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	02/12/2013 - 03/01/2013* FEI NUMBER 1021343

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Zena G. Kaufman, Serior Vice President, Global 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	Sterile Pharmaceutical Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

A. The "Aseptic Media Fill Run" document #B6100_0051 establishes that, "This procedure will document the minimum requirements for performance of aseptic processing simulations at Rocky Mount aseptic solution manufacturing." And, "The purpose of the media fill simulation is to: demonstrate the capability of the aseptic process to produce sterile drug products. Qualify aseptic processing personnel. Comply with Current Good Manufacturing Practice Requirements." The following observations pertain to the media fill operations and aseptic process:

1. There are (b and (b different finished drug products in various container sizes (e.g., 10ml to 100ml) that include a (b) (4) overlay that are produced in the (b and (b manufacturing buildings. However, as confirmed by the Quality Operations Director and the Production Services Officer, they did not perform anaerobic media fills with anaerobic conditions;

2. We observed some of the routine aseptic filling operations in the SVP manufacturing rooms (b) (4), which included observing fill room operators performing a number of reoccurring manual interventions e.g., remove glass vials from line, adjustment of fill equipment, access the fill line via access panels. The Production Services Officer and Production Supervisor confirmed that the media fill runs do not include executing the same number of reoccurring manual interventions and for the same length of time as performed during routine filling operations;

3. The manual interventions include "Replace fill pump", "Replace solution tubing (includes from needle to pump and pump to manifold)", "Replace bladder and Stopper head". One of the fill room operators confirmed that he has performed the intervention during routine filling operations. However, regarding the aforementioned manual interventions he has not performed a similar activity during the media fill simulation process;

4. During routine aseptic filling operations, the (b) (4) filtered production solutions are transferred from the second floor with the use of a transfer hose (e.g., (b) (4)) that is manually placed through a (b)

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(b) (fill lines (b) (4) and (b) (fill lines (b) (b) (4) that (b) (4) The solution transfer hose is subsequently connected manually to a corresponding transfer hose (b) (4) in the aseptic fill room. (Note: the manual connection is performed adjacent to the capping station in an uncontrolled unclassified manufacturing.) With respect to media fill operations, the aforementioned manual operations are not performed in a similar manner. Rather, the microbial growth media if prepared and transferred into the fill room via the use of (b) (4) (b) (4)

5. The "Media fill procedure for vials" (production batch record) describes to "Fill the units aseptically per SOPs, (b) (4) if required", which references the document "B5350_0993" (SOP). However, as confirmed by the Quality Operations Director and the Production Services Officer, the document is silent with respect to a description and/or providing the language regarding how to aseptically fill the units;

   a. During routine filling operations, the fill room operators record the manual interventions that they perform and document the events on the production batch records. However, during media fill operations, the fill room operators do not perform a similar manner of record keeping and frequency of documentation. Rather, the Core Monitor captures the manual interventions and documents the events in the media fill records.

B. The "Aseptic Media Fill Run" document #B6100_0051 establishes the acceptance criteria. Specifically, the "Target value for all media fills is zero positive units. Any (1) positive unit requires an investigation, requirements for alert / action levels of contaminated units for a single media fill trial comply with the guidance in the Aseptic Processing Guideline and the (b) (b) (4) Dependent on the number of units filled the Alert and Action levels range from (b) (4), respectively. Furthermore, "Should a media fill reach the action level, the media fill has failed and an immediate review of pertinent records will be made relating to product manufactured on that line between the current and last successful media fill for that fill line." The following table contains a brief summary of the media fills.

Media Fills	Fill Line	Fill date	Filled Vials	Defect Vial	Assignable cause for discarded vials
12-034-MR	(b)	2/20/12	6357	1652	not specified
12-086-MR	(b)	7/25/12	10675	382	not specified
12-089-MR	(b)	7/30/12	10653	334	not specified
12-090-MR	(b)	8/1/2012	12002	1826	not specified
12-149-MR	(b)	10/29/2012	10736	622	not specified
12-151-MR	(b)	10/31/2012	10190	63	not specified
11-003-MR	(b)	1/5/11	6470	114	not specified
12-082-MR	(b)	7/12/12	11673	242	not specified

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1. The Production Services Officer confirmed that media filled vials are removed and/or discarded during routine filling operations. However, there are no records to document the total number of filled vials that are removed during the media fill operations and there is no record to documents an assignable cause for the removal of the media filled vials;

2. The media fill batch record list a "Defect Categories" which is referenced to corresponding document #B6100_0051 (SOP). However, as confirmed by the Quality Operations Director, the document is silent with respect to a reference or language that addresses defect categories for the filled vials.

3. Fill volume samples are documented as rejects in the defect category for "cap/seal" and not included in the number of units to be incubated in the batch record. The batch record establishes "Fill volume testing will not be destructive testing since all filled units are required to be retained. Fill volume units will be placed on the scale to obtain a gross weight and placed in a separate tray on the inside of the filling suite to be incubated as non-integral units at the end of filling."; nonetheless, all units listed under the "Defect Categories" are not included in the "Number of units to be incubated" and there is no evidence to demonstrate all the units were incubated and evaluated.

C. Regarding the aforementioned observations, the media fill data documents that the company is not able to substantiate that they met their aseptic media fill established acceptance criteria, which is used to support, for example, "the minimum requirements for performance of aseptic processing simulations at Rocky Mount aseptic solution manufacturing"; "demonstrate the capability of the aseptic process to produce sterile drug products" and "Qualify aseptic processing personnel";

D. The media filled vials are inspected for turbidity and visible particulates following the initial 7 day and final 14 day incubation periods. However, the Biological Quality (BQ) Supervisor confirmed that there is no specific document that describes the requisite training for the individuals who perform the visual inspection of media filled vials. Some of the training would include, but not necessarily limited to, for example, visuals aids for turbid and non-turbid liquid media and examples of vials containing particulates. In addition,

1. Microbial growth promotion tests are performed for the microbial growth medium that is used for the aseptic media fill process. The "Growth Promotion Testing" document #B6131_0033 establishes, for example, "For the growth promotion to be valid, the inoculum level must be (b) (4) microorganisms", which requires the use of microbiological positive controls. As confirmed by a Laboratory Analyst-I and BQA Supervisor, the rehydration of the microbial positive controls uses the manufacturer's reconstitution instructions. However, the BQA Supervisor and the Quality Operations Director confirmed that the manufacturer's instructions have not been officially vetted and in conformance with the Quality System.

