

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 158-15 Liberty Ave. Jamaica, NY 11433 (718) 340-7000 Fax: (718) 662-5661 Industry Information: <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>	DATE(S) OF INSPECTION 06/13/2011 - 07/08/2011*
	FEI NUMBER 3001833549

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED  
**TO: John Frank Harmon, Executive Vice President and Chief Operating Officer**

FIRM NAME APP Pharmaceuticals, LLC	STREET ADDRESS 3159 Staley Road
CITY, STATE, ZIP CODE, COUNTRY Grand Island, NY 14072-2028	TYPE ESTABLISHMENT INSPECTED Sterile 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:**

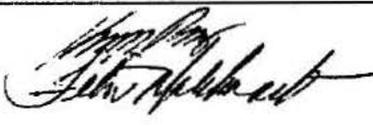
**QUALITY SYSTEMS**

**OBSERVATION 1**

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:

- a. More than 400 customer complaints have been received since January 2010 that involve patient reaction, particulate matter, ineffective, discoloration, cake appearance, low fill, hair in vial, reconstitution issues, cracked vial, leaking/broken vial, stopper coring and other brown contaminant. You have not performed an Initial Impact Assessment as require by your Complaint Management Procedure, Document Number 10-11-02-0003 to any complaints received since January 2010. No explanation was provided for this deviation that affected more than 400 customer's complaint investigation.
- b. There is a failure to thoroughly review your customer complaints:
  - 1. Complaint #PIR 12936 received on 05/10/10, Child PIR 13380 - Pharmacist reported what appears to be an insect stuck on the inside wall of a vial of Lidocaine HCL Injection, USP, lot 407157. You stated in your complaint investigation that without customer sample no evaluation could be made. You have no documented evidence on any attempts to collect the complainant sample. You did not assess your operational areas (filling rooms, aseptic corridor) to determine if they were previous history or trends in your facility with respect to insects. On 01/26/10, you reported (IR 11728) the discovery of an insect floating in the 4 liter (b) (4) waste in filling room (b) (4) after the conclusion of filling of (b) (4) lot (b) (4) and did not include this information in your complaint investigation in order to perform an accurate trend and assessment of your aseptic operational process and processes.
  - 2. Complaint #PIR 12173 received on 03/01/10, Child PIR 12209 - Pharmacist reported dark particulate matter floating in one vial of Heparin Sodium Injection, USP lot 408196. Your Microbiology department reported multiples pieces of flat, rough, brown and black particulate ranging in size from < 10µm to ~ 1420 µm. Your investigation stated that

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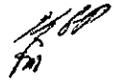
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it was attributed to a spot in the vial that may be a vendor issue. No assessment to the vial supplier was performed nor mentioned in this complaint investigation. You claim in your investigation that the particle is unidentifiable. This product failed to comply with USP <1>. No NDA-Field Alert Report was file with the FDA District Office.

3. Complaint #PIR 15654 received on 01/05/11, Child PIR 15681 – Pharmacy Supervisor reported eleven (11) vials with no labels of Heparin Sodium Injection, USP lot # 6000399. More vials were returned (10 unopened packs of 25 vials each) however; no assessments were ever made to these returned units. Your investigation stated that reserve samples were reviewed; however, review of the reserve sample history form did not disclose any evidence of samples being reviewed. Your investigation disclosed that human error during packaging operation was responsible for the issue. However, multiple complaints for vials missing label has been received before and after the subject complaint. It appears that your corrective and preventive action of retraining the employees was not enough to avoid recurrence. No NDA-Field Alert Report was file with the FDA District Office even when your NDA/ANDA - Field Alert Report procedure (Document number: 10-11-00-0006) states to report any event which may affect the safety, quality, identity, purity or potency of a distributed product. Examples of others inadequate complaints investigation are:
  - I. Complaint #PIR 16849, received on March 24, 2011 (Heparin Sodium Injection, lot #6000826, pharmacy tech reported via e-mail that product arrive without labels) three months later (07/06/11) and the complaint investigation has not been initiated.
  - II. Complaint #PIR 16847, received on March 24, 2011 (Diphenhydramine Hydrochloride Injection, USP unknown lot, pharmacy tech reported via e-mail that product arrive without labels) three month later (07/06/11) and the investigation has not been initiated.
  - III. Complaint #PIR 13506, received on June 29, 2010 (Midazolam Hydrochloride Injection, lot #408477, a pharmacist reported missing vial label) investigation closed on 07/15/10, but no assessment of your retain samples was ever made.
  - IV. Complaint #PIR 12442, received on March 29, 2010 (Heparin Sodium Injection, lot #408018, a pharmacist reported an intact vial was empty). Child PIR 11878 initiated on 04/01/10 and completed on 04/08/10, but no assessment of your retain samples was ever made.
  
4. Complaint #PIR 11871 received on 02/04/10, Child PIR 11878 – A pharmacist reported human hair lodged between the flip cap and the stopper of a Ketorolac Tromethamine Injection, USP lot 408352. You stated that reserve samples were examined. However, the reserve sample history document for the subject lot shows no evidence of been inspected. Your statement of batch manufacturing records review is vague. It does not mention specifics areas reviewed that may have direct or indirect impact in relation to the nature of the complaint. You stated in your complaint investigation that without customer sample no evaluation could be made. You have no documented evidence on any attempts to collect the complainant sample. You did not evaluate nor assessed possible root cause within your manufacturing process and processes to avoid a defect of this type.
  
