DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202 Industry Information: www.fda.gov/oc/industry	05/16/2011 - 06/17/2011 FEI NUMBER 1021343

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Hector E. Jimenez, Director of Quality

FIRM NAME	STREET ADDRESS
Hospira, Inc.	Hwy. 301 N. + 4285 North Wesleyan Blvd.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Rocky Mount, NC 27804	Pharmaceutical and Device Manufacturer / Gamma Irradiator

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.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically, sterility and/or container-closure system integrity testing is not routinely performed as a part of stability protocols designed to assure that purportedly sterile products remain sterile throughout their labeled shelf-life.

In lieu of including sterility and/or container-closure system integrity testing as a part of routinely conducted stability protocols, Hospira utilizes a "Maintenance of Sterility" (MOS) program as outlined in written procedures SOP.C.HPA-0206, "Maintenance of Sterility" and 45.MASTER-0001, "Marketed Drug Product Maintenance of Sterility Family Categories". Written procedure 45.MASTER-0001 groups Hospira-manufactured products into (b) (4) different categories based upon general container-closure system similarities. Examples of MOS categories include: "Fliptop and teartop vials, Glass, Stopper", "Fliptop and teartop vials, Plastic, Stopper", and (b) (4) Glass Syringe, Vials with Stopper & Cap Closure". (b) (4) of product from each MOS category is selected at random each year to represent all lots of products manufactured at all Hospira facilities from that MOS category. Those lots are then placed on a stability protocol that includes sterility testing at 12 month intervals through the products' respectively labeled expiries. In the event that no units from a selected MOS lot are available for inclusion in the protocol, the MOS category can be skipped and (b) (4) from that category will be placed on the MOS program the following year.

Each MOS category may be comprised of a number of different container-closure systems. For example, products manufactured at this facility that fall under the MOS "SV-02" category (Fliptop and teartop vials, Glass, Stopper) utilize (b) (4) different glass vials, at least (b) (4) different stoppers, and at least (b) (4) different aluminum flip-offs. There is no written justification supporting the assumption that the container-closure system of the chosen MOS lot is truly representative of all of the facility's other container-closure systems, let alone all of the other products manufactured at other Hospira facilities that fall under the same MOS category.

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Written procedure SOP.C.HPA-0206 requires, when possible, that products that have not previously been on the MOS program be selected for participation each year. Because (b) (4) from each MOS category is selected at random each year to represent all lots of products manufactured from all Hospira facilities, (b) (4) products currently manufactured at the Rocky Mount, NC facility for commercial distribution have never been selected to participate in the MOS program. These products include various configurations and/or potencies of Cimetidine Hydrochloride Injection; Dopamine Hydrochloride Injection, USP; and, Potassium Phosphate Injection, USP.

Additionally, there is no written assessment of the risk to patients due to a supply shortage in the event that a MOS unit fails sterility testing upon expiry. Hospira manufactures a large number of products for which it is either the only manufacturer or it holds greater than a 50% of the market share in the United States. For example, Hospira identified that it holds more than 50% of the market share for approximately (b) (4) of the (b) (4) different "list number" small volume parenteral products manufactured at the Rocky Mount, NC facility.

OBSERVATION 2

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

Examples include:

A. The written procedures governing the "Maintenance of Sterility" (MOS) program utilized by Hospira to demonstrate its products are capable of remaining sterile through expiry contain contradictory instructions.

Instruction A.5. of written procedure SOP.C.HPA-0206, "Maintenance of Sterility", revision 3.0, effective 5/17/10 states:

> A minimum of (b) (4) of product for each active family category will be tested annually at 12, 24, and 36 months for Sterility.

Instruction D. of written procedure 45.MASTER-0001, "Marketed Drug Product Maintenance of Sterility Family Categories", effective 3/27/09 states:

> Sterility testing of selected lot or lots for each category will be tested annually through their expiration.

The firm reportedly only follows instruction D. of written procedure 45.MASTER-0001. At least (b) (4) manufactured at the Rocky Mount, NC facility has a 60 month expiration date.