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OBSERVATION 2

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

Specifically,

A. The Validation Change Request (VCR) 9799, dated 12/1/10 concerns the establishment of a unidirectional airflow zone above the (b), Line (b) (room (b) capper operation via the installation of (b) self-contained, HEPA filtered air recirculation units and associated laminar flow curtains. The VCR concludes, "...the combines system (HEPA recirculation units and associated laminar curtains) has proven capable of meeting the requirements of QPO.29.002, *Microbiological and Environmental Control of Aseptic Process Operations Procedure,* and has proven capable of maintaining an ISO Class 5 HEPA air supply until the product's final cap seal has been applied." However, there is no non-viable particulate monitoring performed to assure that the laminar flow curtained area is "capable of maintaining an ISO Class 5 HEPA air supply until the product's final cap seal has been applied." In addition;

1. The aforementioned corporate procedure "defines the minimum control limits and monitoring requirements for all Hospira manufacturing environments involved with sterile parenterals products produced by aseptic processing." The following 30ml tear top vial type finished products are aseptically filled and capped with the use of the (b) (b) (4) Capper;

   1. Acetylcysteine 20% Solution, USP, list #3308-04-13
   2. 2% Chloroprocaine T Hydrochloride Injection USP, list #4169-04-86
   3. 3% Chloroprocaine T Hydrochloride Injection USP, list #4170-04-86
   4. Bupivacaine HCL 0.25% EPI 1:200,000, list #9042-04-17
   5. Bupivacaine HCL 0.25% EPI 1:200,000, list #9042-04-87
   6. Bupivacaine HCL 0.5% EPI 1:200,000, list #9045-04-17
   7. Bupivacaine HCL 0.5% EPI 1:200,000, list #9045-04-87

   However, during the capping process, the aforementioned finished products are not maintained within an ISO-5 environment in that they are exposed to an unclassified manufacturing environment in room (b)

B. All materials, fill room equipment parts and utensils that are used for the manufacturing operations that are not subject to a sterilization process are decontaminated via a (b) (4) process in the (b) (4) (b) (4) #RMFJ-0477 (b) feet, room (b)). The following provide a brief summary of observations;

   1. The Engineer (Engineer-I) explained some of the key (b) (4) process parameters, e.g., (b) (4) The process parameters were evaluated

during the (b) Cycle development and ultimately used to establish the (b) (4) process. The Engineer-I confirmed that there exists no record of the cycle development studies to support the current (b) (4) process;

2. The manufacture's cycle development guide defines the validation process to include (b) (4) study, (b) distribution with (b) (4) and a challenge with (b) (4) For example, a (b) (4) must be determined to establish the present sterilant concentration" and the (b) (4) via the use of (b) "are useful for assuring homogenous (b) (4) patterns". The Engineer-I confirmed that they have not performed a (b) (4) profile or a (b) (4) evaluation via an (b) (4) evaluation for the (b) (4) (b) (4);

3. The (b) (4) process validation includes the use of (b (b) (4) monitoring probes positioned at defined locations, each with a corresponding (b) (4) on the (b) (4) (b). However, as previously noted, there exists no (b) (4) evaluation to assure a homogenous (b) (4) distribution within the (b) (4) which will identify and establish the worst case (b) (4) challenge locations of the (b) (4) load configurations, which will in turn assists to assure that all materials are appropriately decontaminated prior to being transfer into the manufacturing controlled and classified areas;

4. The (b) (4) process validations included evaluations with various material load configurations on the (b) (4). Regarding routine production operations, the QA Project Specialist confirmed, excluding the language noted in the aforementioned procedures, they do not have any specific load configurations for the (b) (4);

5.. There is no record to document that the routine production load configurations do not exceed the validated load configurations established via the (b) (4) process;

6. The "Aseptic Sterilization Operations and Procedures" document #B5340_2023, and "(b) (4) Work Order" document #W5300_342, establish the routine production operations, for example, "Do not stack items or allow other items to remain in contact with each other" and "Items loaded into the (b) (4) (b) (4) most be loaded in a configuration that allows no contact with other items or cart", respectively. The aforementioned standard procedures are silent with respect to defining and establishing the routine load configurations.

7. The Enginner-1 confirmed that the is no (b) (4) profile performed or a (b) (4) for the (b) Line (b) production (b) (4) (b) (4)), the (b) (4) and the (b) (4) (b) (4) r that is used for Sterility Tests.

C. For fill line (b), we observed non-viable particulate (NVP) monitoring that is performed in close proximity to the aseptic filling zone. However, NVP measurements are not taken from other ISO-5 areas (e.g., (b) (4)) during the

aseptic filling process.

D. The "Aseptic Gowning and Technique Procedure", document #B5350_0996, establishes the "proper aseptic techniques" when engaged in the aseptic filling operations, which includes to "move slowly and avoid excessive body movements". However, we observed fill room personnel movements and production activities being performed in fill lines (b) (4) that were inconsistent with the established standard operating procedure.