5. Complaint #PIR 11575 received on 01/11/10, Child PIR 12063 -- A pharmacy tech reported "feathery" dark gray matter inside the vial, appears fungal growth, 2 mL of products is missing, and crack vial in Calcium Gluconate Injection, USP 10% lot 407923. The firm complaint investigation did not address the reason of not identifying the

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fungal like growth. Is inconclusive where the vial may have been cracked. The complaint investigation did not address potential areas of the manufacturing, inspection and packaging process where the crack vial may have occurred. Twenty eight (28) additional units were returned due to this complaint, but complaint investigation made no reference to the rest of the units. Complaint investigation does not address an assessment to the vial supplier or even incoming records of the vial lot used on this finished product lot. Complaint investigation revealed that retain samples were reviewed, but assessment of other lots manufactured in the same filling line using the same vial lot number were not addressed.

6. Complaint #11913 received on 02/08/10, child PIR #12064 – The complainant claims that the product contains a small crack with mold forming inside on Calcium Gluconate, lot #407992. Complaints records revealed that the firm QA unit will start their investigation once complainant sample is received. As per complaint investigation records the root cause is unknown. You stated that 100% visual inspection was performed at the time of the lot being manufactured, but investigation did not provided percentage of defects (units) and similarities to complaint category. Your assessments to your own controls records are questionable. No assessment to your process to determine areas where possible breaking of glass vials may occur in order to improve your operation. Your approach of handling complaint investigation appears to only look into the event itself and no corrective actions to prevent recurrence.
- c. You did not perform a Health Hazard Evaluation as part of your Initial Impact Assessment and justification for the release of drug products lots affected under the Deviation (IIR 16793, dated 03/24/11) where thirty (30) lots of drug products filled in a 3 cc plastic vial were implicated for leaking vials. Your Initial Impact Assessment states: "The detectability risk associated with the defective vial is moderate based on the defect type. A majority of the defects were readily visible during the inspection process. However, smaller, less visible defects, or a breach in the vial on the bottom, where and inspector's vision may be impaired by the [b4] may jeopardize the sterility assurance of the vial and go unnoticed during the inspection process. In addition, a defect of this type was identified in an AQL following the inspection process." In addition, some lots implicated were pre-scheduled by planning to be placed on stability. As part of a thorough investigation and assessment to this known problem of defective vials, you did not placed on stability a representative samples of lots implicated that include all material/product codes.
- d. OOS #3361 was raised on 03/8/11 for failing assay specification test results obtained on Gemcitabine HCL, an active pharmaceutical ingredient [b4] % for API lot [b4] and [b4] % for API lot [b4]. These API lots were used to manufacture semi finished drug lots # [b4] and # [b4]. Your assay specifications for Gemcitabine HCL are set at [b4]. Your Phase I investigation report states... "a non-obvious sample preparation error" as an assignable cause of the out-of-specification test result. You conducted [b4].
- e. OOS #3399 (Heparin Lock Flush, stability Lot #504411A) was raised on 3/24/11 due to failing Assay test results of 87.6% at the 3-month test period (specification limit [b4] %). No assignable cause was identified during the phase I investigation. Nonetheless, a phase II investigation was initiated as per Mitigation Plan G10-021, which requires testing of [b4] samples with RSD NMT [b4] % prior to deciding whether or not to include the original OOS result. Of the [b4] samples tested, sample [b4] was not included due to 'multiple invalid results by analyst one,' and the final

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conclusion was based on results of the [b4] samples. No documentation was produce to determine the reason for eliminating test results of sample [b4]. Also, no documentation was provided to explain the reason for the multiple invalid results.

**OBSERVATION 2**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically:

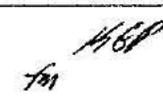
- a. Your Process Simulation Policy, Document Number: 10-01-03-0108 requires that all integral rejects vials must be documented, segregated and incubated. Media fills simulation for parenteral (sterile drug products) filling operations were inadequately performed to qualify aseptic processes. On 06/20/11, it was observed during the [b4] media fill batch (lot 7025353) of a campaign of [b4] no documentation whatsoever, with specific reasons (assignable cause) where integral filled vials were removed after the capping operation and placed in a 5 gallon white pail labeled in part: "TO BE DESTROYED". The removal and destruction of filled vials (integral units) may present a bias to the final media fill results. These media fill runs were executed after the discovery of numerous vials with particulate matter on previous Media Fill Batch 7025073.
- b. In addition, you used [b4] to purge the media from the formulation vessel to the carboy located in the filling room. [b4] exhibits microbial growth inhibitors properties.

**OBSERVATION 3**

Records of returned drug products are not maintained.

Specifically, you have no paper trail to show when the returned drug products was received at your site and all appropriate disposition of such drug products, either destroyed or re-incorporated into the supply chain. Examples are: Complaint (PIR #15654) returned a total of 407 vials of Heparin Sodium Injection USP, lot 6000399 due to missing vial labels and Calcium Gluconate for Injection, PIR #11575 lot #407923 returned 29 units due to possible fungal growth.

**FACILITIES AND EQUIPMENTS**

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**OBSERVATION 4**

Buildings used in the manufacture, processing, packing or holding of drug products are not free of infestation by rodents, birds insects, and other vermin.

