DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, OH 45237 513-679-2700 Industry Information: www.fda.gov/oc/industry	11/7/11 - 12/2/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: George P. Doyle, III, President and Chief Executive Officer Executive Office

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bedford, OH 44146	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 (I) (WE) OBSERVED:

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.

a) There exists a program called "Project Charter" that is used to evaluate, assess, and/or study for example; processing improvements, enhancements and/or removal of for example production and personnel activities that do not provide added value. Project number 61661318, project start date 7/27/2011, describes, "This project will enhance Right-First-Time culture in ILP. Improve/organize the facility appearance and cleanliness, improve delectability of defects in ILP, and reduce incidence of re-occurring deviations associated with cleanliness." The "Project Charter" scope ("Part of process that will be investigated") includes;

-"Walk-through of all inspection/packaging areas at BVL facility (North, South, Phases IV, and Phase V focus factories) to assess adherence to compliance and cleanliness of ILP areas
-GAP Analysis between our SOPs and Regulations and QSITs
-55 Project to organize the inspection/packaging areas for all focus factories
-Improve inspection process
-Revise SOPs where needed
-Identify needed training for ILP personnel
-Reference Library for inspectors with examples of acceptable/unacceptable products

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	Christopher T. Middendorf Dell Moller	Christopher T. Middendorf, Investigator Michael P. Sheehan, Investigator Thomas J. Arista, Investigator Dell S. Moller, Investigator	12/02/2011

-Organizational assessment"

The team members with this project include for example the Quality Unit, Production and ILP (Inspection Labeling & Packaging). The Director of Quality Assurance and the Manager of Quality Compliance explained that there exists other "Project Charter", which have been implemented throughout the BVL site. However, the number of the "Project Charter" that are currently being performed is unknown. The Director of Quality Assurance and Senior Manager, Quality Investigations and Data Management, confirmed that the "Project Charter" as well as the evaluations and assessments performed to address the "Project Charter" are not part of, or included within, the BVL Quality System;

b) The "CAPA System" document #030-SOP-Q-16, dated 19 Nov 2009, describes the Corrective Action / Preventive Action (CAPA) System at Ben Venue Laboratories (BVL) and established the principles used to identify actions to prevent the occurrence /recurrence of quality problems and verify CAPA effectiveness." The "Project Champion" of the above "Project Charter" explained that there are weekly meetings regarding the on-going project, for example, the above project has "ILP Improvement Project" meeting minutes. Despite the establishment of the CAPA System procedure, the "Project Champion" confirmed that there exists no CAPA for the project improvements.

c) Per your Senior Manager, Deviations/Trending, your firm has had in place a "Compliance Dashboard" Group, which has been meeting weekly since approximately September 2009. The intent of this "Compliance Dashboard" is for assuring the timeliness of (b) (4) for deviations, complaints, change controls, CAPAs, and quality protocols, however, the "Compliance Dashboard" is not part of, or within the Quality System.

d) Despite the establishment of Quality Policy, purpose and scope of the "Quality Manual", document 030-SOP-OP-01340, dated 28 Feb 2011, the "Project Charter" and the "BVL Compliance Dashboard" are not part of any Quality System document or any documents in support of BVL "Quality Manual".

e) The "Change Control Program", document #030-SOP-Q-01308, dated 16 Jun 2010, establishes and defines the "overall Change Control Program including initiation, review, approval, implementation and closure of changes that are governed by cGMPs" and it "applies to all changes that have the potential to impact product registration, cGMPs, product attributes (safety, identity, strength, purity and quality) and the state of validation of processes,

equipment, instruments, facilities and system." The North roof was removed and replaced due to rain water leaking into the North manufacturing areas. The North roof replacement of Areas F, G, L and Q was completed on November11. 2011. Despite the establishment of the aforementioned program and procedures no change control was performed for the removal and replacement of the North Facility roof.

d) There is no proceduralized process to notify senior management of issues that could potentially impact the safety or quality of product as it pertains to open and coming due (b) (4) investigations/deviations or preventative maintenance in past due status. Reportedly, meetings are held to update senior management on these issues, however there is no documented evidence to show these meeting occurred or information was conveyed to quality managers across the different manufacturing units.

e) The Quality Unit is not following the established procedures in that senior management is not notified within (b) (4) hours of (b) (4) initiated with an initial assessment of critical per procedure. For example, (b) (4) 115576 (failing vial washer re-qualification), discovered on 3/17/11, was opened on 4/14/11 with an initial critical designation and senior management was not notified. On 4/18/11, this (b) (4) was downgraded from critical to major with no evidence to show management was notified. Furthermore, there is no documented justification to show why this (b) (4) was downgraded.

f) The Quality Unit is not initiating investigations and documentation of those investigations in a timely manner. For example (b) (4) 115576 was discovered on 3/17/11 (failing vial washer re-qualification) and the (b) (4) was not opened until 4/14/11.