E. Senior Purchasing Agent explained that all of the gowning attire (e.g., personnel scrubs, clean room gowning/coverall, over shoe covers and goggles) used by personnel that enter into the manufacturing areas have an established minimum and maximum life of a garment, that is in terms of the number of laundry cycles. For example, the clean room gowning/coverall and overshoe covers have a life cycle of (b) (4) laundry cycles, respectfully. The Senior Purchasing Agent confirmed that there is no standard procedure that defines and establishes the minimum and maximum life of a garment. In addition,

1. There exists no record to document the life cycle of the aforementioned gowning attire, which would assure that the garments and personnel attire are fit for use.

F. "Smoke Profile for Air Flow Pattern (s) & Curtain Lengths" document #B7100_0003 establishes that the, "Smoke profiling helps determine the effectiveness of the unidirectional air flow, (commonly known as laminar air flow) within the ISO 5 curtained areas of that cleanroom or class 100 cleanroom itself." The air flow pattern evaluations include "the smoke profile is done in the operational mode or dynamically" and "the smoke should move down and away from product when introduced at or above product heights. There should be no turbulent flow of air in the critical process areas." The corporate "Facility Qualification Procedure" document #QVO.19.021, establishes the smoke test, "Evaluates the HVAC systems under consideration to determine the effectiveness of the unidirectional airflow under static and dynamic conditions." The following provide a brief summary of some air flow pattern observations;

1. for fill room (b) the evaluations did not include an assessment of the air flow from the HEPA filters that are positioned over the ISO-5 (b) (4) to assure that the air flow from the ISO-7 surrounding area does not adversely affect the ISO-5 area (Note: the distance between the ceiling (HEPA) and the (b) "(b) partition is approximately 3 feet);

2. for fill room (b) the evaluations did not include an assessment to determine the affects of the air flow when opening and closing the "(b) (4) to assure that "the smoke should move down and away from product when introduced at or above product heights";

3. for fill rooms (b) (4) the simulations of a replacement and/or removal of filling equipment e.g., "Replace fill pump", "Replace solution tubing (includes from needle to pump and pump to manifold)", "Replace bladder and Stopper head", the evaluations did not include the routine movements and personnel activities that are commonly performed during routine production operations;

4. there has been no assessment performed to determine and assure that the air flow from the ISO-7 area does not enter into the ISO-5 area when personnel are performing the various personnel activities next to or when accessing the

ISO-5 areas e.g., adjusting the fill equipment/needles, glass vial in feed area in rooms (b) and (b) (approximately (b) (4) [redacted], respectively), and when accessing the ISO-5 via the (b) (4) (b) (4) (room (b)) from the ISO-7 surrounding environment;

5. there are a number of instances when the air flow pattern videos did not demonstrate that "the smoke should move down and away from product when introduced at or above product heights. There should be no turbulent flow of air in the critical process areas". For example, for line (b) during the (b) (4) [redacted]). (Please note that the aforementioned simulations and approximate video time stamps are not intended to be an all inclusive or exhaustive list of examples);

6.. the various pieces of fill room equipment and materials used during routine production operations are transferred from the ISO-8 manufacturing support rooms and into the ISO-7 manufacturing areas (surround the ISO-5 critical zones) with the use of (b) (4) [redacted]. There has been no assessment of the air flow patterns to assure that the air flow of the ISO-7 and ISO-5 areas are not compromised when opening and closing the room doors;

7. the aforementioned procedure establishes to "allow enough smoke to be introduced to the area to observe the air pattern to the approximate exit of the unidirectional air flow area. If a question arises, introduce additional smoke until the air pattern is determined." However, the air flow pattern videos for three individual evaluations (approximately 1 minute each) for fill line [redacted] ((b) bldg.) (b) (4) [redacted] documents no visible or distinctly visible smoke;

G. The microbiology department responsibilities include for example, the implementation of the Environmental Monitoring (EM) program and establishment of the microbial alert and action levels for the manufacturing areas (e.g., ISO-5, ISO-7 and ISO-8) and for personnel monitoring. The Biological Quality Supervisor confirmed that they have not performed an evaluation of the air flow pattern evaluations, which for example would assist to determine the appropriate EM site selections for passive and active sampling, the manufacturing areas and personnel activities that may present a greater degree of microbiological challenge to ultimately assure that the EM program appropriately captures all critical monitoring areas.

OBSERVATION 3

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

(This is a repeat observation)

Specifically,

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A. The firm's Quality unit has failed to evaluate all standard operating procedures/standard test methods to assure they are in compliance with cGMPs, accurately reflect current practices, and do not conflict with other procedures.

For example:

1. SOPs WGTSGLVQC, "TS Glass Vial Quality Control Chart", WGTSPLVQC, "TS Plastic Vial Quality Control Chart", WGASGLVQC, "Aseptic Glass Vial Quality Control Chart", WGASVIALQC and " Aseptic Vial Quality Control Chart" describing in-process checks of defects have an accept/restrict level of (b) for crimping defects. When crimping defects met or exceeded the "restrict" level there was no requirement to conduct an investigation or to evaluate product since the last acceptable in-process check. This practice which had been effect since 2006 was only identified by the firm in January 2013 due to several complaints received for uncrimped vials.

2. Thirteen (13) Standard Test Methods describing how to perform sterility testing based on various container configurations of aseptically filled and terminally sterilized products state if outgrowth occurs "a retest must be performed." This language is misleading and contradicts the required investigation that must occur as described in Standard Laboratory Practice 94.M-001 "Sterility Testing, Effective 8-23-12".

B. Employee practices do not consistently align with written procedures and are not assessed for their impact upon manufacturing efficiency and/or product quality. Examples include:

1. There is no written procedure or means of tracking for Flex Manufacturing Area employees' practice of storing plastic films for use in the fabrication of 500 mL and 1000 mL bags for (b) (4) in the Flex Area Airlock (Room (b) .

