DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, Ohio 45237 (513) 679-2700	5/2-25/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas J. Murphy, President & CEO

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE Bedford, Ohio 44146	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

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1. The "Quality Manual", document #030-SOP-OP-01340, dated 28 Feb 2011, "describes the pharmaceutical quality system (PQS) as implemented at BVL. The Quality Manual identifies the elements of the PQS and the sequences, linkages, and interdependencies of related processes, and the responsibilities of Management to ensure effective implementation." The "Quality Manual includes the principles and responsibilities for implementation of BVL's PQS and pertains to all BVL departments involved in performing and/or supporting the development, manufacturing, testing, holding, distribution, and marketing of pharmaceutical products." However, the following observations document a lack of adequate oversight by the Quality Unit to approve or reject the products manufactured and processed, as well as, approve or reject the established procedures and/or specifications impacting the quality of the drug product.

2. Failure to identify the root cause of foreign material, identified as stainless steel particles in two products, (b) (4) and (b) (4) which are contract manufactured by your firm. These products were all manufactured in the BVL south complex. All of the lots were released and distributed. Your firm has received 9 complaints from 08/16/06 to 02/09/10. In 7 of the 9 complaints, the foreign material was analyzed by a third party laboratory that identified the particles as stainless steel or elementally consistent with stainless steel. In the two other complaints, TRK 46061, the third party analysis identified that the particle appeared to be metallic and TRK 87006, the third party analysis identified the particle to be an iron particle, probably rust.

   Neither a definitive root cause nor a corrective/preventative action has been identified or implemented to address the foreign particle issue. Also, for each of the complaints there are no samples retained to evaluate the foreign particle issue.

Complaint ID	Date received	Product(s)	BVL lot #	Vendor lot #	Analytical results
29846	08/16/06	(b) (4)	0077-00-902093	3911	complaint voided

Tamara M. Kays
Paul A. Bonnema - microbiologist
Sneha S. Patel - Chemist

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Christopher T. Mellad Nicholas L. Paulin	Christopher T. Mellad - Investigator Nicholas L. Paulin - Investigator	5/25/11

FORM FDA 483 (8/00) PREVIOUS EDITION OBSOLETE

Jennifer L. Gustavus
Michael P. Sheehan
Elizabeth L. Edwards

INSPECTIONAL OBSERVATIONS

Jennifer L. Gustavus - Investigator
Michael P. Sheehan, Investigator
Elizabeth L. Edwards, Invest. Editor

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					references Quality Investigation Report (QIR) 30887
(QIR) 30887	09/06/06	(b) (4)	0077-00-774282, 0229-00-895835, 0077-00-715894, 0229-00-604280, 0077-00-902093, 0077-00-874585, 0077-00-604240, 0230-40-715940	3885J 5099J 3864J 5093J 3911J 3888J 3839J 5584J	3rd. party analytical report, 06/21/06, for lot #3885J indicates the particle characteristics suggest metal flakes / stainless steel
36169	04/18/07	(b) (4)	0229-00-1000847	5104J	3rd. party analytical report, 05/9/07 lists metallic flakes / stainless steel variety
46061	03/07/08	(b) (4)	0077-00-1007259	3920	3rd. party analytical report, 02/06/08, identifies, main body of the particle appears to be metallic.
48251	05/12/08	(b) (4)	0229-00-1000847	5104	3rd. party analytical report, 04/07/08,

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		ELLE TMK MER CTM GRH MPS	5/25/11

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		(b) (4)			indicates particle is likely a form of stainless steel
87006	09/01/09		0077-00-1715034	3989	3rd party analysis performed on or about 08/27/09 identifies the particle to be an iron particle, probably rust.
94475 95173	01/28/10 02/10/10	(b) (4)	0229-00-1739828 0229-00-1739828	5123 5123	3rd. party analytical report, 01/27/10, indicates the particle was a piece of stainless steel most likely (b) (4)
95083	02/09/10	(b) (4)	0077-00-1793765 0229-00-1739828	3996 5123	3rd party analytical report, 04/15/10, indicates particle in lot 3996 was (b)(4) stainless steel, elemental[illegible]ent with (b) (4) rd party analytical report, 02/05/10

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					indicates particle from lot#3996 predominantly a piece of stainless steel most likely of (b) (4) (b)(4) series.

In addition,

a. Complaint Report TRK # 95083, date received 02/09/10, contains two, third party analytical labo(b) (4)rts, dated 4/9/10 and 4/15/10 which identify stainless steel particles in two lots (3996 and 4006I). Lot 3996 was identified in complaint report TRK#95083, however, per your Supervisor, Quality System, there was no complaint investigation conducted for the stainless steel particles found in lot 4006I.

b. We observed the metal access doors (e.g., 9-10 doors in building (b)(4) used to transfer various pieces of equipment, and/or production related materials, into and out of the manufacturing areas. The metal access doors and door window frames appear to be severely dented with deep scratches/scoring on the metal surface areas. The damaged door conditions provide a source for metal particle contamination within the manufacturing areas;

c. On 5/6/11, we observed tray racks (b) (4) which were located behind your facility. Your Supervisor Equipment and Component Prep, South Facility stated that these tray racks had been r(b) (4)om the south facility to this area that morning. The underside of tray rack ntained an area that appeared to be rust-like material. We observed apparent scratches on two sides of the outside face of the bottom shelf and on the outside face of two legs of rack numbe(b) (4)

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d. On 5/11/11, we observed glass tray carts, GTC-2006 and GTC-2008 stored in a hallway of the facility. These carts were identified as retrofitted tray racks returned from the vendor for use in the South facility. We observed what appeared to be rust-like material on the underside of carts GTC-2006 and GTC-2008.

3. The "Media Fill Program Parameters and Specifications" document #030-SOP-D29, and the "Outlining Test Parameters and Specifications Required For Process Simulations" document #030-SOP-D-29, effective dates 06 Apr 2011 and 01 Jun 2010, respectively "outline the test parameters and test specifications required for media fills" and establishes the media fill acceptance criteria. A Regulatory Deviation Report TRK #110926, dated 1/4/11 document that "During manufacture of lot 1012-60-2017296 on 12/31/10 in filling suite #(b) (4) the minimum count requirement was not satisfied." The manufacturing batch record document the media fill consisted of fillin(b) (4) vials and the deviation report documents "The batch size for these products is less than the (b) (4) minimum requirement outlined in the validation protocol. This media is recommended for acceptance." Despite the written procedures established in the aforementioned standard operating procedures the media fill was passed and deemed acceptable. In addition;

a. The "Media Fill Validation Master Plan" document #VMP33709M, dated 9/20/2010, establish the media fill test requirements, which references the "rationale for the media fill size" is documented in the "Process Validation Process Simulation Testing Rationale for the Establishment of a Representative PST Size", document #RAT23509M, dated 06/11/09. The PST rationale establishes "a maximum media fill size on compendial guidance, PDA recommendations and industry baseline information." However, the aforementioned procedures do not contain language or establish provisions with respect to having less (e.g.,(b) (4) than the requisite media filled vials (i.e.,(b) (4) established by the media fill protocols;