B. In response to a field action/destruction of Dexmedetomidine HCL Injection (Precedex), 100 mcg/mL, Lot 94538DK due to cross-contamination, CAPA 33446 was opened to review chromatograms of all lots utilizing impurity methods that were manufactured between 10/25-26/10, which was the time frame in which the cross-contamination occurred. The

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CAPA is past due and the review has not been performed.

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.

Examples include:

A. Exception Report Record PR ID 30629 (PR ID 30629) describes an investigation into Bottle of Convenience (BOC) 1 recorded a F_0 value of 16.3, exceeding the in-process specification of (b) (4) during the sterilization Load [redacted] of list 0132-304-89, lot 02-616-EV, Lidocaine Hydrochloride 2% Injection, USP, 5 mL, Ansyr. As noted in PR ID 30629, the investigation failed to identify a definitive root cause for the out of specification sterilization result although it did conclude that the BOC malfunctioned due to improper thermocouple placement in BOC 1. The investigation supported this conclusion by noting that three other nearby BOC units registered acceptable F_0 values. BOC 1 was never physically examined following the in-process failure and operators did not recall any difficulties or irregularities with the thermocouples during placement or otherwise. Load [redacted] was determined to be acceptable for release for commercial distribution.

B. Investigation ER-SOL/RM-005867 describes an investigation into a stability testing failure at 18 months (expiry) for list 6729-0424, lot 71-367-KL, Magnesium Sulfate in Water for Injection, 40 mg/mL, 50/100 mL, Flexible Container where a unit was found to contain 38 mL, outside of the (b) (4) mL specification. The "Regulatory Impact" section of the report includes a statement that reads:

> This event does not present adverse affect to the health or safety of the end user.

There is no justification for the assertion that a low dose of Magnesium Sulfate will not adversely impact patients. Intravenous magnesium sulfate is used to treat or manage a variety of medical conditions including, but not limited to: eclampsia, hypomagnesemia, pre-eclampsia, and seizures.

C. Investigation ER-SOL/RM-004856 describes an investigation into a consumer complaint of underfilled units of list 4887-04-98, lot 81-278-DK, Water for Injection, USP, 10 mL vials. The complainant returned 13 unopened vials that Hospira verified contained volumes of 9.12 - 10.14 mL of solution instead of the specified (b) (4) mL. The investigation failed to include a medical assessment of the impact of underfilled units. Water for Injection in 10 mL vials is typically used as a diluent for other drugs and the use of underfilled units can lead to superpotent drugs being administered to patients. This was the second report of underfilled units from this lot.

D. Exception Report Record PR ID 35380 (PR ID 35380) describes an investigation into the observation of off-white particulate matter in an in-process solution that was noted during the execution of a developmental mixing study for list

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2104, developmental lot 11-035-RD, Multi-Vitamin Infusion. Through the course of the investigation, it was discovered that operators previously observed black particulate matter in the mixing vessel after the addition of list 2104, (b) (4) (b) (4) during the mixing of two previous batches (11-033-RD and 11-034-RD) for the same developmental mixing study. The observation of the black particulate matter went unreported until PR ID 35380 was initiated and operators were interviewed about their observation of the off-white particulate matter. No analysis of the black particulate matter was possible because no samples were taken. The firm's written procedures do not distinguish between whether particulate matter is observed in a mixing vessel in which a developmental batch is being manufactured or in which a batch for commercial distribution is being manufactured.

E. Investigation ER-SOL/RM-005661 describes an investigation into multiple consumer complaints of discolored plastic vials from list 6636-0483, lot 69-429-DK, Potassium Chloride Injection Concentrate, USP, 30 mEQ; list 6653-1384, lot 79-156-DK, Potassium Chloride Injection, USP, 40 mEQ; and, list 6657-0475, lot 85-132-DK, 14.6% Sodium Chloride, Injection, USP, 50 mEQ. Technical Service Reports 10877, 10879, and 23878 were completed by request of manufacturing personnel between 2/12/10 - 3/12/10 and they identified the discoloration as being due to oxidizing metal particles embedded in the vial walls. Specific deficiencies related to this investigation include:

1. The information generated from the Technical Service Reports was never reported to the Quality Systems Group - the Rocky Mount, NC organization responsible for coordinating complaint investigations. As a result of this failure to communicate, the Quality Systems Group was unable to request that the Global Product Safety and Complaints (GPSC) group compile a complete listing of implicated consumer complaints. Only three complaints were returned by GPSC for lot 79-156-DK as of 7/20/10 although at least six complaints were actually logged into the system by that time.