2. There are no written procedures for Flex Manufacturing Area employees' practice of using (b) (4) and (b) (b) (4) at multiple points on and in the (b) machines that place 500 mL and 1000 mL bags into overwraps to prevent jams and possible damage to overwrap pouches and/or bags.

3. There are no written procedures for SVP Manufacturing Area employees' practice of securing a (b) (4) to the stoppering machine with (b) (4) so as to reduce the incidence of line stoppages.

OBSERVATION 4

Drug product production and control records, are not approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

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A. Five hundred forty-three (543) non-viable particulate test results obtained during the production of both aseptically filled and terminally sterilized products were invalidated without the required Biological Quality supervisor approval from 2011 to 2013. SOP B6134_0007 "The Rocky Mount Facility Environmental Quality Program, Effective, 12-11-12" states that a supervisor signature is required within that shift for approval of invalid results. The invalid results were not entered into the (b) (4) (b) (4)), only the passing retest. The Biological Quality Manager stated that the Biological Quality staff was told to stop invalidating data in this manner "around the third week of September." There have been 2 more instances of data invalidation since. No procedures have been updated to address this invalidation practice. The Remediation Manager identified that a protocol was approved on 1/30/13 to detail the review of 2011 and 2012 (b) (4) logbooks for documentation errors. In addition, the protocol needs revision to address the invalidated data and assess the impact that each individual case may or may not have on marketed product.

B. Discussions with the Biological Quality Supervisor revealed that in some instances, the alarms were stopped prior to completion of the sample. Therefore, measurements for both (b) (4) [redacted] size particles are not recorded. A measurement that was stopped on line (b) (b) (4) during simulated water run on 2/28/12 stated that an operator was inside the line. When asked whether it is normal to stop a measurement because someone is in the line, the Biological Quality Supervisor stated that they are not trained to do this. Another instance of the alarm being aborted during an activity occurred on 2/11/2012 when a measurement was stopped and invalidated because of a tank change.

OBSERVATION 5

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.

(This is a repeat observation)

Specifically,

A. Investigation with PR ID # 80622 was created on 05/04/12 to address three separate events associated with product complaints for Bacteriostatic Water for Injection, USP. In the first event, associated with lot # 08-368-DK, the reporter revealed 93 particulate defects (9 specks, 6 fibers and 78 loose glass). In the second event, associated with lot # 17-103-DK, the reporter revealed 54 particulate defects (1 speck, 2 fibers, 51 loose glass). In the third event, lot # 17-104-DK, the reporter revealed 58 particulate defects (55 loose glass, 2 speck and 1 fiber). All lots related to the aforementioned events were manufactured in line (b) . A potential root cause for the glass particulate was identified to be needle to vial strikes; as a result, needle offset and dive settings were established for the affected line.

1. Engineering failed to conduct an engineering study, as established in the investigation report, to establish acceptable

needle offset and dive settings.

2. The investigation fails to address the impact needle offset and dive settings to any other products or lines.

3. In addition, the firm failed to address the failure of the firm's visual inspection process to identify these numerous particulate defects.

B. Investigation with PR ID # 68090 was created on 02/03/12 to address white particulate, "with a very thin fiber like" appearance, observed inside Epinephrine Inj. solution with lot # 14-071-DK. The white particulate was identified to be silicone. The investigation report established (b) (4) may exhibit signs of unadhered silicone" and "these units are not classified as defects"; as a result, the investigation was cancelled.

1. The "signs of unadhered silicone" statement does not specify an appearance or specific location; nonetheless, "these units are not classified as defects" as established in the Aseptic Vial Quality Control Chart, effective 11-03-07.

2. A hazard or manufacturing process assessment was not conducted as part of the investigation.

C. During media fill with fill date 01 AUG 2012, fill line (b) and lot # 12-090-MR, 27 vials were identified as having a "glass" cosmetic defect (glass particulates); nonetheless, an investigation to identify the root cause of these events and prevent occurrence during routine operations was not initiated as confirmed by the Quality Operations Director.

OBSERVATION 6

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

A. In October 2012, Biological Quality Manager identified that "Gram positive rods in (b) (4) increased to 25% from 0%". The (b) (4) trend report for (b) (4) 2012 states "Gram positive (spores), Gram negative rods, and molds (objectionable organisms) occur more abundantly than expected for properly functioning clean rooms." For example in the (b) aseptic core the microbial bioburden consisted of the following: 48% Gram positive spore forming rods, 31 % Gram positive cocci, 9% Gram positive non-spore forming rods, 6% mold, 5% Gram negative rods, and 1% yeast. The small volume parenteral terminally sterilized classified area had bioburden consisting of 27% Gram positive spore-forming rods, 23% mold, 18% Gram negative rods, 18% Gram positive cocci, 8% non-spore forming rods, and 6% yeast. Review of the (b) (4) trend reports from (b) (4) 2012 to (b) (4) 2012 remained similar. The report states that the "vast majority of microbial contamination is human borne in adequately functioning clean rooms." Subsequently, on October 31, 2012 Production Services Manager opened CA-PA PR ID: 105693 in order to create a focus team to review the current Rocky Mount Cleaning and Disinfectant Program to identify gaps, standardize cleaning procedures, and implement continuous improvements around cleaning, sanitization, and disinfection in the ISO classified areas. Although

more than 3 months have passed, no focus team has been established.

B. The microbial action limits for purified water used in the production of aseptic and TS products have not been evaluated to determine if they are appropriate for the Rocky Mount facility based on historical data, resulting in a large spread between the alert and action limits. For example, the alert limit in (b) small volume parenterals is (b) (4) and the action limit is (b) (4).