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b. The "Intervention Conducted During Filling Operations in the Aseptic Processing Area (APA)", document #030-SOP-D-01155, define intervention as "an aseptic manipulation or activity that occurs at a critical area." The media fill records lists the manual interventions that are required to be performed by the specified individuals (i.e., job functions). However, the media fill records do not document that the interventions are performed by all of the individuals listed in the manufacturing batch record (MBR). Rather, the Senior Manager North Facility confirmed that the requisite manual interventions are successfully completed if one of the listed individuals (in the media fill MBR) performs the intervention;

c. A Regulatory Deviation Report TRK #114581 was initiated due to an operator error which occurred during the 3/8/11 Media Fill lot #1038-71-2036542 in filling suite #(b)(4) The documentation for Intervention #14, "Reconfiguration of Trays", was not performed as required in the Master Production Record "Routine Interventions" section RINT100A, which requires the operator to record the identification number of the "Reconfigure Trays" on the lyophilization chamber shelves after loading said chamber. Concurrently, the original and relocation of the trays were not documented on the Chamber Loading Data Sheet MPR 66L by the operator. The Senior Manager North Facility could not confirm that the operator performed the requisite manual intervention as described in the Master Batch Production Record.

d. A 1/20/2010 CAPA, TRK #93875, was implemented to address execution of varied manual interventions (b) (4) pecifically defined interventions) performed during aseptic filling operations. However, not all of the personnel that are currently engaged in the manufacture of finished products have completed the CAPA's requisite training. The number of employees and manual interventions range, for example, from (b) (4) employees performing "stopper bowl change out" and "use trayer plastic to tray vials", respectively (Note: aforementioned examples are not intended to be an all inclusive lists of the number of employees and manual interventions to be accomplished);

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e. The [redacted] Product Specific media fill manufacturing batch record #1105-08-2125730, dated 9/19/10, document process simulations with manual interventions of the lyophilization pre-chilled vial steps, which is performed prior to the aseptic filling process. However, the media fill process failed to include the requisite manual interventions established by the "Media Fill Validation Master Plan" (VMP), document #VMP22709M dated 8/30/10, "Media Fill Program Parameters and Specifications" document #030-SOP-D-29, effective date 01 Jun 2010, and the 9/19/2008 [redacted] assessment document #RA31208M. The observation is applicable for all [redacted] product specific media fill processes;

f. The media fill manufacturing batch records do not accurately account for the number of vials that are filled and there is no reconciliation to assure that all media filled vials are accounted for. The CAPA TRK #107148, dated 10/15/10 provides Regulatory Deviation Reports, for example TRK #105923, dated 7/6/10 describes, "During the [redacted] and [redacted] day reads it was discovered the documented amount of units received for incubation varied from the amount actually incubated. There is currently no specification for accountability of media filled units." The TRK chronology of event document a similar concern occurred f[redacted] media fills dated from 5/27/10 to 8/20/10. In addition, the aforementioned lack of accountability for media filled vials applies to the following media fill lots;

   i. 12/31/10 - #1012-60-2017196, < [redacted] media filled vials of [redacted]
   ii. 03/08/11 - #1038-71-2036541, < [redacted] media filled vials of [redacted]

g. "Media Fill Program Parameters and Specifications" document #030-SOP-D-29, effective date 06 Apr 2011, establish "the test parameters and test specifications required for media fills" and "Each intervention should be documented such that growth positive test results may be appropriately correlated to a designated tray of media filled units." However, after performing the requisite manual interventions the media filled vials are discarded and not included with the incubated vials. Discarding

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the media filled vials precludes the company from adequately assessing and assuring that the manual interventions do not create or provide adverse conditions that result in positive media fill vials. (Note: refer to the air flow pattern evaluations and upward movement of air in Observation #7);

h. The "Media Fill Validation Master Plan" (VMP), document #VMP22709M dated 8/30/10 establish, "the general approach for developing the media fill schedule and is designed to meet the requirements set forth in procedure 030-SOP-D-29, *Media Program Specifications and Parameters*." The procedure establishes the media fill acceptance criteria, for example,

   i. "When filling fewer that [redacted] units, no contaminated units should be detected. One (1) contaminated unit is considered cause for revalidation, following an investigation."
   ii. "When filling from [redacted] units, One (1) contaminated unit should result in an investigation, including consideration of a supplemental media fill. Two (2) contaminated units are considered cause for revalidation, following an investigation." And,
   iii. "When filling more than [redacted] units, One (1) contaminated unit should result in an investigation. Two (2) contaminated units are considered cause for revalidation, following an investigation."

However, the preceding objectionable conditions precludes the company from having the supporting data to document that they can meet the acceptance criteria established by the standard operating procedure and the VMP Statement of Commitment, "that the aseptic manufacturing process consistently produces product meeting an acceptable level of sterility assurance."

4. The VMP and the Corporate Procedure "Simulation of Aseptic Processes", document #OCP-074, dated 01 Jul 2006, establish the frequency for "each aseptic filling

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configuration will be qualified ever(b) (4)onths (b) (4) month)" and for the appro(b) (4) to media fill validation "is a process simulation performed at least every (b) (4) months (plus (4) onth)", respectively. However, regarding the CP-4055 Product Specific media fills performed in fill line (b) (4) media fills #1102-57-2147195, #1102-57-2147196 & #1102-57-2187181, dated 3/09/11, 3/12/11 & 3/14/11, respectively, were performed almost one year after the 3/13/10 media fill.

5. The "Clearance Procedure for Filling Interventions in Buildings (b) (4) document #030-SOP-D-80, effective date 22 Mar 2011, "outlines the steps to be followed for line clearances performed after interventions in sterile filling", which are also performed during aseptic media fill processing. The procedure defines the specified zones (4 to 5 each) within the aseptic filling areas and for example requires zone clearances, "When possible, remove all filled vials from the line prior to performing an intervention". The Senior Manager North Facility confirmed that they did not have the rationale or data to support the establishment of the specified zones.