Specifically, you have reported five field insects incidents discovered in your manufacturing process since January 2010. Your implemented action to mitigate the infiltration of insects into the plant environment appears to be inadequate. In addition, Complaint #PIR 12936 received on 05/10/10 reported by a Pharmacist claiming what appears to be an insect stuck on the inside wall of a vial of Lidocaine HCL Injection, USP, lot 407157. The following are examples of Deviations where you reported insects in your manufacturing facility, mostly in your aseptic manufacturing areas (class 100; 10,000 and 100,000) and visual inspection process:

- a. Deviation IIR #11728, created on 01/27/10 - [REDACTED] Development Stability Batch. Insect was found floating in the 4 liter (b) (4) waste container in Filling Room [REDACTED]. As per your investigation no mitigation plan was required since pest controls are in-place. However, no assessment on areas for improvements.
- b. Deviation IIR #13847, created on 07/30/10 - Aciclovir Sodium, Lot #7021451 manufactured in Fill Line [REDACTED]. During the visual inspection process, an insect (spider) was identified intact within a vial. As per investigation the probability of recurrence is moderate, as this type of incident has occurred several times in 2010. As per your investigation no mitigation plan was required for this incident since pest controls are in place. However, no assessment on areas for improvements.
- c. Deviation IIR #14058, created on 08/19/10 - Ifosfamide 1g 30 mL, lot #7021732; Heparin Sodium 5,000 USP 1mL MDV, lot #7021632 and Media Fill Batch 7021743A live parson spider was found on the floor of the Aseptic Corridor I outside of Fill Room [REDACTED]. As per investigation the probability of recurrence is moderate since there have been 2 other investigation initiated for insects infiltrating your manufacturing process within the past year. No mitigation plan was required for this incident since pest controls are in place. Lots manufactured were release.
- d. Deviation IIR #14210, created on 08/31/10 - [REDACTED] Insect was found in wash fill airlock. As per investigation, the probability of recurrence is moderate, as this type of incident has occurred several times in 2010. No mitigation plan was required for this incident since pest controls are in place. Lots manufactured were release.
- e. Deviation IIR #17217, created on 03/2011 - Heparin Sodium Injection, USP lot #7024033. Two vials were found with two insect parts. The (head/thorax and abdomen) were sent out for positive identification. One insect part (head/thorax) was approximately 1/16 inch length, the other (abdomen) approximately 1/8 inch in length. The insect was identified as a Clover Root Curculio, a form of weevil. Action plans 14493 and 14494 to enhance control and changes to your pest control program to increase effectiveness were executed and completed prior to this incident; late 2010.

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**OBSERVATION 5**

Equipment used in the manufacture, processing, packing or holding of drug products is not suitably located to facilitate operations for its intended use.

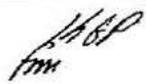
Specifically, the stopper hopper of your fill room line **b4** was noted to be at waist height and not protected by barrier. On the evening of 06/15/11, during the manufacturing operation of Gemcitabine for Injection lot 7025152, was observed the operators inside the class 100 area reaching over the stopper bowl as well as over some empty vials prior to been filled during the unloading empty vials process. In addition, according to your investigation 13762, dated 10/08/10 related to a positive unit found during media fill lot 7021321, even though is subject to a different filling line, filling operators had revealed some concerns on the lack of space in the filling room when needed to perform necessary adjustment to move jammed vials.

**PRODUCTION SYSTEM**

**OBSERVATION 6**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not written and followed.

- a. You do not perform Vent Filter Integrity Testing (prior to, after or both) to any of your vent filters placed on your carboys. Drug products inside the carboys are considered sterilized material. You have no risk assessment that describes the impact. There is lack of written approved scientific rationale for not integrity test vent filters. There is no documents, protocol, study, validation and/or qualification records that address the reason why you do not perform vent filter integrity test knowing that quality has to be build into your process and processes.
- b. Your media fill process simulation procedure/policy and protocol does not address action to take upon discovery of vials with particulate matter during the filling operation as well as during the incubation and inspection process. On 06/18/11, results from Media Fill lot 7025073 were describe as no microbiological contaminated units, but numerous particulate matter (fibers) were reported. As per your management, there were too many units with particulate matter that the total units of vials were not accounted for. Further investigation and information provided by your contract laboratory revealed a potential thermophilic organism. Questionable media fill vials were incubated at **b4** °C and vials the were initially free from fibers, remained clear, but some of the fiber-containing particles became more cloudy and an appearance of turbid, but no viable growth could be subculture. However, in the second attempt to identify the material, your contract laboratory obtained a match for an organism reported as *Geobacillus toebii*, a spore former Gram positive rod with an optimum growth temperature from 60°C - 65°C. As part of your investigation you sampled the formulation area and obtained **b4** samples recovering *Geobacillus toebii*. As of 07/06/11, no root cause has been defined.
- c. On 06/15/11, the filling of Lyophilized Gemcitabine for Injection lot #7025152 took place in filling line #8. Operators in the aseptic processing filling room Line **b4** were observed:

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- Not executing slow and deliberate movements. Instead, this operator was observed rapidly walking within area of same classification and from one area (class 10,000) to the other (class 100) opening the plastic curtains that separate each area with the respective classification.
- Extremely shaking the stopper bag while loading them in the stopper bowl.
- Reaching over the stopper bowl as well as over some empty vials prior to been filled during the unloading empty vials process. Stopper bowl is approximately at the waist height level of the operator.
- Knocking twice at the **b4** /conveyor belt with his hands to fix a stuck empty vial.

As stated in your General Requirements, Clean Room Behavior and Aseptic Techniques procedure, Document Number: 03-05-03-1019, the above listed behaviors increase turbulent air which, in turn, increases particle counts. There is no mandated instruction in the batch manufacturing record as well as in any procedure to list incidents when filling operators are not performing their duties as require in preventing contamination to the finished drug product with any source of unknown and known material.

