine Sulfate 5/120 mg tablets lot (b) (4) approved November 18, 2009.

REPEAT OBSERVATION

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,

Pertaining to NDA (b) (4) Levodopa/Carbidopa IPX066

A. The firm's bulk hold studies data for the drug product and intermediate component lots (b) (4) (b) (4) (b) (4) show a tailing and/or co-eluting on the Levodopa peak in the chromatogram. There is no assurance that the results generated from these studies are accurate and precise.

Furthermore, the six (6) month hold time data submitted for intermediate components (b) (4) and the IPX066 (b) (4) and (b) (4) finished bulk drug product was not complete at the time of filing this application.

B. Two (2) deviations occurred during the execution of the air and ocean shipping studies for the finished bulk drug product. These deviations included the following:

1. The refrigerated truck cooling system was not turned on.
2. A plastic strap was noted on the finished bulk container shipment in lieu of the metal strap specified in the protocol during the ocean shipping study.

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These deviations were never discussed or evaluated in the air and ocean shipping validation report.

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Established manufacturing process parameters are not always validated.

C. The established sampling plans during process validations are not statistically representative of the batch size. For example, the firm uses the generic sampling plan to collec(b) (4) samples from the blender for blend uniformity and(b) (4) samples for dissolution during compression/encapsulation irrespective of the batch size of(b) (4) nits or(b) (4) (b) (4)units.

D. The inlet air temperature used during coating to accelerate the drying process of hygroscopic Colestipol tablets has an established process parameter of(b) (4) C and a target of(b) (4) C in the batch production record. The validation data only supports a process parameter range of(b) (4) °C.

1. In 2012, 33 of the(b) (4) Colestipol 1000 mg tablets batches manufactured were outside the validated process parameter range of(b) (4) °C during the coating process. The firm has received five (5) complaints of swollen Colestipol tablets in 2012.

E. The compression force feeder speed that is used to maintain uniform die fill and compressibility during tablet compression for(b) (4) ablets has an established process parameter of(b) (4)RPM in the batch production record. The validation data only supports a process parameter o(b) (4)RPM.

F. On 1/8/2013 during a tour of Building(b) (4) warehouse, we observed several in-process materials being stored at the compounding, blending, and compression stage of the manufacturing process. SOP #2QUA-036.06: Tracking Bulk Holding Date of Intermediate and Finished Product in SAP states that in-process hold-times in the warehouse are (b) (4) The firm has no scientific data through validation to support the assigned(b) (4) days.

REPEAT OBSERVATION

OBSERVATION 3

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 already distributed.

Specifically,
There is a failure to thoroughly review and document unexplained discrepancies. Examples include:

A. The cleaning solution rinse water from the Sampling Thief-(b) (4) was tested on 07/25/2012 and unknown peaks were identified on the HPLC chromatogram. There is no deviation report, investigation, or root cause assessment for the unidentified peak observed in the HPLC chromatogram from this test. The sample was re-injected(b) (4) nd re-vialed without documentation.

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B. Eight (8) complaints from seven (7) different lots were received for broken tablets of Carprofen 75mg and Carprofen 100mg between September and November 2012. During the investigation of these complaints, broken tablets were confirmed in two of the seven complaint lots. In addition, nine (9) broken tablets were also observed in the Carprofen 100mg lot (b) (4) during 104 week stability sample testing. The investigations failed to identify the root cause and stated that broken Carprofen tablets are a known occurrence.

C. Deviation PR ID #: 1302 was initiated to investigate condensation and clumping in (b) (4) drums of (b) (4) Pyridostigmine Bromide, USP, lot (b) (4) This API is hygroscopic, thus sensitive to temperature / humidity. The deficiencies in this investigation report are as follows:

1. It fails to address the impact of the warehouse storage conditions especially since the firm does not monitor humidity in the warehouse.

2. This deviation report fails to explain why assay for Pyridostigmine Bromide, USP, lot (b) (4) was not performed prior to use to manufacture finished drug product: Pyridostigmine Bromide 60 mg tablets lots (b) (4) and (b) (4)

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,

Pertaining to NDA (b) (4) Levodopa/Carbidopa IPX066

A. The software that controls the (b) (4) spectrophotometer, (b) (4) and (b) (4) particle size analyzer used for NDA (b) (4) (b) (4) (IPX066) were not validated. These instruments/equipment were used to analyze the NDA product. The firm did not validate the instruments data integrity acquisition system to ensure that analysts cannot re-write or delete analytical data during analyses. Data audit trails are not maintained and instrument audit logs are not saved. These instruments generated data for the NDA submission.