2. There is no written procedure addressing the communication of investigational findings from manufacturing area investigations to the Quality Systems Group to facilitate effective investigations.

3. The investigation failed to address findings of particulate matter in affected units including that reported in Consumer Complaint 553925 (for lot 79-156-DK) and Technical Service Report 23878.

OBSERVATION 4

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

For example:

A. Laboratory Investigation Single Record Report PR ID 27903 (PR ID 27903) described the investigation into an unknown impurity that was detected in Active Pharmaceutical Ingredient epinephrine lot (b) (4) PR ID 27903 reports the detection of the impurity and the specifications for impurities; however, there is no mention of the amount of impurity.

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Additionally, the corrective and preventative action is designated to be created in the "Main Incident Report" although this document is not specifically identified.

B. PR ID 25442 described the investigation into particulate matter observed in the mixing tank during the mixing of list 3178-04-15, lot 96-066-EV, Lidocaine HCl 1% and Epinepherine 1:100,000 Injection, USP. Although the solutions area personnel reported the incident and verbally described the particulate matter, there was no attempt to recover the particulate matter so that the investigation into the event could more accurately identify the root cause and possibly implement appropriate preventative actions. Furthermore, no preventative action was generated to ensure that solutions area personnel would collect samples of particulate matter in mixing tanks in the future.

OBSERVATION 5

Deviations from written sampling plans and test procedures are not justified.

The firm failed to investigate out of specification (OOS) laboratory results as per SOP QCP.05.002, "Laboratory Investigation Procedure" and the investigations have lacked scientific justification to support the dismissal of OOS results and conclusions of the investigations. For example,

Dopamine HCl in 5% Dextrose Injection, Lot 03-436-KL:

LIR/PR 31947 was initiated for the low OOS assay result of 102.4% (Specification: (b) (4) for the in-process sample. A (b) (4) retest was performed using the original sample which resulted in another OOS result (b) (4) and (b) (4) The OOS retest result of 102.9% was then remeasured with a result of 103.1%. Additionally, the lot was then resampled with no justification and an additional (b) (4) samples were tested with results ranging from 103.6-103.9%. The two OOS results (original and one retest) were invalidated even though a clearly assignable laboratory cause was not determined. Only the within specification results were reported. However, PR32835 (parent ID: PR 31947) was initiated on 3/23/11 and stated that this investigation did not identify a potential root cause for the OOS reported on the original in-process sample for lot 03-436-KL. It further stated that all values generated during the course of this investigation will be reported. This PR was then closed/cancelled on 3/24/11; the firm could not provide an explanation as to why this was closed or the conflicting conclusions.

Atropine Sulfate Injection, Lot 94-688-EV:

ER-SOL/RM-006420 was initiated for the low OOS assay result of 95.9% (Specification: (b) (4) for the in-process sample. A (b) (4) retest was performed using the original sample with all results found to be within specification (b) (4) (b) (4) Additionally, the lot was then resampled with no justification and an additional 3 samples were tested with results ranging from 100.3-100.5%. The original OOS result was invalidated even though a clearly assignable laboratory cause was not determined and only the within specification results were reported.

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OBSERVATION 6

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Specifically, on 2/1/10, Hospira's Global Product Safety and Complaint group received Complaints 493553 and 494024 related to underfilled vials of list 4887-04-98, lot 81-278-DK, Water for Injection, USP, 10 mL vials. This product is manufactured under New Drug Application (NDA) 18-801. Although no samples were available from Complaint 493553, the complainant associated with Complaint 494024 returned 13 intact vials to Hospira for analysis. On 2/5/10, Technical Service Request 38373 was issued for the analysis of 13 returned vials returned to Hospira by the complainant. The returned vials were determined to contain 9.12 - 10.14 mL of solution per vial instead of the specified (b) (4) of solution per vial. This product is used as a diluent for other drugs and the use of underfilled units can lead to superpotent drugs being administered to patients.