- d. Poor aseptic techniques have been uncovered earlier in July 2010 thru one of your investigation (IIR 13762, media fill with a positive unit – organism identified was *Staphylococcus epidermidis*), lot 7021321 where you attributed to poor aseptic techniques by your operators as well as a possible manufacturer contaminated stopper. Your corrective action on training your personnel appears to have not satisfactorily meets your expectation and inadequate aseptic techniques appears to prevail based on the above observed incidents on 06/15/11 during the manufacturing of Gemcitabine for Injection lot 7025152.
- e. On 06/24/11, during the filling of Heparin Sodium Injection, USP lot 7025157 were observed filling operators plating themselves after exiting the fill room **b4**. It was noted that one of the operators did not plate his forehead properly. He barely touches his forehead and this was witnesses by your Director of Manufacturing. Furthermore; it was noted that the contact time to different areas of their gown including finger pads were not performed as per your procedure for Daily Production Environmental Monitoring (Document Number: 03-10-01-0009). The procedure request to hold to surface from **b4** and this was not accomplished. Moreover, it was noted the employees disinfecting their gown with **b4** immediately prior to plating themselves. This action may not allow adequate recovery of any organism present in the environment during the filling of any drug products.

**OBSERVATION 7**

Deviations from written production and process control procedures are not justified.

Specifically:

- a. Your visual qualification program for inspectors performing the 100% visual inspection of parenteral products to ensure that inspectors can consistently and effectively remove non-conforming vials during typical production operations are not representative of the actual conditions of usage. On 06/15/11, during the **b4** **b4** 100 % visual inspection of Thiamine Hydrochloride Injection, USP lot 7025079 filled in a 2 cc amber glass vial was noted being

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performed at a rate of [b4] vials per minute, while the visual qualification inspector testing data for same type of vial (2 cc amber) was noted to be performed on an average of [b4] vials per minute. You have no supporting data to prove neither that your inspectors are capable of inspecting [b4] vials per minute nor that your inspection processes of the subject lot were performed at the rate where your inspectors were initially qualified. The inspection AQL sampling form (3R4D1R-a) confirm the [b4] from [b4] vials per minute (VPM) which is out of the employees visual inspection performance qualification.

On 06/15/11, during the [b4] 100% visual inspection of Thiamine Hydrochloride Injection, USP lot 7025079 filled in a 2 cc amber glass, inspector were observed to stair twice outside the [b4] booth instead of inspecting continuously the drug products vials.

- b. Your Process Simulation Policy, Document Number: 10-01-03-0108 requires that all integral rejects vials must be documented, segregated and incubated. Media fills simulation for parenteral (sterile drug products) filling operations were inadequately performed to qualify aseptic processes. On 06/20/11, it was observed during the second media fill batch (lot 7025353) of a campaign of [b4] integral vials been removed after the capping operation and placed them in a 5 gallon white pail labeled in part: "TO BE DESTROYED" and no documentation was performed as to the specific reasons (assignable cause) why integral filled vials were removed. The removal and destruction of filled vials (integral units) may present a bias to the final media fill results. These media fill runs were executed after the discovery of numerous vials with particulate matter on previous Media Fill Batch 7025073.
- c. You failed to follow your standard operating procedure Sterility Testing Procedure (Document Number: 03-10-07-0001). The procedure requires to document in the Sterility Control Record (SCR) any aseptic technique problems encountered by the technician; page 8 of 30. During the sterility test of Magnesium Sulfate, 96410P lot 7024651, positive growth was obtained in one canister, OOS 03-MICRO-11-021. The investigation revealed the recovery of *Staphylococcus warneri*, gram positive cocci. Your investigation revealed that is mainly attributed to laboratory error during subculture in that pinch clamps were not positioned [b4] cm above the canister entry. However, this deficiency was not documented on the SCR as require by your procedure. Therefore, your investigation is not conclusive. There is a hold notification into the lot, but no final decision as to release or reject.

**OBSERVATION 8**

Master production and control records lack complete manufacturing and control instructions, special notations, and precautions to be followed.

Specifically:

- a) There has been a minimum of two reported deviation within three months apart where your personnel failed to install adequately the filters used in your aseptic filling process. Deviation #12423, dated 03/25/10 for Rocuronium Bromide Injection lot #7020191, criticized the use of only a single [b4] pre-sterilized filter as opposed of [b4] in-series as require by the Component Preparation [b4] document. This [b4] document only shows that component

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER 158-15 Liberty Ave. Jamaica, NY 11433 (718) 340-7000 Fax: (718) 662-5661 Industry Information: www.fda.gov/oc/industry		DATE(S) OF INSPECTION 06/13/2011 - 07/08/2011*
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED <b>TO: John Frank Harmon, Executive Vice President and Chief Operating Officer</b>		FEI NUMBER 3001833549
FIRM NAME APP Pharmaceuticals, LLC	STREET ADDRESS 3159 Staley Road	
CITY, STATE, ZIP CODE, COUNTRY Grand Island, NY 14072-2028	TYPE ESTABLISHMENT INSPECTED Sterile Drug Manufacturer	

preparation personnel supplied the respective filters to the filling operators. Less than three month later a second incident occurred (Deviation #13283) where incorrect filtration set-up was performed during the production of Adenosine Injection, USP lot 7021015. Both products were manufactured in filling room **b4**

In addition, your master control records do not indicate the specific location (upstream/downstream) where filters are to be installed.