C. Procedures do not define how data must be presented in the (b) (4) trend reports generated by Biological Quality. Corporate SOP QPO.29.002 "Microbiological and Environmental Control of Aseptic Process Operations Procedure, Effective:11-20-09" states that normal operating trends of all ISO Class 5 environments must be reviewed (b) (4). A standard operating procedure describing how the data must be evaluated and presented is necessary to assure that negative trends are discussed during the management review meeting. For example, the (b) 2012 trend data presented during management review on 7/5/12 presented that there were "no negative trends in (b)." However, review of the (b) (4) trend report indicated that there was a negative trend for non-viable air on aseptic critical site Line (b). This information was not discussed during management review because of the format in which the trend information was presented.

D. There were 5 instances of Gram negative rods (objectionable organisms) recovered from the aseptic core within the ISO Class 5/EU Grade A area of the (b) (4) and filling lines during 2011 and 2012. Review of associated Exception Reports PR ID 67333, PR ID 107671, PR DI 102686, PR 51460, and PR ID71321 investigating the recoveries revealed the following deficiencies:

1. The investigations failed to adequately evaluate a possible route of contamination. Each investigation describes the type of organism and its usual source. However, they do not explore how the organisms entered the controlled environment. PR 107671 suggested the most probable root cause as being "attributed to water condensation from outside of the (b) (4) settling onto the settle plate during fill machine set-up activities." During discussion, the Biological Quality Manager and Biological Quality Supervisor agreed that the likelihood of this occurring from (b) (4) materials is 0%. The investigation was approved by Quality.

2. The interviews conducted as part of the investigations were poor in that they only involved the BQ technicians responsible for taking the environmental samples. No interviews were conducted with the line operators whom are in the aseptic environment longer periods of time and are more likely to witness any unusual events. Additionally, the interviews were conducted approximately 2 months after the occurrence.

3. The investigations include environmental data for the aseptic area that is reviewed for trends. However, there is no procedure that defines the search criteria for trending. No evaluation of environmental monitoring data for the support areas within the aseptic core were conducted during the investigations. The BQ Manager agreed that this process needs improvement.

E. There exist no established procedures to define the evaluation process when establishing sample site rationales for

environmental monitoring of ISO classified areas. The sample sites for locations within the ISO Class 5/EU Grade A areas were established without review of the smoke studies. Biological Quality Supervisor who established the sample site locations did not review this material. The Biological Quality Manager added that she was in the process of training him on how to review smoke studies.

OBSERVATION 7

Equipment for adequate control over air pressure, humidity, and temperature is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.

Specifically,

A. The (b) (4) (b) (4) is a computer based automated system that is used to provide control and monitoring of both CGMP and non-CGMP systems throughout the(and(facilities. Examples of CGMP functionality at this plant include Differential Air Pressures (ΔP) monitoring and alarming in the Aseptic/TS cores and HVAC systems. Regarding the(b) (b) measure points, the Senior Maintenance Supervisor confirmed that(b) measurement points monitor CGMP "important" parameters. The following provide a brief summary of observations;

1. The(b) (4) (b) is accessed remotely by designated and approved Level 1 (administrative privileges) individuals that include a(b) (4) contractor. The Level-1 privileges include for example, configure items, adjustments, resets and override capability, analysis, and trending report. However, there is no record to document that the(b) (4) contractors and the individual who has remote access privileges for the(b) computer system have taken the requisite CGMP training modules;

2. Regarding the aforementioned access by the(b) (4) contractor with Level 1 access privileges, there is no standard procedure that establishes a periodic review (e.g., Quality Assurance oversight) of the remotely accessed computer data related events e.g., configure items, adjustments, resets and override capability, analysis, and trending reports;

3. The Senior Maintenance Supervisor confirmed that in the last nine months there have been approximately 4,000 and 3,800 alarmed events that have occurred in the(b) and(b buildings. However, there is no record to document that the(b) alarms are reviewed on a periodic base to assure that the alarmed events do not document a negative trend for the(b) measurement points;

4. The(b) (4) (b) will provide an audio and visual alarm to alert the production and engineering staff of the air pressure alarm when the differential air pressure exceeds the established upper and lower levels between the aseptic fill rooms and the surrounding manufacturing areas. An alarm text message is printed out in a production office. However, the computer print out does not include the actual air pressure measurement that generated the alarm event. The Senior Maintenance Supervisor confirmed that the actual air pressure measurements can be printed out

and the information can be provided, that is, if the Manufacturing Quality (MQ) personnel specifically request a print out;

5. In the absence of an air pressure alarm print out, the Senior Maintenance Supervisor and the MQ personnel do not periodically review the air pressure measurements to assure that the differential air pressures do not present a negative or outward drift from the established upper or lower air pressure levels.

B. The Senior Maintenance Supervisor confirmed that there are no As Built engineering diagrams for the Air Condition (AC) (b) (4) The (b) (4) units provide high quality HEPA filtered air for the fill rooms (b) (4) (ISO-5 and ISO-7) aseptic filling rooms and for the ISO-7 and ISO-8 manufacturing support areas leading to the aseptic fill rooms, respectively. And, the simplified block Air Flow Diagrams K-RM-5-M101c and K-RM-5-M101a for AC-1 and AC-2, respectively, that illustrate the air systems are not current or up-dated.

OBSERVATION 8

Aseptic processing areas are deficient regarding humidity controls.

Specifically,

Review of the temperature and humidity monthly measurements from 2010 to present for all controlled ISO 5 to ISO 8 aseptic processing environments in (b) and (b revealed that relative humidity readings repeatedly exceeded the specification of (b) % R.H. (relative humidity) with excursions ranging from (b) - 99%. "Humidity is only controlled in rooms having specific product parameters that require control"..."All other rooms will be controlled and monitored for personnel comfort only" as stated in SOP S7100_1002 "Room Temperature and Humidity Testing, Effective: 10/29/2012." This approach to temperature and humidity control has not been evaluated with regard to impact on controlling the propagation of microorganisms.