The investigation into Complaint 494024, ER-SOL/RM-004856, was initiated on 2/10/10. Preventative actions associated with ER-SOL/RM-004856 were completed by 10/14/10 and the investigation was closed on 12/30/10. No Field Alert Report was issued for this verified complaint of multiple filled vials not meeting the critical quality attribute of product volume.

OBSERVATION 7

Investigations of an unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

For example:

A. As detailed in ER-SOL/RM-004413, between the period of 1/29/09 - 3/12/10, four lots each of list 1141, 23.4% Sodium Chloride Injection, USP (80-355-DK, 82-513-DK, 83-391-DK, and 85-432-DK) , and list 2102, 0.9% Sodium Chloride Injection, USP (80-245-DK, 80-591-DK, 84-334-DK, and 87-420-DK) yielded high out of specification pH results. Additionally, LIR-SOL/RM-000532 and ER-SOL/RM-004330 were initiated on 9/27/09 and detailed the investigation into a high out of specification pH result for list 1141, lot 81-393-DK. More recently, Laboratory Investigation Single Record Report PR ID 29507 was initiated on 2/14/11 as a result of a high out of specification pH result for list 7983, lot 01-240-KL, 0.9% Sodium Chloride Injection, USP. None of the implicated lots were commercially distributed and the firm has ceased further manufacturing of (b) (4) pending the completion of its investigation into these events and implementation of preventative actions.

Through the course of the investigations conducted under ER-SOL/RM-004413, ER-SOL/RM-004330, and PR ID 29507, the firm determined that contributing factors to these events included pH meter drift and interactions with the plastic cup typically used to hold the solutions being tested. Experiments performed by the firm as a part of PR ID 29507

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demonstrated that these factors can result in artificially elevated pH results during the testing of sodium chloride solutions. The same experiments performed as a part of PR ID 29507 also demonstrated that retests of different samples from the same batch resulted in the variance between results by as much as 0.9 units and that the currently utilized pH meters are subject to upward drift over time. PR ID 29507 was closed on 5/31/11. Preventative actions identified by the firm as a result of these findings include the acquisition of new pH meters and the use of glass containers to hold the solutions instead of plastic cups.

Despite identifying contributing factors and preventative actions through the course of the PR ID 29507 investigation, the firm has not performed any testing to determine the pH of lots of potentially affected product currently remaining on the market. There are no lots of list (b) (4) remaining on the market within expiry. The following lots of list 2102 remain on the market: 79-425-DK (expires 7/11), 80-580-DK (expires 8/11), 81-516-DK (expires 9/11), 85-362-DK (expires 1/12), and 86-167-DK (expires 2/12).

B. As detailed in ER-SOL/RM-005414, ER-SOL/RM-005524, ER-SOL/RM-00 5942, and ER-SOL/RM-006104, between March - September 2009, three lots of list 9093, Fentanyl Citrate Injection, USP, 0.05 mg/mL (88-297-DK, 88-472-DK, and 88-476-DK) and two lots of list 9094, Fentanyl Citrate Injection, USP, 0.05 mg/mL (87-382-DK and 91-507-DK) yielded high out of specification single impurity results. Through the course of the investigations, the firm determined that the root cause of the impurities was trace amounts of leeched chemicals from the pharmaceutical grade (b) (4) and (b) (4) flexible hoses used to transfer product solutions between pieces of mixing and filling equipment.

The impurities were not previously identified in these products due to a revision of the products' finished product impurity specifications in March 2010 that resulted in the establishment of an individual unknown impurity limit of not more than (b) (4) Because of the low concentration of fentanyl citrate in the product solution (0.05 mg/mL), the level of impurities in the product solution was high enough to exceed the individual impurity specification. The impurities could not be identified in either affected product solutions or studies specifically designed to maximize the extraction of leechable chemicals from the tubing due to their low concentrations in the solutions.

Despite identifying leechable chemicals from the flexible hoses as a root cause, and the implementation of corrective actions designed to limit the amount of leechables in Fentanyl Citrate Injection, USP, 0.05 mg/mL, the investigation did not include an assessment of the potential impact of this issue to other low concentration drug products that use similar hoses. One such drug product is NDA 21-146, list 9630, Atropine Sulfate Injection, USP, 0.05 mg/mL. The analytical methods for the detection of impurities for the Fentanyl Citrate Injection, USP, 0.05 mg/mL and Atropine Sulfate Injection, USP, 0.05 mg/mL are different and the Atropine Sulfate Injection, USP, 0.05 mg/mL method has not been shown to be able to detect the impurities seen in the affected Fentanyl Citrate Injection, USP, 0.05 mg/mL lots.