g) Routine preventative maintenance activities are not performed at their scheduled intervals. As of 11/11/11, there were approximately 107 required preventative maintenance activities for GMP equipment past their scheduled due date. To be considered past due, the event must be greater than (b) (4) days past scheduled due date. There is no evidence to show the Quality Unit took action on these overdue preventative maintenance issues concerning equipment qualifications and validations of the respective processes.

h) The quality unit failed to open an investigation on Sestamibi lot #0077-00-2055354 when the packaging record indicated the lot exceeded the (b) (4) limit for "Percent Defects", when inspected on or around 10/21/11. According to the packaging record the "Percent Defects" for lot #0077-00-2055354 was 2.4%.

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i) The quality unit failed to follow established procedures during the deviation investigation ((b) (4) 123629) of an unknown liquid found in a 10-gallon can in a storage area of the North facility. According to documentation in (b) (4) 123629 memo, an independent laboratory "performed a Creatinine, Urine test on the substance. The results found a level of 137.3 mg/dL…These results are consistent with the values found in Urine.". The investigation of the liquid was opened on 09/19/2011 with a scheduled due date of 10/19/2011. At the time of our inspection, the investigation was past due. According to SOP 030-SOP-Q-1205 "Event Classification and Investigation Process" a detailed risk assessment is required if an investigation is projected not to close within (b) (4) days of initiation. A detailed risk assessment has not been performed for (b) (4) 123629.

2 The "Media Fill Program Parameters and Specifications" document #030-SOP-D-29, dated 19 Aug 2011 defines media fill as "A process conducted in order to demonstrate the acceptability of aseptic processes from the point of filtration of the product of the completion of the filling and closing of the aseptic container system, including aseptic equipment assembly steps." The procedure requires "Interventions are planned and performed to ensure that the routine procedures involved in the manufacturing process are supported by the performance of an acceptable media fill." Routine planned 'worst-case" interventions are those interventions that occur less frequently but are potential aseptic interventions." Furthermore, "an employee must have been an active participant in a media fill while completing the intervention which they would be performing during the routine filling operation" and "All employees must perform the interventions associated within their job function (b) (4) " Despite the establishment of the aforementioned requirements, 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. In addition,

a. After performing the requisite manual interventions the media filled vials that were within or near area where the manual intervention was performed are discarded (e.g., approximate (b) (4) of media filled vials) and not included with the incubated vials. There is no record to document that the manual interventions performed during aseptic media fill adequately "demonstrate the acceptability of aseptic processes form the point of filtration of the product of the completion of the filling and closing of the aseptic container system, including aseptic equipment assembly steps";

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b. Discarding the media filled vials precludes the Quality Unit from adequately assessing and assuring that the manual interventions do not create or provide adverse conditions that can result in having microbial and/or non-viable contamination during the aseptic filling process to "ensure that the routine procedures involved in the manufacturing process are supported by the performance of an acceptable media fill";

c. The Senior Manager North Facility confirmed that the media filled vials within their so-called manual intervention "zone clearance" are discarded and not included with the incubation of the media fill batch. The Senior Manager North Facility confirms that they do not have a scientific rationale to demonstrate how the removal and discarding of the media fill vials following the manual interventions is an acceptable practice in support of the aseptic process;

d. The "Simulation of Aseptic Processes" document #028-OCP-00074, dated 01 Jun 2006 defines interventions as "All interventions that may be encountered during a routine process must be appropriately simulated during any media fill run, for example, line stoppages, shift changes, equipment exchanges or interventions by maintenance personnel." The corporate procedure does not provide language with respect to the removal and discarding vials following the manual interventions performed within the so-called "zone clearance";

e. The Senior Manager North Facility explained that during routine aseptic filling operations of finished products there exists a practice of having multiple manual interventions that are occurring simultaneously. The Senior Manager North Facility confirmed that a similar practice is not performed during the aseptic media fill process, which documents that the company is not adhering to the aforementioned corporate wide established written procedure;

f. The routine operations described in the aforementioned observations also apply to the aseptic media fill processes performed in the South and Phase-IV manufacturing facilities;

g. The manufacturing fill equipment (FILLR-FL05) used for the media fills performed in 2011 for the South manufacturing facilities has not met the periodic requalification;

h. The "Media Fill Validation Master Plan" (VMP), document #VMP22709M dated 9/20/10 establish, "the

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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(b) (4) units should be detected. (b) (4) contaminated (b) (4) considered cause for revalidation, following an investigation."
ii. "When filling from(b) (4) contaminated (b) (4) should result in an investigation, including consideration of a supplemental media fill. (b) (4) contaminated (b) (4) considered cause for revalidation, following an investigation." And,
iii. "When filling more than(b) (4) contaminated (b) (4) should result in an investigation. (b) (4) contaminated (b) (4) 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."