The Failure Mode and Effect Analysis performed regarding temperature and humidity as described in SOP 7100_0255 "Rocky Mount Engineering (P/M) Preventative Maintenance Program, Effective: 09/28/2012" was performed and identified that this task has a priority ranking (b) (4) This is documented on Maintenance Work Order Forms identified as "Task No: RM (b) " and "Task No: RM (b) ." Priority ("task(s) have major affect on safety, product, quality or process." The Quality Operations Director stated that the actual FMEA matrix was discarded as part of Hospira's corporate record retention policy.

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Zena G. Kaufman, Serior Vice President, Global 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	Sterile Pharmaceutical Manufacturer

OBSERVATION 9

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

Specifically,

A. The (b) (4) is the (b) (4) used to perform sterility test on aseptically filled finished products. Review of the last performance qualification entitled "2011 Periodic Performance Qualification (PPQ), Biological Quality Laboratory (b) (4) (b) (4) (b) (4) revealed the following deficiencies:

1. The study does not include a documented rationale for the placement of (b) (4) (b) (4) within the (b) (4). Additionally, there were no air distribution studies performed to demonstrate adequate distribution of (b) throughout the (b) (4) and visualize the hardest to reach areas within the (b) (4)

2. Performance qualifications for the unit are performed every (years. The rationale for this timeframe is not documented. Aside from normal preventative maintenance performed by the BQ technicians, no periodic review is performed between qualifications. Validation stated that as a part of the periodic review which is currently on schedule for approximately every (years, they look back at the environmental trending data in a report provided by the BQ laboratory. However, the report that is provided by the BQ laboratory is not based on a protocol detailing what information must be included and in what format. Therefore, all negative trends may not be revealed during the periodic review.

B. SOP 6131_0013 "Procedures for Testing Positive Isolates Found in Sterile Products, Effective: 11/21/2005" describes procedures that may result in a false negative being reported during a sterility test positive investigation by instructing the following:

1. The subculture incubation period is only (b) This could preclude the proliferation of slower growing organisms.
2. The subculture procedure for (b) (4)) only requires anaerobic incubation. (b) also supports the growth of organisms with reduced oxygen requirements that may be excluded if aerobic incubation is not performed as well.

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OBSERVATION 10

Written specifications for laboratory controls do not include a description of the testing procedures used.

Specifically,

During the incubation of anaerobic environmental monitoring samples the anaerobic indicator is being used incorrectly. The appropriate use is not detailed in SOP B6117_4013"Operation and Use of the (b) (4) Water Baths, (b) Anaerobic System (b) (4), (b) (4) Pipet Washer, (b) (4) Sealing Machine, and the Use of (b) (4) Glassware, Effective 10-08-02." Since no positive control is incubated concurrently with the samples, there is no assurance that anaerobic conditions are achieved.

OBSERVATION 11

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

(This is a repeat observation)

Specifically,

A. The 2011-2013 (b) (4) logbooks used to adhere non-viable air raw data to bound worksheets were reviewed. Requirements for this documentation are described in SOP "The Rocky Mount Facility Environmental Quality Program, Effective, 12-11-12." The following documentation errors and omissions were revealed:

1. The non-viable particulate test results are incompletely entered into the (b) logbook, incorrectly documenting whether a retest was or was not performed. In many instances, "No retest" is selected when in fact there was a retest attached to the form.

2. Omission of the term "invalid" on the invalidated over alert and/or over action results.

3. Details describing why the measurement is invalid are not properly documented on the form.

4. Signature missing from the BQ technician and/or the reviewer showing that no review was performed at all.

B. The raw data generated from the semi-automated thickness tester used to measure the thickness of perimeter seals on

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fabricated 500 mL and 1000 mL bags used as container closure systems for injectable drugs can be overwritten with new data without explanation and the original data is erased from the computer's memory upon being overridden. For example, the first three pages of the "FLEX FAB SEAL THICKNESS REPORT" for bags fabricated for list number 7983-04-49, 0.9% Sodium Chloride Injection, USP, lot 26-806-FW recorded that 17 out of 48, 16 out of 47, and 12 out of 48 measurements were overridden.

OBSERVATION 12

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

Specifically,

A. The periodic performance qualification protocols for the (b) (4) (b) (4) used to terminally sterilize 500 mL and 1000 mL drug products do not require that biological indicator D-values be comparable to those previously used to qualify the terminal sterilization process. Written procedure 90.M-0330, "D-values Associated with Microorganisms used for Sterilization Validation", effective 7/20/12, allows for the stipulated biological indicator organism, (b) (4) to possess D-values ranging from .

B. There is no written procedure requiring that sporulation counts of the biological indicator organisms used to validate the performance of the (b) (4) (b) (4) are compared against each other and against scientifically justified specifications prior to heat shock processing, after heath shock processing, and with the positive controls. Personnel at this facility currently utilize a non-proceduralized requirement that the post-heat shock sporulation counts must be within (b) % of the pre-heat shock counts.

OBSERVATION 13

Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable.

Specifically, potentially defective 500 mL and 1000 mL bags fabricated onsite and used as drug product container closure systems are not appropriately bracketed upon discovery of one or more defective units during routine in-process testing for seal integrity conducted on the final set of (b) bags on each shelf of approximately (b) bags. A failing in-process test results in (b) random sets of (b) bags being sampled from the implicated shelf. If any of the bags from the (b) random sets fails the additional in-process testing, all of the bags on the shelf are rejected. If all of the bags from the (b) random sets of (b) bags pass the additional in-process testing, all of the bags on the shelf are accepted. There are no assurances that all of the defective units fabricated before and after the failing unit are appropriately bracketed and/or specifically identified.