You opened an Action Plan (12666, dated 04/20/10) after the first incident to update the master production records to instruct personnel to install and document at the time of performance the installation of filters. However, it was not until this inspection on 06/16/11 when you initiated a change control (DCR #110533) to updated multiples products codes. In addition, you have deviated from your Internal and External Corrective and Preventative (CA/PA) Action Plan Tracking procedure (Document Number: 10-11-01-0062). This procedure requires that extensions of the action plan above **b4** days are requiring to be approved by the Vice-President of Quality. The action plan was closed on 05/27/11, but the DCR 110533 was initiated on 06/16/11.

- b) Batch production and control records do not include the identification of the persons performing each significant step in the operation, for each batch of drug product produced, specifically on the installation of sterilizing filters.
- c) Your batch production and control records for all parenteral drug products do not indicate the speed limits of the **b4** when it is used for the **b4** 100% visual inspection.

**OBSERVATION 9**

Procedures for the preparation of master production and control records are not followed.

Specifically, there are multiples events where you have not completed in a timely manner the reports associated to the investigation of complaints, media fill simulation reports and process deviations along with respective action plans to mention a few. The followings are examples:

- a. Media Fill lot #7023133 executed on Filling Room **b4** performed on 12/21/10. There is no complete approved report. The same for all **b4** media fills simulation executed at your site after December 2010.
- b. There are approximately more than seventy (70) action plans open with more than 60 days; ranging from 770 to 60 days.
- c. Your April 2009 to March 2010 Annual Product Quality Review for Lyophilized drug products was completed on 08/27/2010 when the procedure for such require to be completed by the month of July.
- d. Deviation IIR #15312, Vancomycin HCL particulate matter related, initiated on 12-08-10 and close on 06/14/2011 during this inspection - open for approximately 6 month.

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**LABORATORY SYSTEMS**

**OBSERVATION 10**

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically:

- a) Samples taken of drug products for determination of conformance to written specifications are not representative and properly identified. You can not assure that samples drawn are based on a rational criterion such as random sampling and that the sample tested accurately portrays the material being sampled.
  - 1. According to the product sampling plan worksheet of any of your Batch Manufacturing Records if applicable and Product Testing Plan procedure, Document Number: 03-08-09-0001, samples for micro and chemistry are to be pulled for finished product testing. Your sampling method is not appropriate. You can not guarantee that representative samples were collected and appropriately delivered for testing to the microbiology and chemistry laboratory. As per attachment H (In-process sample form) of Heparin Sodium lot #7025243 fill on 06/19/11, all samples were collected throughout the filling process, but they were composite and placed on a bench top within the capping area. As a result of current inadequate sample identification system in addition to not having a written approved standard operating procedure that describes thoroughly the sorting of samples in the manufacturing area prior to sending them to the respective laboratory, the results obtained on each test for finished products may be questionable in that it may not reflect a true representative sampling and testing approach of the filled product.
  - 2. The batch size (units) of Sodium Chloride lot #7023732 below is approximately **b4** times less than the Heparin Lock Flush lot #7024042. Based on the batch size and percentage collected on each batch size per fill volume, it was collected approximately **b4** times more samples for particulate matter testing on the Sodium Chloride in comparison to Heparin Lock Flush which is a greater batch size. Your approach for collecting samples of finished drug product for particulate matter testing independently of the batch size and fill volume is not scientifically sound.

Heparin Lock Flush		Calcium Gluconate		Sodium Chloride	
Lot #7024042 <b>b4</b>	1 mL vial	Lot #7024977 <b>b4</b>	50 mL vial	Lot #7023732 <b>b4</b>	100 mL vial
# samples require for particle = <b>b4</b>	# sample require for chemistry = <b>b4</b>	#samples require for particle = <b>b4</b>	# sample require for chemistry = <b>b4</b>	#samples require for particle = <b>b4</b>	# sample require for chemistry = <b>b4</b>
Total Collected	Total Collected	Total Collected	Total Collected	Total Collected	Total Collected
<b>b4</b>	<b>b4</b>	<b>b4</b>	<b>b4</b>	<b>b4</b>	<b>b4</b>

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Sterile Drug Manufacturer

Total % sampled =					
% = b4					

3. The sampling size used by the QC Microbiology Laboratory to determine sub-visible particulates via (b) (4) method in your small volume parenteral products is not scientifically sound. For example, your Product Testing Sampling Plan procedures (Document Number: 03-08-09-0001) requires the following:

For a Container Volume of	No. of Containers for testing	Pooled samples size in mL
1.0 mL	b4	b4
2.0 mL		
3.0 mL		
Greater than 3.0 mL to 200 mL		
For all current Lyophilized products		

Only one reportable value that is taken from the average of a pooled sample is used for consideration to accept/reject the lot/batch. The vials sampled for the (b) (4) test method for the following listed products consist from:

Product	Fill / vial size	Min Batch / vials	Max Batch / vials	Vials in one (1) pooled for testing	Amount of Reportable Values based on the average of a pooled sample
Dexamethasone Sodium Phosphate Injection (Pres. Free) 10 mg/mL	1 mL in 2 cc vial	b4	b4	b4	1
Potassium Chloride for Injection 30 mEq (2mEq/mL)	15 mL in 20 cc vial				1
Sodium Chloride Injection, USP 0.90%	2 mL in a 3 cc vial				1
Gemcitabine for Injection, USP	1 g in a 50 cc vial				1
Ifosfamide Injection, USP	50 mg/vial, fill volume in a 60 mL				1
Heparin Sodium Injection, USP	30 mL in a 30 cc vial				1

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Tobramycin Injection, USP	51.17 mL in a 60 mL vial	b4	b4	b4	1
Potassium Chloride For Injection Concentrate, USP	60 mEq in a 30 mL vial	b4	b4	b4	1
Calcium Gluconate Injection 10%, USP	100 mL in a 100 cc vial	b4	b4	b4	1

According to your Product Testing Sampling Plan procedures (Document Number: 03-08-09-0001), for vials/units greater than b4 mL fill volume you collect a total of b4 units independently of the batch size and product physical chemical characteristics. On 06/22/11, in a one on one dialogue with your Microbiology Managers, Supervisors and other employees, it was reiterated that the amounts collected were necessary to perform the respective micro and chemical test due to the milliliters require for each testing. Your local top officials of respective Departments did not provide the scientific statistical rationale behind current sampling practices.