Commercial Products

B. (b) (4) moisture analyzer and UV spectrophotometer are used for (b) (4) testing. The firm did not validate the instruments data integrity acquisition system to ensure that analysts cannot re-write or delete analytical data during analyses. Data audit trails are not maintained and instrument audit logs are not saved. These instruments are used in the quality control and research and development laboratories.

C. The in-process weight checks performed during the compression and encapsulation process are performed on equipment scales that allow all production personnel to alter dates and time when performing these in-process weight checks. In addition, the (b) (4) test machine (b) (4) allows for printing of tablet

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hardness raw data results during in-process testing. However, the firm has never enabled this function, hence does not have or store raw data of this operation during production or process validations.

OBSERVATION 5

Written procedures for cleaning and maintenance fail to include description in sufficient detail of methods, equipment and materials used, description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance, and parameters relevant to the operation.

Specifically,

Cleaning procedures and operations are deficient. Examples include:

A. The cleaning validation protocol failed to address the swab location and the swabbing technique on manufacturing equipment during cleaning validation.

B. Swab studies have not been performed to determine the best swab for maximum recovery of active ingredient and other chemical residues after the cleaning operation of non-dedicated manufacturing equipment.

C. There's a failure to establish scientific rationale for the use of (b) (4) as a cleaning agent on production equipment used to manufacture finished drug products.

D. During the cleaning validation of Terbutaline Sulfate, two (2) lots (lot# (b) (4) failed maximum Terbutaline Sulfate chemical product carryover after the initial cleaning process from the (b) (4) spray gun. The equipment was re-cleaned and the incident was never discussed in the cleaning validation summary report.

E. Equipment swab locations performed during the (b) (4) routine cleaning monitoring do not always include the most difficult to clean equipment parts specified in SOP 2VAL-001: Cleaning Verification and Validation Program.

   1) For example, not all difficult to clean equipment parts included in this procedure are tested during (b) (4) routine cleaning monitoring. The (b) (4) and (b) (4) parts specified for routine sampling on the (b) (4) Blender are not performed. Additionally, SOP 2VAL-001: Cleaning Verification and Validation Program does not include the cleaning verification of non-dedicated sampling thief used for sampling multiple raw materials and APIs.

F. On 1/11/2013, during a tour of production area in Building (b) (4), we observed the storage of loose (b) (4) swabs used for swabbing cleaned manufacturing equipment for the evaluation of API and chemical residue in a glass beaker. These (b) (4) swabs expire within seven (7) days from the date they are removed from the vendor packaged plastic wrap and the firm does not document the traceability of these swabs through documentation of vendor expiration dates.

G. SOP # 2MFG-002.17: Cleaning Procedures for Processing Equipment that describes the preparation of in-house cleaning agents (diluted (b) (4) is inadequate because the preparation of this cleaning agent is not documented. A batch record with manufacturing instructions, lot numbers and expiration date have not been established for this process.

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OBSERVATION 6

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically,

A. Start and stop times for critical process parameters (CPP) are not recorded in the batch record during production operation. For example, the start and stop time is not documented for Pyridostigmine Br CPP during pre-blending and final blending that affect blend uniformity.

B. API Assay results are not always used to calculate the amount of active ingredient needed to manufacture a given batch of drug products. For example, during the manufacture of Pyridostigmine, Tamsulosin, Colestipol, Carprofen, Fludrocortisone, Primidone, Promethazine, Fenofibrate, Dipyridamole, Galantamine, Terbutaline, and Oxybutynin; the amount of active ingredient to add during manufacturing is determined by a theoretical value of 100% and not the actual potency value.

C. There is a failure to maintain raw data during in-process parameter checks for tablet hardness and thickness. For example, all batch records and process validations reviewed during the EI do not have raw data printouts for hardness and thickness.

OBSERVATION 7

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically,

The firm does not perform testing of raw materials for conformity with all written specifications reported on the vendor's Certificate of Analysis (COA). They only perform limited testing and have not established the reliability of the supplier's test results. The firm has no documented justification for not performing all tests listed on the certificate. For example:

Pertaining to NDA(b) (4) Levodopa/Carbidopa IPX066

A. For Carbidopa lots(b) (4) used to manufacture NDA lots(b) (4) (b) (4) the firm has not performed bulk and tap density. The firm has not established the reliability of the vendor's analyses for this test.