6. The design of the aseptic filling room (b) (4) layout of the fill room equipment and the plastic airflow curtains within the Class 100 do not prevent the ingress of objectionable microorganisms and non-viable particles. For example, dependent on the production activities, there can be up to (b)(4) Production / Quality personnel that are needed to perform the aseptic filling operations, which include access into the aseptic fill Class 100 areas via the plastic barrier curtains. The personnel entry and exit activities performed via the plastic barrier curtains promote the ingress of objectionable microorganisms and non-viable particles within the Class 100 filling areas. In addition;

   a. The "Aseptic Technique Guideline for Personnel Working in the Aseptic Processing Area" document #030-SOP-D-132, effective date 21 Jan 2011, "provides the guidelines for the proper aseptic techniques to be utilized when working in the Aseptic Processing Area (APA)." (b) (4)
(b) (4)

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(b) (4)

area can pose a risk to product sterility." We observed some of the routine filling operations and personnel activities for fill line (b)(4) and # (b) (4) (b) (4) We observed personnel manually transferring partially stoppered filled vials from the aseptic fill line to the lyophilizers and the personnel movements were not consistent with the aforementioned established procedure.

7. The "Dynamic and Static Air Flow Pattern Test Procedure for Grade A, Class 100 and Surrounding Areas" document #030-SOP-J-230, effective dated 31 October 2008 describes "the test procedure and acceptance criteria utilized to verify the presence of unidirectional air flow patterns with Grade A, Class 100, and Grade B active areas under dynamic and static test conditions for qualification." The air flow pattern evaluation failed to include and assessment of the routine manual transfer process of partially stoppered vials from the aseptic fill area to the lyophilizer and fail to include an evaluation for the transfer from the stoppered vials from the aseptic fill area (fill room # (b) (4) to the inner seal production room # (b) (4) , respectively. In addition;

a. The aforementioned procedure establishes (b) (4)

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b. The air flow pattern tests failed to include an assessment of the air flow patterns when manually transferring (i.e., routine dynamic operations) production equipment and/or monitoring equipment when opening and closing the entry door ways;

c. The air flow patterns performed for the aseptic fill rooms were captured on video. The videos for fill lines # (b) (4) document the air moving in an upward direction during manual interventions # (b) (4) And, there were no air flow pattern evaluations over the manual operations performed for interventions (b) (4) 1 (b) (4) (Please note: the personnel manual operations simulated by the manual interventions are designed to demonstrate that the personnel manual operations do not promote the ingress of viable microorganisms and non-viable particles, as well as, non-disruption of the unidirectional air flow);

d. The 10/13/10 air flow pattern video document a number of dynamic personnel activities and manual operations (e.g., placement of EM sampling equipment, entry and exit of barrier curtains & access panels of the fill equipment) for aseptic fill line # (b) (4) & (b) (4) However, the air flow pattern evaluations do not include an assessment (smoke study) of the locations where the specific manual operations/personnel activities take place (e.g., work surfaces).

e. The 8/17/09 Laminar Flow Verification was performed via Study document #S41109M, "to verify that laminar air flow exists within the (b) (4) cart." The air flow pattern evaluations did not include an assessment of the air flow of the interior of the (b) (4) Transfer Cart with the normal configuration of the partially stoppered vials. In addition;

i. The air flow pattern evaluations failed to include an assessment to determine that the laminar flow of air is not negatively affected during the manual transfer of the partially stoppered vials into the lyophilizers from the (b) (4) Transfer Cart.

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FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, Ohio 45237 (513) 679-2700	5/2-25/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas J. Murphy, President & CEO

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE Bedford, Ohio 44146	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

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f. The Director of Microbiology confirmed that the air flow pattern evaluations have not been reviewed by the microbiology department and the air flow pattern studies have not been evaluated with respect to microbiology e.g., unidirectional air flow patterns, dynamic operations, personnel activities, Environmental Monitoring (EM) Program sampling site locations in support of the aseptic filling processes.

8. The "Environmental Monitoring Site Selection Rationale" dated 1/31/11, provides "the rationale for environmental monitoring site locations at Ben Venue Laboratories aseptic manufacturing facilities, and to provide a tool to formally document and justify the Environmental Monitoring location selections." However, the site selection process did not include, from a microbiological perspective, an assessment of the air flow pattern studies. In addition;

   a. The above mentioned EM site selection rationale consisted of an evaluation of the historical, previously existing, EM sampling locations. The 1/31/11 site selection rationale does not document, for example, the evaluation of the air flow patterns and their affect on the dynamic operations with the varied aseptic personnel activities and/or when opening and closing the multiple entry ways and their collective impact upon the aseptic filling process;

9. The sterility failure found on 01/20/10 associated with (b) (4) lot # 2378-44-1157184 (TRK #93890) identified *Paenibacillus woosongensis* as the contaminant. This lot was manufactured on 01/25/08 in fill room (b) (4) in the North facility. The environmental monitoring program, from dates 12/10/07 through 07/17/0X, identified the recovery of *Paenibacillus* from Class 100 personnel monitoring and from Class 10,000 area and it was not recovered from the sterility tests isolator. The Senior Microbiologist explained that they believe that the microbial contaminant was due to concerns with the sterility test isolator. The aforementioned locations were not considered as a source for the microbial contamination.

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10. On 08/08/10, the firm's microbiology department detected a sterility failure for the aseptically filled parenteral drug product (b) (4) lot #2205-08-1907417 (TRK #104155). The investigation found that during fill operations for this product, operators were using (b) (4) gloves. These gloves are neither sterilized, sanitized nor cleaned prior to use and they are composed of a material that appears to shed fibrous material. It was determined that the root cause of this sterility failure was most likely a compromised outer sterile glove, which led to the exposure of the fill line equipment to the (b) (4) glove material. In addition;

    a. Document 030-SOP-D-55, Aseptic Gowning for Entrance to and Exit from the Aseptic Processing Area, establishes the instruction with specific procedures for donning the required aseptic gowning. However, the SOP is silent with respect to the use of (b) (4) gloves. The Senior Manager of the North facility and the Quality Assurance Manager stated that they were unaware that these (b) (4) gloves had historically been used by operators during certain fill operations.

11. The 01/21/11 sterility failure associated with (b) (4) lot #2499-49-2055596 (TRK #111988), identified *Propionibacterium acnes* as the contaminant. The investigation (TRK #111988) attributes that the anaerobic contaminant came from the isolator gloves, which failed the integrity testing after the sterility tests were performed. However, the environmental monitoring program does not include an assessment for the presence of anaerobes. In addition, a root cause analysis has not been performed to determine the source of the anaerobic microorganism.