- b) The Non Regulatory Reference Standards used in the QC Laboratory for finished product and raw material analysis are not tested against reference standard to verify the purity and identification of the standard prior to use. You relied on the supplier's Certificate of Analysis as the source of standard qualification and re-qualification. For example:
- Alkaline Phosphate lot # b4 used on Dexamethasone Sodium Phosphate Injection, batch #6001950 and released on 06/01/11
  - Esmolol Hydrochloride lot # b4 used on Esmolol Hydrochloride Injection, batch #6001810 and released on 05/10/11
  - Rocuronium Bromide lot # b4 used on Rocuronium Bromide Injection, batch #6001730. The (b) (4) were not documented and it was released on 04/25/11.
  - Diphenhydramine HCl lot # b4 used on Diphenhydramine HCL on batch #7024735 the (b) (4) were not documented and not released yet.

**OBSERVATION 11**

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release.

Specifically,

- a. You perform the Particulate Matter testing by the (b) (4) method using USP (b) (4) to your parenteral drugs products. All finished product release and stability testing as well as your decision to approve or reject a lot is based on the acceptance criteria related to one reportable value that is taken from the average of a pooled sample for all products independently of the fill volume. In acceptance sampling, the sample size is the number of reportable values. You maintain a constant sampling size of b4 throughout all your drug product testing regarding USP (b) (4). For many

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products, your approximately average batch size is from **b4** units and fill volume are from **b4**.  
**b4** Within USP (b) (4) Particle Count Test, the method states that, "The number of test specimens must be adequate to provide a statistically sound assessment." The following are examples of drug products where you have recorded one reportable value that is taken from the average of a pooled sample:

- Gemcitabine for Injection, USP 1 g in a 50 cc vial, lot #7024237
- Ifosfamide Injection, USP 50 mg/vial, fill volume in a 60 mL glass vial, lot #7023284
- Heparin Sodium Injection, USP 30 mL in a 30 cc vial, lot #7024807
- Tobramycin Injection, USP **b4** mL in a 60 mL glass vial, lot #7021565
- Potassium Chloride For Injection Concentrate, USP 60mEq in a 30 mL vial, lot #7024959
- Calcium Gluconate Injection, USP 10%, lot #7024966 100 cc in a 100 mL vial among others products.

You report the average of a pooled sample of each batch/lot of drug products tested when fill volume is greater than **b4** mL, not knowing that the purpose of this method is to measure and limit intra-batch variability.

Your standard operating procedure for Product Testing Sampling Plan (Document Number: 03-08-09-0001) and procedure Monitoring for Particles (Document Number: 03-10-02-0002) does not indicate amount of samples to be collected for Gemcitabine for Injection, USP. In a one on one conversation with your microbiology personnel, it was revealed that samples collected are provided by production personnel based on a product sampling plan provided by the development department in conjunction with the tech transfer personnel on 10/2007. Units collected are based on the minimum amount require to complete the test and no rationale for statistical representation to assure a sound assessment. Both production personnel and your Quality Control personnel can not determine if samples collected and tested are representative of the manufactured batch.

- b. You have not appropriately defined the sampling plan for drug products inspection after failing the initial 100% visual inspection. Your **b4** documentation only states the total amount of units to be inspected, but no reference from where or frequency the samples are to be collected to guarantee representative samples are collected and examined. For Lyophilized products you also perform a **b4** for Vancomycin lot #7023899 and lot #7022266, respectively). Your documentation only states the total amount to be inspected, but it is uncertain from where the samples are collected to assure representative samples are adequately examined. Examples are:
1. IIR Number 15852, dated 01/19/11 – Release lot of Ganciclovir #7022614 is over action level in visual inspection obtaining a 0.21% reject for particulate matter, limits are set to **b4** %. The source of the particulate matter could not be definitively determined. Microscopic evaluation indicated metal particulate. Lot was released because both the **b4**. However, your manual visual inspection process may only detect the presence of an unexpected material adhere to the surface of the vial or on top of the cake and not within. (b) (4) of two 500 mg vials of lyophilized product selected from the rejects of the initial inspection revealed (vial 1) multiples metal particulate ranging in size from < 50 µm to ~ 290 µm and (vial 2) one metal particle of ~ 300 µm. Your "Medical Assessment Particles Metal deriving from production equipment" performed on 10/05/09, states that in principal particle greater than **b4** µm could stick to the lung capillaries and affect the micro-vascular blood supply. Your detectability section of your investigation

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explicitly states that with lyophilized product, particulate within the cake is not detectable and particulate on the cake may be hidden. This Medical assessment was not based on current finding based on the physical characteristics of the product. Furthermore, you were not able to determine the source of the particulate matter. The Medical Assessment performed is for particulate inherent to the manufacturing process.