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OBSERVATION 8

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, Fill Line (b) (4) process validation (VCR-9868) for Filler (b) (4) does not include the processing parameters utilized during the validation study. Management reports that the nominal line speed for this filler was arbitrarily set at NMT (b) (4) (vials/minute); however, the specification is not supported as one utilized during the validation study.

OBSERVATION 9

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

Specifically, a number of design and/or structural defects related to equipment or the location of equipment in the facility were noted through the course of this inspection including:

A. The fill room for aseptic filling line (b) (4) contains a "U" shaped conveyor belt that necessitates operators to enter the curtained ISO Class (b) (4) area of the fill room from the ISO Class (b) (4) area of the fill room by ducking beneath a conveyor belt that is no more than 4 ft high in order to make and/or inspect connections between the surge bottle and the filling machine. Monitoring of the connections between the surge bottle and the filling machine is otherwise impaired by a plastic curtain and the distance between the exterior of the conveyor system and the connections.

   On 6/9/11, during the filling of list 3178, lot 06-189-DK, Lidocaine HCl 1% and Epinephrine 1:100,000 Injection, USP, several manufacturing deviations indicating non-integrity of the sterile product pathway were observed including: a leak at the junction between a product supply hose and the second piston pump from the viewing window to the room, drops of a clear liquid at the base of the fourth pump from the viewing window to the room, and clear solution pooled in a collection tray beneath the pumps. Neither the leaks nor the pooling liquid could be visualized by the operators without their stooping beneath the conveyor belt to enter the curtained area.

B. The design of the areas in which compounding equipment resides results in the equipment either not being easily accessible for routine maintenance activities and/or results in manufacturing conditions that can lead to the contamination of in-process materials that will be processed into products labeled as being sterile. Deficiencies include:

   1. Multiple mixing tanks are situated in a manner that the bottoms of the tanks are located in interstitial areas that are only inspected during (b) (4) inspections. Examples of this include Tanks (b) (4) in Room 691 that are used to compound flexible container products (flexible containers and Vis-IV bags). Similarly affected are Tanks (b) (4)

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(b) (4) in the Large Volume Solutions tank area that are used to compound solutions for semi-rigid bottles and part fill IV bags.

2. Air handling vents are located either directly above or immediately adjacent to mixing tanks with open orifices resulting in the formation of condensation that either could, or was directly observed to, drip back into the orifices of the tanks. The condensation typically formed as a result of chilled air being pushed through the air handling vents interacting with warm, humid air from tank cleaning and compounding operations. Examples of this include:

   a. Tank (b) (4) in the Small Volume Parenterals solutions area where the interaction between an adjacent overhead air handling vent and moisture rising from a hot water rinse of the tank in preparation of initiating compounding operations for list 4887, lot 05-365-DK, Sterile Water For Injection, USP, 100 mL resulted in the formation of condensation the covered the adjacent ceiling area and overhead pipes as observed on 5/16/11. The condensation was observed to be dripping onto the top of the tank, including a dual vent orifice on the top of the tank.

   b. Tank (b) (4) in Room 691 where the interaction between an adjacent overhead air handling vent and moisture rising from compounding operations during the compounding of list 7962, lot 05-721-FW, 5% Dextrose and 0.45% Sodium Chloride Injection, USP resulted in the formation of condensation that covered the adjacent ceiling area and overhead pipes as observed on 5/18/11. The condensation was observed to be dripping in and around an open orifice to the tank that was also being used to feed water for injection into the tank.

C. Some pieces of equipment used to manufacture purportedly sterile products are not either operated properly or are structurally defective in a manner that prevents them from being utilized in a manner that minimizes the introduction of materials from outside. For example, lids on mixing tanks are not sealed so as to limit the introduction of materials outside of the mixing tanks. Examples of this include:

1. Tank (b) (4) in the Small Volume Parenterals solutions area where liquid was observed to be leaking from the junction between the main portal and its lid on the top of the tank during the manufacture of list 4887, lot 05-300-DK, Sterile Water for Injection, USP, 50 mL on 5/16/11. The solution was observed to leak out from the junction in both single drops and in approximately 5 - 10 mL portions.