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OBSERVATION 14

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

A. The validation study to evaluate sanitizers used on surfaces within the aseptic core entitled, "Microbial Evaluation of Germicidal Effectiveness (b) (4) (b) (4)) on Bacterial Microorganisms, Protocol # RM BQ 12.043" is inadequate in that:

1. Critical surfaces that the aseptic filling rooms are constructed of ((b) (4) (b) (4) were not evaluated. Regarding the grade of stainless steel that is used for the aseptic filling lines in (b and (b , the Engineering Services Manager stated that "it could not be determined."

2. (b) (4) failed when challenged with (b) (4) isolate and Rocky Mount isolate #H201214BQ on the wall (b) (4)) surface with (b) (4) reductions, respectively. Although the acceptance criteria of a(were not met, Production Services Manager concluded that the result "rounds to a(b) reduction, therefore it meets the acceptance criteria." The study was approved by Quality Operations Director designee and the Biological Quality Manager.

3. There is no documented scientific rationale detailing the surface selection evaluation. The Lead Director for Manufacturing Science and Technology confirmed that (b) (4) were used in the previous corporate efficacy studies because they were considered to be worst case surfaces that were more difficult to clean than (b) (4) . However, Rocky Mount did not evaluate either the (b) (4) . Additionally, the corporate studies did not evaluate isolates from the Rocky Mount site.

B. While viewing the set-up of aseptic filling line (b) for the filling on 1% Lidocaine Lot#26-416-DK, List #4279, a white residue was observed on the stainless steel filling cabinet, around a hose leading from a trough beneath the filling zone, on the floor immediately beneath the filling cabinet, on the floor beneath the (b) (4) system, in between the (b) (4) particle counters and the stoppering machine. The room was cleaned the morning prior to set-up on 2/20/13 with a start time of 0036 hours and a completion time of 0245. According to SOP 5000_0001 "Hospira Rocky Mount Cleaning and Disinfection Program", Effective: 13-01-28, the area is inspected "to ensure that all equipment is clean and that no product residues or extraneous particles are present." Although the room was inadequately cleaned and residue remained in several locations in the ISO 5 and ISO 7 areas, the records indicate that the cleaning was verified by the Line Coordinator as acceptable.

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OBSERVATION 15

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

Specifically, Small Volume Parenteral filling area operators do not recognize aberrant conditions. For example:

A. Filling nozzle(b) on the filler located in Line (b) was observed to be misaligned which resulted in product solution spilling over the edge of the respective vials being filled. This, in turn, resulted in product solution pooling in a catch basin beneath the vial conveyor system and forming puddles on the floor and an indention in a wall as the conveyor system transported spilled product solution from the filling machine to the capping machine on 2/17/13. Line (b) was filling list number 4778, Lot 26-292-DK, Ciprofloxacin Injection, 400 mg/40 mL.

B. The tubing connecting a pump to the fill nozzle(on the filler located in Line (b) was observed to be pulling tight upon each filling cycle on 2/17/13. Line (b) was filling list number 4778, Lot 26-292-DK, Ciprofloxacin Injection, 400 mg/40 mL.

C. Filling nozzle(on the filler located in Line (b) was observed to be misaligned which resulted in product solution spilling over the edge of the respective vials being filled. This, in turn, resulted in product solution pooling in a catch basin beneath the vial conveyor system and a puddle formed on the floor as the conveyor system transported spilled product solution from the filling machine to the capping machine on 2/17/13. Line (b) was filling list number 4276, Lot 26-229-DK, 1% Lidocaine HCl Injection.

OBSERVATION 16

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

Specifically,

A. Deficiencies related to the manual 100% visual inspection of in-process drug products and finished drug products include:

1. Personnel engaged in the manual 100% visual inspection of in-process drug products and finished drugs products are not qualified to detect defects successfully at the rate at which the products are presented to them for inspection. For example, personnel assigned to perform manual 100% visual inspection of 500 mL and 1000 mL bags of drug

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products in the Flex Manufacturing Area are qualified, in part, to perform the inspections after passing a seeded defect qualification in which they have (b minutes to inspect and identify defects in (b bags. Inspection rates for specific work stations include:

a. Personnel in the Flex Manufacturing Area fabrication room inspect approximately (b bags per minute.
b. Personnel in the Flex Manufacturing Area filling rooms inspect approximately (b bags per minute.
c. Personnel in the Flex Manufacturing Area overwrap rooms inspect up to approximately (b bags per minute.
d. Personnel in the Flex Manufacturing Area (b) (4) loading space and pack-off space inspect up to approximately (b bags per minute.

2. The defect kits used to qualify personnel assigned to perform manual 100% visual inspection of 500 mL and 1000 mL bags of drug products in the Flex Manufacturing Area include at least one defective unit that is identified with large "X"s across both the front and back panels.

3. An assessment of the manual 100% visual inspection process for 500 mL and 1000 mL bags of drug products manufactured in the Flex Manufacturing Area written by a third party consultant between 6/23/11 and 6/22/12 concluded that it is not suitable to detect defects in the bags as reported in PR41875 which reads, in part: "... this is not a 100% inspection process and the manufacturing line (speed, product orientation, configuration) does not allow for inspection of all of the bags."

4. Quality defects, including critical quality defects, with high levels of detectability are not consistently being identified and rejected from in-process materials. Examples of end user complaints reporting units of 500 mL and 1000 mL bags of drug products possessing defects that are readily identifiable include, but are not limited to:

a. Complaint 1234277 in which a 500 mL bag of list number 07953-04-44, lot 95-618-FW, Lactated Ringers Solution Injection, USP, was reported and confirmed by Hospira to contain a pinhole leak resulting in the bag leaking into the overwrap.
b. Complaint 1376716 in which a 1000 mL bag of list number 07953-04-49, lot 17-929-FW, Lactated Ringers Solution Injection, USP, was reported to contain a melted administration port resulting in the healthcare provider electing to select another bag for use.
c. Complaints 1434281 and 1434294 in which two 500 mL bags of list number 07922-13-44, lot 01-815-FW, Dextrose 5% Injection, (b) (4) were reported to be missing the white port cover and/or z-port (administration port) resulting in the solutions contained within the bags to spill out as the healthcare providers were preparing to administer the drugs to patients.
d. Complaint 1508549 in which a 1000 mL bag of list number 07926-04-49, lot 19-612-FW, 5% Dextrose and 0.45% Sodium Chloride Injection, USP, was reported to be leaking from the filling port cover resulting in the product solution leaking into the overwrap.