2. IIR Number 16812, dated 03/22/11 – Release lot of Ganciclovir #7023481 is over action level in visual inspection obtaining a 0.25% reject for particulate matter, limits are set to **b4** %. As per your investigation, the source of the particulate matter could not be definitively determined. Three 500 mg vials of Ganciclovir rejected during the initial 100 % inspection process were characterized microscopically after **b4** Particulate matters were determined to be metals for all three vials and ranging in size from < 60 µm to ~ 250 µm with all different shapes and colors. **b4** of two 500 mg vials of lyophilized product selected from the rejects of the initial inspection revealed (vial 1) multiples metal particulate in size from < 50 µm to ~ 290 µm and (vial 2) one metal particle of ~ 300 µm in size. Lot was released because both the **b4**  
**b4** As in IIR 15852, you stated that the metal and fiber particulate that was observed in subject batches is recognized to originate from materials that are inherent to the manufacturing process; however, there is no circumstantial evidence of such. You were not able to determine the source of the particulate matter. You photocopied an existing Medical Assessment, dated 10/05/09 and used in this IIR as an attachment.
3. IIR Number 15312, dated 12/08/10 – Rejected lot of Vancomycin #7022266 is over action level in visual inspection obtaining a 0.10% reject for particulate matter defects, limits are set to **b4** %. A **b4** passed, but the **b4** of 20 vials failed. This is an example of visual examination of lyophilized products with passing results, but (b) (4) failed because was able to identify particulate matter. The investigation was closed on 06/2011, six (6) month later.

**OBSERVATION 12**

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once **b4** for evidence of deterioration.

Specifically:

- a. Even though your standard operating procedure Reserve Room Procedure, Document Number: 03-11-00-0005, Version 8.0 requires "at a minimum" **b4** to be used for inclusion in the (b) (4) Reserve Inspection program, your rationale for reserve samples (b) (4) inspection is not based on acceptable statistical sound assessment. You do not include in your (b) (4) inspection reserve sample program, lots of parenteral drug products experiencing manufacturing deviations. Approximately **b4** lots have been produced since January 2010. It was randomly counted more than **b4** lots for a give period experiencing a deviation/excursion at any given time during the manufacturing, filling, and visual inspection process. These **b4** lots were not included in the (b) (4) reserve sample inspection program. No answer was provided for the scientific rationale of not including these drug product lots in your (b) (4) retain sample inspection program. Representative selection of lot to be place in your (b) (4)

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stability program should also consider products experiencing operational deviations, among others.

- b. In the month of March 2011, approximately **b4** lots of parenteral drug products were manufactured. Only **b4** lots were pre-selected and incorporated into the **(b) (4)** reserve sample inspection program. Based on Investigation IIR 17217 dated 06/21/11 related to the two vials uncovered with insect parts (head/thorax, and abdomen) on a lot of Heparin Sodium Injection, USP, lot 7024033 filled on March 13, 2011 in Line **b4** the "representative lots" terminology was not considered after this event. One insect part (head/thorax) was approximately 1/16 inch length, the other (abdomen) approximately 1/8 inch in length. The insect was identified as a Clover Root Curculio, a form of weevil. You did not take a conservative approach to at least include lots manufactured during the same time period in your **(b) (4)** inspection program. Action plans 14493 and 14494 were executed and completed prior to this incident, therefore, others lots of drug products may be questionable even though they go through a 100% visual inspection process. Visual inspection for lyophilized products may only detect particulate matter located on the surface of the vials and on the top of the cake, but not within the cake.

**OBSERVATION 13**

Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use.

Specifically:

- a. The competence of the receiving laboratory to use the validated methods was not demonstrated through the test. For example; running samples in parallel between the transferring and receiving laboratories, the rational of the test, knowledge of critical parameters, the accuracy and precision of system suitability, and samples and standard preparation. Additionally, the SOP #10-08-00-001 'Transfer of Analytical Methods' was not followed during method verification. The precision of the method was not performed by the Transfer Site Analyst, instead was done by the originating site analyst. Process knowledge depends on accurate and precise measuring techniques used to test and examine the quality of drug components, in-process materials, and finished products. For instance:
- Test Method TM 10-08-03-6398 Determination of Impurities in Gemcitabine HCL, USP and Gemcitabine for Injection, USP
  - Test Method TM 10-08-6389 Determination and Identification of Gemcitabine HCL in Gemcitabine HCL, USP and Gemcitabine in Gemcitabine for Injection, USP
  - Test Method TM 10-08-03-6463 Determination of Assay and Impurities in Levetiracetam Injection by HPLC
  - Test Method TM 10-08-01-6400 Determination of Residual **b4** in Levetiracetam raw Material by **b4**
  - Test Method TM 10-08-01-6391 Assay **b4** Purity and Identification of Levetiracetam in Levetiracetam Raw Material.
- b. During method transfer or verification performed at APP Pharmaceuticals, LLC Grand Island, NY between November 2009 and January 2011, API samples have been tested concurrently with the technology transfer samples. Additionally, SOP 10-08-00-0001 'Transfer of Analytical Methods' V.4 and V.3 effective during the aforementioned time period does

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not address the requirements of completing the appropriate transfer or verification and approval of the method prior to testing of API samples. The following are examples where you have tested products without having a completed approved method transfer or verification and specification:

<i>Method</i>	<i>Lot number</i>
Rocuronium, <b>b4</b> limit test method 10-08-01-6384	0907346
Ifosfamide Injection, assay test method 10-08-01-6078	1003831 & 1004759
Ifosfamide Injection, impurities test method 10-08-01-6092	1003831 & 1004759
Ifosfamide Injection, <b>b4</b> test method 10-08-01-6077	1003831
Ifosfamide Injection, <b>b4</b> test method 10-08-01-6565	1003831
Ifosfamide Injection, <b>b4</b> test method 10-08-01-6564	1003831
Levetiracetam, assay and <b>b4</b> purity in Levetiracetam raw material test method 10-08-01-6391	0908327, 0908342, 0908343 & 0908344
Tipotecan, <b>b4</b> test method 10-08-05-6004	1006257

**OBSERVATION 14**

Input to and output from the computer and related systems of formulas are not checked for accuracy.