12. The 2010 and 2011 quarterly environmental monitoring (EM) data document the percent of microbial identification for gram-positive rods (i.e. spore formers and non-spore formers) isolated via the EM sampling program for the manufacturing areas (Class 100 and Class 10,000, for example:

Percent gram-positive rods	Q1 2010	Q2 2010	Q3 2010	Q4 2010	Q1 2011

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North Class 100	13%	24%	10%	14%	33%
North Class 10,000	65%	25%	28%	27%	30%
North Class 100,000	33%	49%	30%	61%	67%
North Personnel	10%	6%	14%	8%	9%
Phase IV Class A	17%	8%	21%	33%	29%
Phase IV Class B	23%	15%	6%	33%	17%
Phase IV Class C	33%	33%	23%	64%	63%
Phase IV Class D	85%	51%	44%	61%	70%
Phase IV Personnel	7%	11%	12%	14%	11%
South Class 100	21%	15%	7%	N/A	N/A
South Class 10,000	21%	15%	15%	N/A	N/A
South Class 100,000	24%	24%	29%	N/A	N/A
South Personnel	10%	11%	7%	N/A	N/A

The EM sampling identifies the locations where the microbial contaminates were recovered. However, the evaluations fail to identify the source(s) of the microbial contaminants, for example, the root cause for the recurrent presence of the Bacillus species contamination. The root cause evaluation(s) in turn assist to address, and ultimately control, the ingress of objectionable microorganisms.

13. The firm has recovered at least 1,171 microbial contaminants between 01/01/10 and 03/30/11, including 1,047 actions of gram-positive organisms, 108 actions of gram-negative organisms, and 16 actions of mold organisms from various locations within the firm's classified areas, including the Class 100 and Class 10,000 manufacturing areas. However, the firm has not investigated these microbial contaminants to determine the root cause of the contamination, nor have they initiated any corrective action to address the contamination.

14. The firm contracted the validation of disinfectants and received the results in November 2009 for a disinfection efficacy study performed by the contactor. However;

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a. The Quality Control Unit did not review and approve the raw data associated with the Disinfection Efficacy study. Rather, they reviewed the Qualification Summary entitled "Disinfection Qualification for (b) (4) Ready to Use (RTU), (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) by the Surface Method," dated 11/20/09;

b. The materials that were tested in the Disinfectant Efficacy study were not representative of all of the surfaces present in the Aseptic Processing Area. For example, the firm maintains rubber wall bumpers, carts with wheels, and castors which appeared to be coated with rust-like material. These materials were not tested in this study. Furthermore, we observed stainless steel walls and doors that were scratched, dented and gouged. The stainless steel coupon tested did not represent these damaged surfaces;

c. The firm was unable to provide scientific rationale for the use of the selected organisms used in the Disinfectant Efficacy study. These organisms were not representative of organisms isolated from the facility nor were they representative of the USP guidelines;

d. According to a Senior Microbiologist, the acceptance criteria for the studies were established from USP <1072> as is referenced in the Test Protocol – Disinfection Protocol, as well as USP <1227>. The USP <1072> indicates that the surface being decontaminated should measure 2" X 2" square. However, the stainless steel and plexi-glass coupons the firm used in these studies measured approximately (b) (4) square. The firm did not provide any scientific rationale to support this change.

15. The "Validation of the Microbial Effect of Utilizing a Sterilized Hose, for An Extended Period of Time", study number (b) (4) dated 03/21/08, states that the water "hoses are

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hung, while not in use, to prevent any dead legs for the accumulation of moisture." The testing methodology states that (b) (4) feet in length hoses "will be acceptable." However, we observed two braided stainless steel hoses (Gen Comp Hose 1029/Gen Comp Hose 1033) connected in-series to the WFI Valve WFI-1-9, totally an approximate 30 feet in length. The Formulation Supervisor and Senior Manager North AM confirmed that both ends of the hoses were closed and fully charged with stationary water. These two braided hoses containing stationary water lack the ability to vent and drain, thereby creating a dead leg. Furthermore, the above-mentioned validation does not provide language or establish the use of hoses with a length greater than (b) (4) feet.

16. Document 030-SOP-K-99, "(b) (4) Monitoring of Aseptic Areas with Swabs", Effective Date: 08/29/07, "provides the procedure to perform a qualitative assessment of the viable aseptic environment on a (b) (4) basis with the use of swabs." However, the Associate Director of Quality Control Microbiology and Supervisor of Microbiology confirmed that there is no (b) (4) trending of the microbial contaminants. In addition, Gram stain and colony morphology is performed for the microbial contaminants recovered via the (b) (4) swab monitoring program. However, no further identification or characterization is performed of the microbial contaminants.

17. The Environmental Action Coordinator is responsible for confirming non-viable actions by comparing results to alert/action levels and is also responsible for entering all product-related actions or trends into (b) (4) as established in the Document 030-SOP-K-21, Responses to Viable and Non Viable Results from Aseptic Areas and Critical Systems. The 030-SOP-K-01029, Environmental Action Committee (EAC), Effective Date: 10/28/09, states that the EAC will review trends and all non-viable particulate data, and review (b) (4) summaries of all action and alert excursion data.

However, according to the Supervisor of Physical Monitoring, the EAC nor any other department/component in the Quality Control unit does not track, trend or review NVP alert excursions which are detected through the (b) (4) system (b) (4)

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during the manufacture of aseptically filled products. Furthermore, the firm failed to review the year-to-year trends of the viable and nonviable particles taken via the Environmental Monitoring (EM) program.

18. According to the Supervisor of Physical Monitoring, the firm has defined the limits of non-viable particulates to be not more that (b) (4) micron and not more than (b) (4) micron particulates in 1 cubic meter of air, as defined in Annex 1 and ISO 14644. However, between 09/01/10 and 01/31/11, the firm detected 112 events during which these NVP limits were exceeded during the manufacture of aseptically filled products. The firm did not initiate investigations to determine the root causes of these excursions, nor did they take corrective action to address the excursions.

19. There is no record to document that the air pressure readings (inches per water column) for the aseptic filling areas (Class 100 and 10,000) and the surrounding manufacturing areas are reviewed by the Physical Monitoring Department and/or the Quality Unit. In addition;

    a. The Physical Monitoring Department and the Quality Unit perform verifications that the air pressure monitoring records and the (b) (4) Pressure Reversal Alarm Reports are complete and accurate. The alarm reports document the air pressure monitoring location, alarm start and end time as well as the alarm duration. However, the records do not document the actual air pressure measurements (inches of water column);

    b. The Quality Compliance Manager and the Supervisor of Physical Monitoring confirmed that the differential air pressure alarm measurements and non-viable particle (NVP) alarm conditions are not periodically reviewed. And, they confirmed, that the alarms are not trended to assure that the aberrant events and/or conditions that created the alarms do not present a state of control that is inconsistent with the requisite NVP and air pressure specifications.

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20. Document 030-SOP-K-01166, Daily Operation of the Continuous Non-Viable Particulate Monitoring System, states that if an NVP Action level is detected using the continuous monitoring system, then the operators must halt production and notify the QA auditor. QA will determine how to proceed with remediation prior to restarting fill operations. The established written procedure is silent with respect to providing directions on how the QA auditor should determine appropriate remediation. In addition;

    a. Between 03/16/10 and 11/24/10, 16 reports were reviewed which investigated one or more NVP Action levels which took place during filling operations of aseptically filled finished drug products. In these reports, 14 of these Action levels were remediated by halting production and air washing the fill line for at least (b) (4) minutes. Operators and QA did not include clearing and sanitizing the lines during the remediation of the14 separate events.