3 There exists an Environmental Monitoring Performance Qualification (EMPQ) for the South Complex, study number PQ39810M.AD4, dated 7/25/11, which is a "comprehensive environmental monitoring performance qualification is a required component of the overall complex qualification." A similar EMPQ has not been performed for the North and Phase IV manufacturing facility.

4 The "Dynamic and Static Air Flow Pattern Test Procedure For Class 100 / Grade A and Surrounding Areas", document #030-SOP-J-230, dated 16 Nov 2011, establish the test procedure and acceptance criteria utilized to verify the presence of unidirectional air flow patterns within Class 100 / Grade A active areas, and portable equipment and components staging locations in Class 10,000 / Grad B spaces, under dynamic and static test conditions for qualification." The Quality Engineer Manager confirmed that the air flow pattern testing has to be performed for the North, South and Phase IV manufacturing areas and fill zones. In addition:

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a. The 6/18/11 South Dynamic Air Flow pattern evaluation did not include the filling equipment in a dynamic state of operation; and,

b. The August 2009 Verification of Class 100 Air Flow in Aseptic Filling Suite 4147 and 4165 did not include an evaluation under dynamic operations.

5 The 2010 and 2011 quarterly EM Trend data document the percent of microbial identification for Gram Positive rods (i.e., spore formers, non-spore formers) isolated via the EM sampling program for the manufacturing areas (Class 100 and Class 10,000), for example;

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

6 The validation group lacks appropriate oversight and technical expertise to perform their duties. Specifically:

a) The validation group failed to perform periodic reviews and (b) (4) qualifications as required by their Validation Controlled Lists. Regulatory Deviation report (b) (4) 118217, details 10 pieces of GMP equipment that were not qualified within the required timeframes.

b) The report for the (b) (4) qualification of vial washer VIAL (b) (4) located in the Phase IV facility, that was performed on 5/23/10, was not reviewed by the validation staff or other quality unit personnel. The report was misplaced and the firm did not discover the error until 3/17/2011 during the preparation of the next (b) (4) qualification. This incident is detailed in (b) (4) 114632. Furthermore, the (b) (4) qualification of vial washer VIAL (b) (4) conducted on 5/23/10 did not meet acceptance criteria for the particulate challenge test for the (b) (4) vial size and continued to be used in manufacturing operations.

c) The investigation (b) (4) 115576) into the misplaced report ((b) (4) 114632) concluded that human error was the

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root cause, however, the investigation failed to examine other possible causes such as the lack of an oversight system to alert the validation group that equipment qualifications were past due.

d) There is no scientific rationale for event driven re-qualifications to various pieces of equipment such as, Portable Laminar Flow (HEPA) carts, clean steam system, distillation system, vial fillers, and headspace analyzers. This equipment is only re-qualified on this event driven basis, whereby the system must undergo a change or atypical event before the need to re-qualify is assessed. Furthermore, the required periodic review to assess the need for re-qualification for the Phase IV clean steam system, Phase IV and South vial fillers, various distillation systems, and the portable headspace analyzer units is either past due by approximately 1 year or has not been performed.

e) Although the quality unit discovered the missing (b) (4) qualification report for VIAL (b) (4) on 3/17/2011 the investigation (b) (4) 115576) into the incident was not opened until 4/14/2011.

f) The quality unit failed to follow procedure 030-SOP-Q-10 which requires immediately reporting "Critical" findings to the Vice President of Quality Operations and the Vice President of Operations. (b) (4) 115576 was opened as a critical deviation on 4/14/11 and downgraded to "Major" on 4/18/11 without the approval or knowledge of senior management. During this current FDA inspection, the Vice President of Quality Operations and the Vice President of Operations, when asked of this event, replied they did not know about this and were just informed of this issue. Furthermore, the firm did not provide any justification for this downgrade.

g) Personnel did not follow company procedures (030-SOP-P-11) requiring employees to "tag out" equipment during (b) (4) qualification. Vial washer VIAL (b) (4) was not tagged out during (b) (4) qualification. The tag out procedure is a visual notification to production employees that a piece of equipment is out-of-service until returned to service by the quality unit.

h) There is no oversight ensuring validation group employees complete required training. For example, one validation manager is overdue for process validation safety training by more than 168 days.

i) There is no scientific rationale for the location for the placement of the thermocouples used to monitor incubator rooms WH (b) (4) WH (b) (4) and WIP (b) (4) Room (b) (4) used to incubate media fills in that the thermocouples are not

placed in the appropriate locations to detect the maximum and minimum temperatures as determined by the respective qualifications. The locations were determined by taking the lowest and highest temperature registered during qualification and not the locations registering the overall lowest and highest temperatures. Rooms WH[redacted] ([redacted] ft3), WH[redacted] ([redacted] ft3), and WIP[redacted] ([redacted] ft3) were used to incubate the media fill vials for qualifications performed in 2010 and 2011.