Specifically, the **(b) (4)** **b4** software program version **b4** used in the Quality Control Laboratory, has not been validated to generate results from the electronic data generated during testing. Additionally, the analytical formula used in the **b4** to calculate the result of moisture in raw material and finished product has not been verified or validated. The following are examples of finished product and raw materials tested. This was used on Gemcitabine HCL raw material lots # **b4** and # **b4**, Gemcitabine for Injection, USP lots # **b4** and # **b4** and Levetiracetam Injection lot **b4** and **b4**.

**MATERIAL SYSTEMS**

**OBSERVATION 15**

Drug product container and closure test procedures are deficient in that containers are not tested for conformance in accordance with appropriate written procedures.

Specifically:

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- a. Your General Procedure for Sampling, Inspection, and Approval/Rejection of Incoming Quarantine Material, Document Number: 03-08-01-0064 is subjective in that requires to measure for (b) (4) of plastic vials only if (b) (4) (b) (4) You do not have an established approved well define sampling plan for th (b) (4) (b) (4) for plastic vials, especially the 3 cc plastic vials. In a one on one dialogue with your incoming inspection personnel were stated that based on their experience on inspection they can determine any (b) (4) present on the vial.

During the visual inspection process of lot #7023884 Heparin Sodium (b) (4) (03/17 - 19/11) filled on 02/23/11, lot 7023883 Heparin Sodium (b) (4) (03/18 - 19/11) filled on 02/21/11 and Magnesium Sulfate 50% 1g lot #7023835 (03/19 - 21/11) filled on 02/24/11 was discovered non-integral vials where product was leaking from damage to the bottom portion of the vials. These lots were manufactured using the 3 cc vials (material code (b) (4)) from the new supplier's location. In addition, Deviation #16793, does mention that during visual inspection of finished drug product Sodium Chloride for Injection, USP lot #7024325 and lot #7024548 a total of (b) (4) vials and (b) (4) vials were rejected, respectively, due to soft walls for a different material code (10 cc plastic vials manufactured by the same supplier).

**OTHERS POST MARKETING REPORTS**

**OBSERVATION 16**

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning significant chemical, physical, or other change or deterioration in a distributed drug product.

Specifically, all complainants finished drug product samples received at your firm and acknowledged to be intact as well as your positive identification of particulate matter during annual reserve sample examination.

- Your April 2009 to March 2010 reserve sample inspection report for lyophilized products, dated 08/25/10 (7 months after the close out period) revealed three lots where Major defects were observed. According to your records these defects may include vials with foreign matter, vials with particulate matter, vials with defective glass, and vials with product on stopper. You failed to maintain data associated to the reserve history documentation which provides details on of the lots in question. No NDA-Field Alert report was file with the agency.
- Confirmed complainant sample of Heparin Sodium Injection, lot #408196 was received with particulate matter floating in one vial (PIR 12173). No NDA-Field Alert report was file with the agency.
- Complaint #PIR 15654 received on 01/05/11, where a Pharmacy Supervisor reported eleven (11) vials with no labels of Heparin Sodium Injection, USP lot # 6000399. Multiples complaints for vials missing label has been received before and after this complaint. No NDA-Field Alert Report was file with the FDA District Office.

<b>SEE REVERSE OF THIS PAGE</b>	EMPLOYEE(S) SIGNATURE Kevin A. Gonzalez, Investigator Felix Maldonado, Chemist James D. Bridges, Investigator	DATE ISSUED 07/08/2011
		

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

158-15 Liberty Ave.  
Jamaica, NY 11433  
(718) 340-7000 Fax: (718) 662-5661  
Industry Information: [www.fda.gov/oc/industry](http://www.fda.gov/oc/industry)

DATE(S) OF INSPECTION

06/13/2011 - 07/08/2011\*

FEI NUMBER

3001833549

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

**TO:** John Frank Harmon, Executive Vice President and Chief Operating Officer

FIRM NAME

APP Pharmaceuticals, LLC

STREET ADDRESS

3159 Staley Road

CITY, STATE, ZIP CODE, COUNTRY

Grand Island, NY 14072-2028

TYPE ESTABLISHMENT INSPECTED

Sterile Drug Manufacturer

**\* DATES OF INSPECTION:**

06/13/2011(Mon), 06/14/2011(Tue), 06/15/2011(Wed), 06/16/2011(Thu), 06/17/2011(Fri), 06/20/2011(Mon), 06/21/2011(Tue),  
06/22/2011(Wed), 06/23/2011(Thu), 06/24/2011(Fri), 07/06/2011(Wed), 07/08/2011(Fri)

**SEE REVERSE  
OF THIS PAGE**

EMPLOYEE(S) SIGNATURE

Kevin A. Gonzalez, Investigator  
Felix Maldonado, Chemist  
James D. Bridges, Investigator

DATE ISSUED

07/08/2011