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B. For Levodopa lots(b) (4) (b) (4) used to manufacture NDA lots(b) (4) and(b) (4) the firm has not evaluated the presence of the enantiomeric impurity, d-Dopa. The firm has not established the reliability of the vendor's analyses for this test.

C. For "Hard Gelatin Capsule Shells, Size 00,(b) (4) (b) (4) Body and(b) (4) Cap", manufacturer lots(b) (4) and(b) (4) used in the submission, NDA(b) (4) , the firm did not perform tests such as identification of TiO_2, acetic acid content and loss on drying. The firm has not established the reliability of the vendor's analyses reported on the COA for these tests.

D. For(b) (4) manufacturer's lot(b) (4) used in the submission lots, NDA(b) (4) , the firm did not perform tests such as sieve, apparent density, tapped density and an acid value as reported on the manufacturer's COA. The firm has not established the reliability of the vendor's analyses reported on the COA for these tests.

E. For(b) (4) (b) (4) manufacturer's lots(b) (4) and respectively, the firm did not perform the residue on evaporation tests and did not report an acid value. The firm has not established the reliability of the vendor's analyses reported on the COA for these tests.

OBSERVATION 8

Drug products are not stored under appropriate conditions of humidity so that their identity, strength, quality, and purity are not affected.

The firm stores hygroscopic drug products, such as Pyridostigmine and Colestipol, in warehouse(b) (4) and warehouse(b) (4) without establishing control limits and monitoring procedures to prevent product degradation from moisture.

OBSERVATION 9

An annual report did not include a full description of the manufacturing and control changes not requiring a supplemental application, listed by date in the order in which they were implemented.

Specifically,

A. SOP has not been established describing or referencing the criteria for filing changes being effected (CBE) or prior approval supplement submissions.

B. Change in humidity specification from(b) (4)RH to(b) (4)RH during production for Pyridostigmine was not addressed in a Changes Being Effected (CBE) submission or in the 2004 Annual Report submission to the Agency. Pyridostigmine is a hygroscopic drug product.

C. Change in final blending time from(b) (4)minutes to(b) (4)minutes during production of Pyridostigmine was not addressed in a Changes Being Effected (CBE) submission or in the 2004 Annual Report submission to the Agency. The increase in blend time was changed to improve blend uniformity.

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OBSERVATION 10

Procedures describing the warehousing of drug products are not followed.

Specifically,

SOP 2WHC-004.14: Staging & Allocating Manufacturing Materials in Section 4.3 states that the electronic enterprise resource planning system is used to document the location, transfer and movement of materials in the warehouse.

On 1/10/2013, we requested printouts from the electronic enterprise resource planning management system. The status and location of (b) (4) drums of raw material Copovidone lot (b) (4) that were stored in the warehouse were unaccounted for in the electronic enterprise resource planning management system.

REPEAT OBSERVATION

OBSERVATION 11

Written procedures are not followed for evaluations done at least annually and including provisions for a review of complaints, recalls, returned or salvaged drug products, and investigations conducted for each drug product.

Specifically,
SOP 2QUA-040.06: Annual Product Review that describes the review and approval of APR states in Section 5.1.5 that (b) (4) (b) (4) This procedure is not followed. For example on 1/22/2013, the most recent annual product review (APR) for Bupropion Hydrochloride Extended Release 100mg between 1/28/2011-1/27/2012 was not complete (approximately 12 months after the due date).

OBSERVATION 12

Employees engaged in the manufacture and processing of a drug product lack the training and experience required to perform their assigned functions.

Employees involved in all aspects of production and analytical testing of drug products are not adequately trained to perform their duties, see OBS 1-11.

* DATES OF INSPECTION:
01/08/2013(Tue), 01/09/2013(Wed), 01/10/2013(Thu), 01/11/2013(Fri), 01/12/2013(Sat), 01/14/2013(Mon), 01/15/2013(Tue), 01/16/2013(Wed), 01/17/2013(Thu), 01/18/2013(Fri), 01/19/2013(Sat), 01/21/2013(Mon), 01/22/2013(Tue), 01/23/2013(Wed),

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CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Hayward, CA 94544-7905	Drug Manufacturer

01/24/2013(Thu), 01/25/2013(Fri), 01/28/2013(Mon), 01/29/2013(Tue), 01/30/2013(Wed), 01/31/2013(Thu), 02/01/2013(Fri), 02/04/2013(Mon), 02/05/2013(Tue), 02/08/2013(Fri), 02/12/2013(Tue), 02/26/2013(Tue), 02/28/2013(Thu)

	EMPLOYEE(S) SIGNATURE	DATE ISSUED
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