2. Tank (b) (4) in the Small Volume Parenterals solutions area where liquid was observed to be leaking from the junction between the main portal and its lid on the top of the tank during the manufacture of list 4887, lot 05-300-DK, Sterile Water for Injection, USP, 50 mL on 5/16/11. The solution was observed to leak out from the junction in single drops.

3. Tank (b) (4) in Room 691 where water for injection was being added, through a pipe that was inserted into a portal with a larger diameter, under a high flow rate resulting in the water for injection splashing upwards through the portal, hitting adjacent piping, and either dripping down the dome of the tank or falling back into the tank during the manufacture of list 7926, lot 05-271-FW, 5% Dextrose and 0.45% Sodium Chloride Injection, USP on 5/18/11.

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60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202 Industry Information: www.fda.gov/oc/industry	05/16/2011 - 06/17/2011
	FEI NUMBER 1021343

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Hector E. Jimenez, Director of Quality

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Hospira, Inc.	Hwy. 301 N. + 4285 North Wesleyan Blvd.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Rocky Mount, NC 27804	Pharmaceutical and Device Manufacturer / Gamma Irradiator

D. Equipment and facilities used to manufacture purportedly sterile products are not consistently inspected at a frequency sufficient to detect irregular events or conditions. For example:

1. Plastic and metal portions of the rupture disk on Tank (b)(4) in Room 691 were observed to be missing on 5/18/11 although there are no reports of the disk having ruptured during production and/or cleaning activities.

2. Several 5 - 6" strips of plastic were observed on a large mesh screen covering the drain to sewer on the lower level of the Large Volume Solutions tank area on 5/25/11. The strips were observed to be located directly beneath the outlet to a pipe used to drain Tanks (b) (4) There is no way to determine when the strips got there, which tank the strips came from, or what product was in the tank at the time that the strips were in the tank.

OBSERVATION 10

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, pools of liquid were noted on the metal mezzanine area towards the backside and between Tanks (b) (4) and separate pools were observed behind Tanks (b) (4) in the R2 Facility on 5/27/11. Active ingredients and excipients are added to these tanks at the mezzanine level. The R2 facility manufactures terminally sterilized and aseptically produced products.

OBSERVATION 11

The separate or defined areas and control systems necessary to prevent contamination or mix-ups are deficient.

Specifically, bulk containers of active pharmaceutical ingredient (APIs) desmopressin and calcitrol are stored in the Chemistry Quality Laboratory in a refrigerator and a freezer, respectively. The desmopressin canister is stored in clear plastic-like desiccant boxes on the top shelf of refrigerator F-2418 amongst numerous similarly labeled canisters and file samples of other chemicals. The calcitrol canister is stored on a frost-laden middle shelf of freezer RM-2582 amongst numerous similarly labeled canisters of other chemicals.

Furthermore, the locations of the desmopressin and calcitrol APIs are designated by same location code of "888" in the (b) (4) electronic inventory system even through they are not co-located. The "888" location code is also assigned to a freezer located in the warehouse area.

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OBSERVATION 12

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

Specifically, Quality Chemistry Laboratory isolator (b) (4) which is used to weigh and dispense potent active pharmaceutical ingredients for manufacturing (i.e. desmopressin and calcitrol) and to weigh potent chemicals for laboratory use (e.g. sufentanil and paricalcitol), was observed to have multiple structural defects on both its interior and exterior and debris on its interior on 6/14/11. The isolator was supposed to have been in a clean state per written procedure B6120_0193, "*** Chemistry Laboratory Potent Drug Isolators Operating and Cleaning Procedure ***", effective 6/21/10. Observed deficiencies include:

A. Two large cracks in the inner pane of the viewing glass between the right-hand glove and the bottom of the pane.

B. The interior portion of the right-hand glove sleeve was detached from the interior glove sleeve for approximately 1/3 of the sleeve's circumference. Additionally, double-sided tape was observed to be present on the interior of the detached portion of the sleeve.