21. The "Environmental Monitoring (EM) Program" Clean Room Characterization, 028-OCG-00021, Effective Date: 08/01/03, establishes the baseline requirements reflecting current regulatory ruling and industry thinking rather than to identify the highest expectation from the existing Standards and Guides. Specific regulatory situations may require higher clean room conditions than described here. With respect to the EM Program the following standard operating procedures (SOP) are used;

    a. 030-SOP-D-84, Viable Monitoring with the Use of Settling Plates, Effective Date: 03/07/11;
    b. 030-SOP-D-15, Sampling of Surface-Derived Viable Particulates, Effective Date: 09/01/10;
    c. 030-SOP-D-99, (b) (4) Monitoring of Aseptic Areas with Swabs, Effective Date: 08/29/07;
    d. 030-LST-00127, Viable Monitoring Sites in Building No. 20 Aseptic Complex, Effective Date: 04/19/10;

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e. 030-LST-00022, Viable Monitoring Sites in Building No. 24 Microbiology Laboratories, Effective Date: 01/31/11;
f. 030-LST-00126, Viable Monitoring Sites in Building No. 19 Aseptic Complex, Effective Date: 03/19/11;
g. 030-LST-00128, Viable Monitoring Sites in the Building No. 22 Aseptic Complex, Effective Date: 02/08/11

However, the aforementioned standard procedures fail to contain EM sampling maps/diagrams to document the EM sampling locations for either work surfaces, settle plates or for the active air sampling. In addition, the Associate Director of Quality Control Microbiology and Manager Quality Assurance confirmed that there has been no evaluation performed to determine the validity of the EM sampling locations.

22. Document 030-SOP-J-204, Dynamic and Static Environmental Monitoring Using Portable Non-Viable Particulate Counters, states that NVP monitoring during dynamic filling operations will be performed according to 030-LST-00033, Dynamic Non-Viable Particulate Sampling Locations. However, this list does not clearly define the locations of where the portable NVP machines are to be placed within the room classified areas. In addition;

a. The Supervisor of Physical Monitoring explained that the Environmental Control (EC) technicians are verbally instructed to place the NVP machines randomly inside the classified areas. However, the SOP does not address the verbal instructions nor does the firm have any controls in place to ensure that the EC technician is objectively placing the NVP-machines in the appropriate location.

23. We observed that three tools maintained in aseptic fill room 4165 of the Phase IV facility had rust-like material inside the sockets. These tools are used during the set-up and interventions of aseptic fill line (b) (4) and come into contact with the fill line equipment. These tools are not sterilized prior to use. And,

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a. Document 030-SOP-F-2 states that tools are sanitized with (b) (4) before and after use, then placed in a toolbox in the room. The firm does not have a procedure in place to document this sanitization, nor is there a formal procedure in place in which firm employees inspect tools for defects such as rust-like material or dents and scratches.

24. Document 030-SOP-K-46, Personnel Monitoring Program, states that every employee who participates in the set up for the active filling portion of the aseptic filling operation is required to contact Environmental Control (EC) for glove and gown testing. The Supervisor of Environmental Control explained that the personnel monitoring requirement includes the EC technicians who take environmental samples during filling operations. However, the SOP does not address personnel monitoring of the EC technicians. Furthermore, the Quality Unit cannot assure that the EM monitoring of the EC technicians is objective, in that, the EC technicians perform the EM gloves and gown monitoring on themselves.

25. The Manager Quality Assurance and Supervisor Physical Monitoring confirmed that the temperature and relative humidity of the sterile storage area in building (b) (4) was not monitored in response to a rain water leakage from the ceiling on 4/23/11 as required per SOP "Contingency Plan", Document #030-SOP-D-48, effective date 05 Jul 2007. The rainwater that leaked from the roof through the plenum above the HEPA filters ultimately leaked into the sterile storage area via seams in the curtain tracks. The plastic curtains affixed to the tracks serve as a barrier between Class 100 and Class 10,000 areas. This area is also used to store depyrogenated glass vials.

26. The "Facility and Equipment Qualification Master Plan", document #030-SOP-OP-13, effective date 30 Dec 2009, "applies to all Facilities, Utilities, and Process Equipment involved in the manufacture, packaging or holding of raw materials or drug products at BVL. This master plan details the Qualification process for new facilities and systems and re-qualification of existing facilities and systems." The (b) (4) Closed Circuit

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Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE Bedford, Ohio 44146	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

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Television (CCTV) System, WV-CU650 consists of (b) (4) cameras and new replacement color monitors. The CCTV is routinely used by Production, Physical Monitoring and Compliance Departments to observe personnel and production activities performed in the North, Phase IV and South manufacturing controlled areas (e.g., Class 100, 10,000) and varied personnel entryways/rooms. However, the camera monitoring system has not been appropriately qualified as per the aforementioned procedure. In addition;

a. There are no written standard operating procedures that establish and describe the use of the (b) (4) CCTV Monitoring System;
b. There is no records to document the production and/or personnel activities that are observed by the above mentioned departments;
c. The CCTV monitor in the Quality Assurance Lab room 209 has the capabilities of capturing the observed data via the DVD recorder that is electronically attached to the CCTV monitor. (b) (4)

(b) (4)

27. A 9/19/2008 assessment (Document #RA31208M) was prepared by a pharmaceutical consultant company and the assessment is used "To ensure that interventions occurring during normal production are covered, BVL is performing an assessment to determine if any other enhancements are needed", which included observing the aseptic operations. The visual observations were performed via the (b) (4) Closed Circuit Television (CCTV) System and by observing via the production room door windows.

(b) (4)

a. The production room entry doors for fill lines # (b) (4) have viewing windows (i.e., 23" x 29" and 19" x 31", respectively). However, the windows do not provide for an unobstructed view of the Class 100 and Class 10,000 production areas.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, Ohio 45237 (513) 679-2700	5/2-25/11
	FEI NUMBER 1519257

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28. The (b) (4) CCTV System can be used to observe the production and/or personnel activities, independently or collectively, by the Production, Physical Monitoring and Compliance Departments. However, the reason(s) for observing the production or personnel activities via the CCTV and the final conclusions and/or evaluations of the observed activities are unknown to the Quality Unit.