B. Hospira personnel were unable to locate the scientific justifications for in-process specifications for 500 mL and 1000 mL polyvinylchloride (PVC) bags (e.g. (b) (4) d test (b) (4) integrity tests, etc.) fabricated onsite and used as container closure systems for sterile drug products. Additionally, these in-process specifications are not subject to

periodic review to assess whether they are appropriate.

OBSERVATION 17

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

Specifically, written procedures related to the manufacture of sterile drug products may contain conflicting instructions. For example, written procedure MPRM_1500, "PERIODIC PERFORMANCE QUALIFICATION FOR THE (b) (4) (b) (4) ", effective 2/14/12, establishes the maximum time that 500 mL bags can remain in the (b) (4) section as (b) (4) which corresponds with the validated maximum ( ) whereas instruction 3.43 of written procedure BFCF_STER_OPER00.EW1, (b) - Routine Operation Of The (b) (4) (b) (4) ", effective 8/27/12, allows 500 mL bags to remain in the (b) (4) section for up to (b) minutes which exceeds the validated maximum F_O o(b)

OBSERVATION 18

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

Specifically,

A. All(b) (4) machines used to place 500 mL and 1000 mL bags into overwrap pouches are not suitable for use without significant *ad hoc* modification by area personnel. Examples of modifications include:

   1. Adhesive tape is used to secure a(b) (4) (b) (4) to prevent jams and possible damage to the bags.
   2. Adhesive tape is used independently and also to(b) (4) (b) (4) prevent jams and possible damage to the bags.
   3. Adhesive tape is used to secure stacks of(b) (4) (b) (4) to prevent jams and possible damage to the bags.

B. The metal guard plate shielding the(b) (4) on Line(b) was observed to be held in place by two pieces of bent tubing wedged beneath it and a metal spring bowed across it. The bent tubing and spring held the plate in place and prevent excessive line stoppages do to displacement of the metal guard plate.

C. A stainless steel panel situated between the(b) (4) (b) (b) (4) separating the filling zone Class 5 area from the surrounding Class 7 prevents inspection of critical operating equipment

and operations by Manufacturing and Manufacturing Quality personnel in an area where products are filled aseptically.

OBSERVATION 19

Equipment and utensils are not cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

A. Substantial amounts of debris that were too numerous to count were observed on metal plates located immediately beneath the conveyor belts supplying 500 mL and 1000 mL bags to the (b) machines used to place the bags into overwrap pouches. The edges of the metal plates are located above the areas where the overwrap pouches are opened to receive the 500 mL and 1000 mL bags.

B. Tank (b) in the Small Volume Parenterals area was observed to be leaking from the main valve on the bottom of the tank on 2/12/13. It was holding bulk solution for List 4283, Lot 26-340-DK, Lidocaine 4% HCl Injection, USP.

C. Tank (b) in the Small Volume Parenterals area was observed to be leaking from a (b) (4) connection on tubing connected to the main valve on the bottom of the tank on 2/12/13. It was holding bulk solution for List 4921, Lot 26-156-DK, Epinephrine Injection, USP. This is an aseptically filled product.

D. A large gasket in the Tank (b) manway in the Small Volume Parenterals area was observed to be degrading (delaminating at the edges and pieces were missing) following clean in place activities on 2/12/13.

E. There are no preventative maintenance activities for dipsticks used in the Small Volume Parenterals Solutions Area to measure the volume of solutions during formulation activities in bulk solution tanks. Tank (b) dipstick G3439 was observed to be bent at an approximate 5° angle slightly below the handle during an inspection of the Small Volume Parenterals Solutions Area on 2/12/13.

F. The thermal paper used in the (b) (4) non-viable particle counter is not decontaminated prior to use within the aseptic core. Once inside the core and placed in use, the unit and all of the required supplies can remain there for up to one month according to SOP B6134_0131 "(b) (4) Electronic Particle Counter Operation, Calibration, Maintenance and Usage, Effective: 12-10-22." The Biological Quality Supervisor confirmed that the thermal paper is not subject to cleaning and sanitization process to preclude the ingress of non-viable and viable particles.

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OBSERVATION 20

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

Specifically,

A. Thick strips of a caulking material were observed around the edges of ceiling tiles located in the Flex Northside Filling Area (Room (b)) and the Flex Southside Filling Area (Room (b) where 500 mL and 1000 mL bags of injectable pharmaceuticals are filled and sealed.

B. Caulking material around multiple ceiling tiles was observed to be cracking and degrading in the Flex Northside Filling Area (Room (b)) where 500 mL and 1000 mL bags are filled and sealed. At least one ceiling tile was observed to have displaced slightly upwards into the interstitial space above on 2/13/13.

C. A brick, metal beams, and large metal cogs were among the objects used to weigh down ceiling tiles as observed from the interstitial space directly above the Flex filling areas on 2/13/13.

*** DATES OF INSPECTION:**
02/12/2013(Tue), 02/13/2013(Wed), 02/14/2013(Thu), 02/15/2013(Fri), 02/17/2013(Sun), 02/18/2013(Mon), 02/19/2013(Tue), 02/20/2013(Wed), 02/21/2013(Thu), 02/22/2013(Fri), 02/23/2013(Sat), 02/25/2013(Mon), 02/26/2013(Tue), 02/27/2013(Wed), 02/28/2013(Thu), 03/01/2013(Fri)

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