C. A build-up of a dry, brown substance on the isolator-side hinges to the vacuum oven.

D. Black debris on the analytical balance platform and the base of the isolator's work surface.

E. An amber-colored sphere located to the right of the analytical balance and on the base of the isolator's work surface.

F. White spots on the upper isolator-side hinge to the pass-through.

G. Raised white spots on the electronic control panel for analytical balance.

OBSERVATION 13

Employees are not given training in the particular operations they perform as part of their function.

Specifically, there is no documentation of training or instructing laboratory personnel to restrict their usage of balances and scales to "use ranges" as opposed to calibrated ranges and/or manufacturer-suggested ranges.

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THE FOLLOWING OBSERVATIONS RELATE TO MEDICAL DEVICE MANUFACTURING AND THE QUALITY SYSTEM REGULATION

OBSERVATION 14

Corrective and preventive action activities and/or results have not been adequately documented.

Specifically,

A. Several Exception Reports documented non-conforming production lots that exceeded rejection rates for glass particulates/cracks in sterile empty vials (ER-SOL/RM-003693 (5/30/09), ER-SOL/RM-004730 (1/15/10), ER-SOL/RM-005260 (4/23/10), and ER-SOL/RM-06587 (11/19/10). The root cause for the non-conformances in all instances is attributed to mechanical failures of the processing equipment on the production line (filler, stopper carriage, plunger tool, stopper machines). Management is aware of the malfunctions and the need to replace or improve SVP production/equipment (Line (b) (4) owever, corrective actions have not been implemented to improve the processes to decrease or prevent broken/ cracked vials.

B. Several customer complaints have been received in which customers complain of receiving broken PCA sterile empty vials, List 6021-03 (Record #, 754380, 754355, 754329, 754383, and 754382). At least two customer complaints of broken PCA sterile empty vials (75343 and 754378) were made on production lots 74-206-R1 and 87-313-R1, which were 200% re-worked for exceeding AQL sampling requirements for cracked vials. Complaint investigations are inadequate in that none of the returned devices were evaluated.

C. Exception Report PR26557 (1/3/11), PR28611 (2/2/11) and PR 30359 (4/25/11) indicate these lots of sterile empty vials and injectors, List 6021-03, exceeded the limits for reject rate for particulates. The firm identified preventive actions in January 2011 that included assigning a cross-functional team to fully evaluate glass breakage and establish reject requirements for particulates on the Lines (156/157). The CAPA (#28182) is overdue and planned actions have not been performed.

OBSERVATION 15

Process validation activities and results have not been adequately documented.

Specifically,

A. The firm does not have data showing the efficacy of manual cleaning of all surfaces that come into contact with the

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products in the aseptic filling area (Stopper bowls).

B. The periodic performance qualification for SVP Line (b) (4) dated 1/4/2011 (media fill) does not contain data showing each vial contained the required minimum (b) (4) fill volume.

C. Process Validation for SVP Aseptic Filling Line (b) (4) Protocol # 8256-P01 does not document the Container Closure Integrity testing was performed as required in the established protocol.

OBSERVATION 16

Design plans that describe or reference the design and development activities and define responsibility for implementation have not been established.

Specifically,

A. Design activities and project progression of the HepLock Flush 11-001 design project have not been documented and/or approved as required in the Design Control Policy, Document Number QSD.11. The firm has not formally identified design inputs/outputs and or/conducted design reviews. The design project is reportedly in design verification stage.

B. Design transfer activities have not been established in the Design and Development Plan (DDP) as specified in the Design Transfer Procedure, Document Number QDO.11.016.

OBSERVATION 17

Management with executive responsibility has not reviewed the suitability and effectiveness of the quality system with sufficient frequency.

Specifically, risk management and design control activities are not reviewed during management reviews as part of review inputs as required in QCO. 01.001, Management Review and Quality Governance Procedure

OBSERVATION 18

Procedures for quality audits have not been adequately established.

Specifically, the established procedure, B6100_0013, Internal Audit Program, lacks detail on the areas scheduled for audit within the facility. A combination of business unit areas and quality subsystems are listed on the current audit schedule, however, areas scheduled for auditing are not clearly defined and there is no assurance that necessary quality systems are

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audited within a two year period.

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