29. An Operational Qualification of the North Complex Air Handling System Dehumidifier, study number (b) (4), study performed September 1996. The objective of the OQ is "To verify that the "new" North Complex Air handling system dehumidification unit (BVL I.D. (b) (4) operates appropriately", which includes "Velocity Testing of North Complex (b) (4) filters". The 1996 OQ report documents the filter velocity test status as "SAT"; the Manager of Quality Assurance Engineering confirmed that there is no raw data to document the filter velocity test measurements.

30. The written procedure 030-SOP-OP-13 (Version 12.0 dated 12/30/2009), "Facility and Equipment Qualification Master Plan" fails to identify the (b) (4) system as a qualified system subject to a routine re-qualification. In addition;

a. A performance re-evaluation has not been conducted for the (b) (4) systems serving the Phase IV Complex to access the (b) (4) system servicing the lyo corridor, room 4115, subsequent to the extension of the corridor and addition of (b) (4) filters and air handling units servicing this corridor;

b. The IQ/OQ/PQ for the (b) (4) systems servicing building (b) (4) as well as routine air velocity testing conducted in building (b) (4) lack a determination of the air velocity at work surfaces in the class 100 areas of fill suites (b) (4)

31. The Quality Unit lacks the responsibility and authority to review and approve BVL Engineering or Contractor/Vendor CAD drawings. "BVL CAD Standards Revision

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Control", SOP # 030-SOP-P-26, version 3.0, effective date 11 Jun 2008, "covers both the generation of new drawings and the subsequent revision to existing drawings" and states that "The Project Engineer/Manager (or AMMS requester): Is responsible for the final approval and sign off of the revised drawing." On 11/12/2010 CAPA TRK #108615 was opened to revise "BVL CAD Standards Revision Control", SOP # 030-SOP-P-26, version 3.0, effective date 11 Jun 2008, to require changes to CAD drawings go through the Change Control Process. The CAPA also states that the aforementioned SOP-P-26 is to be revised "Include in the revision the requirement for quality review/approval of changes to level 1 equipment and drawings that would have a regulatory impact. The Due Date according to the CAPA was 3/31/2011. The CAPA has yet to be closed. In addition;

a. The Manager Project Engineering confirmed that there is no written procedure at BVL for CAD drawings which describe the departmental use of BVL Engineering CAD drawings. The Manager Project Engineering also confirmed that Engineering drawings are used by Engineering as well as Facility Maintenance when performing maintenance related activities. However;

   i. On 5/3/2011 Work Order #05031106001 was completed and "removed rooms 4166B &C" as well as "renamed room 4166A to 4166" from "Building No (b) (4) Flow Diagram Class "A" &"B" ACOND-401", drawing #HVACFD401, revision E, revised date 11/09/2010.

   Rev. E of the aforementioned CAD drawing # (b) (4) FD401 illustrated proposed modifications to the air handling system pertaining to a future addition of exit airlocks in fill rooms (b) (4) and sterile storage.

b. The "Velocity Testing of (b) (4) and (b) (4) Filters", SOP #030-SOP-J-212, version 13.0, effective date 01 Jun 2010, establishes that "For each filter tested, record the velocity test data on an applicable facsimile of an Engineering drawing and the appropriate test document." The Supervisor Environmental Control confirmed that

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Environmental Monitoring uses Engineering drawings during the performance of velocity testing at the (b) (4) and (b) (4) filter face and confirmed that Environmental Monitoring does not have access to the (b) (4) database which contains the most current revision of BVL Engineering CAD drawings.

32. The (b) (4) Hot Air Oven is used to depyrogenate vials and glassware for the manufacture of finished products. The depyrogenation processes are controlled via the equipment automated control system (b) (4) Controller), which contains the password protected depyrogenation cycle recipes. The Manager – Process Controls Engineering confirmed there is a password that is used for each of the controller's multiple levels of access (i.e., Level I, Level II, and Level III) for Process Operators, Supervisory Staff and Administrators, respectively. However, there are no records to document the individuals (b) (4) each) who have access and their respective levels of access for the automated control system to assure that the depyrogenation recipes that are used for the validated process are not inadvertently changed and/or modified. In addition;

a. The Hot Air Oven controller maintains a history file of the individual cycles e.g., date, time, duration of events and any alarm events that occur. The Manager of Quality Compliance confirmed that the equipment's history file is not reviewed;

b. During routine operations, if there is an alarm event (e.g., time out, high & low temperature for washing & siliconizing, instrument line failure, jacket gauge failure and steam header failure) during the wash & depyrogenation process, the (b) (4) Stopper Washer captures the alarm condition via a print out and the data is retained with the manufacturing batch record. The Quality Compliance Manager confirmed that the alarmed events are not periodically reviewed or trended to assure that the (b) (4) stopper washer and/or wash & depyrogenation process is not drifting from the validated state of control;

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c. The Manager – Process Controls Engineering confirmed there exists a similar concern, as noted in the preceding observation, for other automated control systems (approximately [redacted] which are used for the manufacture, process, packaging and holding finished products. A 4/15/11 CAPA, TRK #115713, describes an action to be completed with the creation of a new procedure, which "will address security access approval and changes to levels for all pieces of equipment, including lyophilizers.";

33. The 1/25/93 "Sterilization/Depyrogenation Cycle Validation for Various Glass Carboys in Hot Air Oven [redacted] Study [redacted] document the time [redacted] and temperature ([redacted] of the depyrogenation of glass ware. However, there is no record to document that the device that measure time is calibrated to a reference standard. In addition;

a. The "Retrieval of [redacted] Solution", study [redacted] dated September 23, 2001, documents a reduction (i.e., 3-log) of the bacterial endotoxin challenge. However, there is no raw data to support the results of analysis.

34. Per SOP 030-SOP-E-10 (7.0), "Operating the Exterior Vial Washer", your firm uses a vial washer on packaging lines [redacted] in building [redacted] of the south complex, to ensure that the exterior of vials are clean of any foreign material. The vial washer consists of an enclosed conveyor line in which water jets pour tap water onto the shoulder of each individual vial and then each individual vial is dried with compressed air before exiting the vial washer. There is nothing documented to assure that various temperatures of tap water used in the vial washer have no effect on packaged lyophilized products contained in crimped and sealed vials which pass through the vial washer.

a. Per SOP 030-SOP-E-10 (7.0), "Operating the Exterior Vial Washer", Section III, C. 1. b. identifies that the water temperature is to be controlled by the water valve on each line and states that for room temperature products ([redacted] , room temperature water is to be used, and for [redacted] and [redacted] products, the water valve

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should be set to the coldest adjustment possible. Per your packaging supervisor, the vial washer water temperature is not monitored, nor is it recorded for any products that are run on packaging lines (b) (4) in buildin (b) (4) of the south complex.

b. The water valve for lines (b) (4) in building (b) (4) of the south complex, each contain a sticker that reads: "NOT CALIBRATED" "NOT FOR OFFICIAL USE". However, per your packaging supervisor the water valve determines the water flow and water temperature of the water supplied to the vial washer.