Furthermore, for WI[redacted], the monitoring thermocouple TC B601 could not be located during this inspection. Upon investigation by the firm, this monitoring thermocouple, that is actively monitoring the room, was determined to be located behind a wall and not within the incubator room. This was not discovered until brought to the firm's attention during this inspection. This monitoring location corresponds to a location that registered approximately 15 minimum temperature data points during the most recent qualification dated 11/2008.

7 Your firm uses a[redacted] database system for investigating deviations, complaints, change controls, CAPAs, and quality protocols. On November 16, 2011, your Manager, Quality Data Management provided a list to us, containing 470[redacted] reports that are past their completion due date and remain in an open status. The significance of these open reports have not been fully evaluated by the quality unit with respect to the potential impact to the manufacturing processes and quality control testing in support of the finished drug products.

For example:

[redacted] report 54175, date opened 11/12/08. Completion due date 9/30/10.
reports 87615, 87616, 87618, date opened 9/20/09. Completion due date 3/31/10, 7/31/10, and 5/31/10 respectively.
[redacted] report 104061, date opened 8/6/10. Completion due date 8/5/11.
report 107869, date opened 10/27/10. Completion due date 6/30/11.
report 121770, date of discovery 8/22/11. Completion due date 9/21/11.

8 Complaint investigations are inadequate and fail to follow established procedures. For example;

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a) The firm failed to retain a written record of employee interviews during the investigation of a complaint ((b) (4) 117662) for Sestamabi lot#0077-00-1911930 regarding metal particles.

b) As part of investigation (b) (4) 117662, the firm visually inspected and obtained wipe samples of equipment used in the production of Sestamibi in the South facility, however, the firm did not provide justification of the sample sizes.

c) (b) (4) 117662 is deficient as it does not include an impact assessment of other products manufactured in the South Facility.

d) The sample sizes used in the Protocol for Non Sterile Water Run Products 0077-00 and 0229-00 fill study ((b) (4) #123119), used in the investigation into metal particulate complaints, such as (b) (4) 117662, were not reviewed by an appropriate person knowledgeable in statistics to ensure statistical significance.

e) In response to the complaint of metal particles in Sestamibi (multiple lots, multiple complaints), the firm initiated a visual inspection of product for the appearance of foreign material on the lyophilized cake. However, the firm did not provide evidence that the visual inspection is scientifically sound and ensures detection of particles within the lyophilized cake.

f) Firm investigators failed to follow procedures (030-SOP-Q-7) in that they did not perform a detailed risk assessment when complaints remained opened longer than 30 days. FDA Investigator reviewed 15 complaints during this inspection related to Bedford Laboratories products, 13 of which were classified as "Major" and required a detailed risk assessment per the SOP. Your firm's complaint investigators did not perform a detailed risk assessment of five complaints ((b) (4) 116883, 118079, 116778, 119361 and 116819) and did not perform the assessment within 30 days for four complaints associated with contract manufactured products (b) (4) 116740, 122261, 122461 and 116851).

g) The criteria for inspecting retain samples is inconsistent and not in writing. For example, retain samples were examined for a complaint ((b) (4) 118079, Cytarabine 1gm, lot#2098694), received on 6/8/11 regarding a "short count", but not examined for a complaint ((b) (4) 118094, Prochlorperazine Edisylate 5mg/ml, lot# 2006537) received on 6/8/11 regarding apparent "cloudiness" of the product.

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h) A FAR for Placlitaxel Injection U.S.P. SD vial, lot 2378-00-2006737 for a complaint received on 4/14/2011 by the firm involving defective closures was submitted to the Agency. The defective units were received by the firm on 4/28/11 and the information was not entered into the firm's (b) (4) system until 5/13/11 and a FAR was submitted on 5/16/11.

9 Vial filling checks are regularly performed during the filling operation, however do not include appropriate vial fill rechecks when vials are found out of control or out of action. For vials found either out of control limit or out of action limit, a recheck is performed. If this recheck is acceptable, production continues without checking any other vials. Only if the recheck is found either out of control limit or out of action limit, is the product from the last good check isolated for further evaluation.

Midazolam 1mL (5mg/mL), lot 0938-40-1828861 was filled on 11/11-12/10 and on multiple instances had deviations from target weights of either out of control limits or out of action limits exceeded. The operators performed vial fill rechecks with acceptable results. This lot of product was reviewed and released for commercial distribution and later recalled due to low fill volume units.

10 Routine preventative maintenance activities are not performed at their scheduled intervals. As of 11/11/11, there were approximately 107 required preventative maintenance activities for GMP equipment past their scheduled due date. To be considered past due, the event must be greater than 30 days past scheduled due date.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."