c. Vial washer ID: (b) (4) is currently located on packaging line (b) (4) of building (b) (4) of the south complex. Work Order Report #12130709003 for vial washer ID #: (b) (4) identifies that the vial washer was moved from line (b) (4) to line (b) (4) on 12/14/07. There is no qualification for the vial washer since it was moved to line (b) (4) There is also no qualification for the vial washer for the period that it was used on packaging line (b) (4) The most recent IQ/OQ/PQ for vial washer (b) (4) was performed under study no: IQ/OQ/PQ 00198M in 1998 when the vial washer was on line (b) (4)

35. The " (b) (4) Clean Air Carts Used For Transferring Trays in Building # (b) (4) and (b) (4) document #030-SOP-D-131, effective date 07 Feb 2007, establishes that the clean air carts are 'used by the Production Department to maintain an air quality environment of "Class A" during transfer of filled and stopped vials to the "Class A" environment located in front of the freeze drier chambers.' The written procedure requires to "Periodically check the (b) (4) gauge on the clean air chart when the unit is plugged in and unplugged. The gauge must be within the high (b) (4) inches of water column) and low (b) (4) inches of water column) validated alarm specifications." However, the Quality Compliance Manager confirmed that there is no record to document that the requisite (b) (4) alarm specification check is achieved.

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36. We observed numerous (approximately 30-40+) ceiling panels (i.e., "wet-formed mineral fiber" with "factory-applied latex paint") within the personnel corridors [controlled non-classified (CNC)area] that lead into the controlled manufacturing areas (Class 10,000 and Class 100) that appeared to be slightly opened and not seated securely on the ceiling panel supports. The Quality Compliance Manager confirmed that the ceiling panels are not sealed or secured on the ceiling panel supports. The unsecured and unsealed panels propagate the ingress of non-viable particles and/or viable microorganisms from the uncontrolled environment above the ceiling panels and into the manufacturing areas.

37. We observed various mobile carts that are used to transfer material or equipment into the Class 10,000 manufacturing fill rooms with what appears to be rust-like, non-smooth, uncleanable surfaces on the wheel supports.

38. On 5/16/11, spray bottles labeled as (b) (4) and water were observed on packaging lines (b) (4) 6 located in building (b) (4) of the South complex. There is no SOP for preparing the solution and there are no records regarding the preparation of the solution. Your monthly packaging line cleaning record identifies that (b) (4) and water is used for cleaning packaging line equipment including the interior of the (b) (4) vial washer and conveyors. Also, there is no documentation to justify the (b) (4) day expiration date assigned to the (b) (4) and water.

39. As outlined in Appendix 002 of the written procedure, "Freeze Dryer Chamber Cleaning/Condenser Defrost for (b) (4) Remediated Freeze Dryers", document #030-SOP-CC-20, version 6.0, effective date 28 Feb 2011, a squeegee is used to remove WFI rinse water from the shelves of the freeze dryer chambers in the North Facility and Phase ~~W~~ Facility Complex (Chamber #'s (b) (4) The manufacturer's specifications state that the blue colored squeegee is constructed of "reinforced PP and rubber" suitable for "sweeping wet and smooth floors to remove large amounts of dirt". However;

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a. The MPR fo[redacted] lot #2120886 was found to contain 4 copies of the Start-Up Check Sheet, document number 030-SOP-CC-20 GFRM 001, for the sterilizati[redacted] checks performed on Freeze Dryer [redacted] located in the class 100 area of fill suite[redacted] dated 4/26/2011, 5/3/2011 (0340 hr), 5/3/2011 (1826 hr) and 5/11/2011. The Production Manager of the North Complex confirmed that operators performed several cleanings of Freeze Drye[redacted] due to blue specs found in the chamber after the initial cleaning performed on 4/26/2011;

b. Although a deviation was not initiated, the Production Manager North Facility attributed the blue specs found in the lyophilizer chamber to the use of the blue colored squeegee during the cleaning of Freeze Dryer[redacted] and, [redacted]

c. A study has not been performed to qualify the use of the blue colored squeegee during the cleaning process of the [redacted] Remediated Freeze Dryers in the aseptic core of both building [redacted] no

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40. The [redacted] Sterility Test Isolators were qualified and validated on 3/26/07 and 4/2/07. The following document a number of concerns with the data to support the validation and current use of the Sterility Test Isolators;

a. According to TRK #93890 and #94127, the validated concentration of [redacted] is [redacted] However, the firm used a [redacted] concentration of [redacted] which is inconsistent with the validated concentration, to decontaminate the [redacted] Isolators [redacted] and [redacted] from 11/01/09 to 02/04/10. The firm detected three lots which failed sterility testing during this time period, including lot #2378-44-1157184 discovered on 01/20/10, lot #2080-10-1859569 discovered on 01/23/10 and lot #2413-12-1925943 discovered on 01/23/10;

b. A Senior Microbiologist confirmed that the initial validation of the isolators was performed by the manufacturer (i.e., [redacted], which consisted of using multiple (i.e.,

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four) doses of (b) (4) However, the 09/01/09, 12/01/09, 01/26/10 and 05/14/10 revalidations consisted of using two doses of (b) (4)

c. A Senior Microbiology confirmed that low-pressure alarms and high-velocity alarms were ignored during the decontamination cycle of isolators (b) (4) and (b) (4) Microbiology employees were instructed to disregard these alarms if the dosing of (b) (4) was performed correctly. According to the Senior Microbiologist, the firm does not have written instructions to define when it is appropriate to clear isolator alarms and proceed with testing;

d. The Quality Control Unit does not review the charts which record the temperature, humidity, air velocity and differential pressure of the isolators (b) (4) and (b) (4) (Note: Temperature and humidity impact upon the decontamination cycle. Air velocity and differential pressure impact the site selection for Biological Indicator challenges.);

e. The firm did not review the raw data to support initial validation of the Chemical Indicator and Biological Indicator testing performed by the isolator manufacturer (b) (4)

f. The firm did not perform smoke evaluation or air flow pattern testing on the isolator. These studies are used to evaluate the Chemical Indicator (CI) placement to support the Biological Indicator (BI) challenge, which is used to validate the decontamination process; and,

g. According to the Senior Microbiologist, the firm did not perform any qualification testing after maintenance on air dampners was performed on isolators (b) (4) and (b) (4) on 02/16/2010. Furthermore, the investigation did not include corrective action to address the cleaning of the isolator for metal and plastic debris.

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41. Document 030-SOP-K-79, Detection of Bacterial Endotoxins Utilizing the (b) (4) System, states that precautions are to be taken in handling all samples to be tested to minimize contamination. However, the firm cannot ensure that all utensils used in the testing of finished parenteral drug products are free from endotoxin. On 05/17/11, a microbiologist was observed performing endotoxin testing as part of the release testing for 2 finished parenteral drug products. In addition;

a. In order to remove the metal outer seal on the 6 glass vials containing the drug product samples, the microbiologist used a wrench that appeared to be coated with a rust-like material;

b. The microbiologists performing endotoxin testing do not use barrier pipette tips to mitigate the risk of contaminating the barrels of the pipettors with solutions containing high levels of endotoxin. For example, one microbiologist used the 100µL pipettor to prepare the endotoxin standard control solutions. Immediately following this, another microbiologist used the same pipettor to aliquot water samples for endotoxin testing without cleaning or sanitizing the barrel of the pipettor;

c. On 11/06/09, a microbiologist obtained out of specification results while performing finished product endotoxin testing on (b) (4) lot # (b) (4) using method (b) (4) issue date 12/15/00. This method requires removal of the stoppers from the vials containing the drug product followed with water bath sonication for (b) (4) minutes. This OOS result was attributed to the water bath sonicator, which apparently poses a risk of contamination to the samples because the water is not free from endotoxin. On 03/05/10, another microbiologist performed finished product endotoxin testing on (b) (4) lot # (b) (4) using method (b) (4) and again obtained out of specification results. Despite the OOS results the firm has not modified this method to minimize the risk of endotoxin contamination from the sonicator.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, Ohio 45237 (513) 679-2700	5/2-25/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thomas J. Murphy, President & CEO

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE Bedford, Ohio 44146	TYPE OF ESTABLISHMENT INSPECTED Pharmaceutical Manufacturer

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42. On 05/10/11, we observed a batch of (b) (4) media #LB031811, prepared on 03/18/11, which was labeled "at risk." Document 030-SOP-K-11 states that media may be used at risk if it is needed prior to qualification. However, this media must pass qualification prior to the product being released. If qualification testing is not acceptable, then a deviation must be initiated.

This media was used during the release testing of finished drug product (b) (4) lot #0553-52-2053109, which was authorized by Quality Assurance on 04/06/11 to be shipped to the customer in quarantine status. A Senior Microbiologist explained that microbiology department management was unaware that this (b) (4) batch had not passed growth promotion testing. Document 030-SOP-K-11, Media and Rinse Qualification, states that if nonconforming results are detected, then one retest may be performed with Supervisory authorization. The microbiologists performing this growth promotion study did not obtain supervisory approval before repeating a portion of the growth promotion testing with a different organism. Furthermore, these microbiologists did not initiate a deviation to address the unacceptable qualification testing results.

43. Document SOP 030-SOP-K-85, Atypical Endotoxin Results, when Out of Specification (OOS) endotoxin results are obtained while testing finished product, the second repeat testing consists of analyzing (b) (4) of finished drug product. However, when (b) (4) (b) (4) the second repeat testing consists of (b) (4) According to a Senior Microbiologist, the firm does not have a scientific rationale for determining how many retests are required to determine that initial OOS results can be attributed to laboratory error.

44. On 08/08/10, the parenteral finished drug product (b) (4) lot # (b) (4) failed sterility testing, which was determined to be caused by the use of (b) (4) gloves used during the transfer of pre-chilled glass vials from the lyophilizer to the infeed fill table. The Senior Manager of the North Facility and Quality Assurance Manager confirmed that the

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operators, manufacturing supervisor and Quality Assurance Auditors were aware of the use of these gloves. However, they did not intervene in the practice of using the gloves, the firm did not initiate any retraining of personnel in regards to acceptable aseptic practices, which will decrease the risk of contaminating product during fill operations.

45. On 04/02/11, an Environmental Control technician collected a water sample from a valve in the Water for Injection Loop I, which is use in the manufacture of aseptically filled parenteral drug products. This water sample was tested for endotoxin levels and failed to meet specifications. During the resulting investigation, it was determined that the sample had most likely been contaminated during collection, due to the fact that the technician had dropped the water sample tube onto the ground where a pool of water was located. The technician had picked up the sample and submitted it to the microbiology laboratory for processing. The technician was not retrained after this incident on proper aseptic practices and correct collection techniques.

46. The investigation into an OOS investigation for a finished product was not initiated in a timely manner. A Laboratory Interview Worksheet was not initiated, nor was a (b) (4) system regulatory deviation report initiated until 18 business days after OOS results were obtained for (b) (4) Final Product lot (b) (4) According to SOP, #030-SOP-J-113 (effective 10/30/09), entitled "Management and Investigation of Discrepant Results" the initial laboratory assessment is to be initiated on a Laboratory Interview Worksheet and in the (b) (4) system within (b) (4) after recognizing a discrepant result. The QC chemist obtained discrepant results for (b) (4) Final Product lot # (b) (4) for (b) (4) purity, (b) (4) and % largest unknown impurity on 3/19/2010.

The Regulatory Deviation Report TRK #98292 for this investigation indicates that the investigative testing was performed on the original samples "approximately 27 days" after the initial testing. However, according to Quality Control Analytical Test Method # (b) (4) (b) (4) ssue date 5/19/00), samples are to be run with (b) (4) hours of preparation.

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47. The Regulatory Deviation Report TRK #98283 indicates that standard preparation error (i.e. the standard did not dissolve completely) was the probable root cause for two OOS After Filtration (AF) assay results for (b) (4) In-Process lot (b) (4). Despite the probable root cause finding, the QC Chemist used the original standard solutions to re-analyze the original AF assay samples using Quality Control Analytical Test Method # (b) (4) (issue date 11/13/02). While the TRK #98283 indicates that the impact of using the original standards is negligible, it does not provide empirical data to support this conclusion.

48. According to SOP #030-SOP-J-36 (effective 12/30/08), entitled "Training of Quality Control Analysts" all chemists and technicians in the Quality Control Laboratory must successfully complete a (b) (4) paper evaluation of knowledge. However,
- Documentation does not exist of the 2009 (b) (4) knowledge check for (b) (4) Quality Control Chemists.
- No (b) (4) knowledge check was administered in 2010 for (b) (4) chemists who began work in the laboratory in 2008.
- None of the (b) (4) technicians working in the Quality Control Laboratory have received a (b) (4) knowledge check since the SOP became effective.

Tamara M. Kays
Paul A. Bonness - microbiologist
Sneha S. Patel - Chemist

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	Christopher T. Midden Nicholas R. Pinski Jennifer K. Gustavus Mary P. Smith Elizabeth Edwards	Christopher T. Midden, Jr. Investigator Nicholas R. Pinski - Investigator Jennifer K. Gustavus - Investigator Mary P. Smith - Investigator Elizabeth L. Edwards, Investigator	5/25/11

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