DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
22215 26th Ave SE Suite 210 Bothell, WA 98021 (425) 302-0340 Fax:(425) 302-0404 Industry Information: www.fda.gov/oc/industry	03/26/2014 - 04/15/2014
	FEI NUMBER 3010477

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Rajesh Kapoor, Ph.D., Global Head, Quality

FIRM NAME	STREET ADDRESS
Jubilant HollisterStier, LLC	3525 N Regal St
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Spokane, WA 99207-5788	Contract drug manufacturer

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

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

The following Observations pertain to the manufacture of drug products aseptically filled, and sterile injectable drug products.

LABORATORY SYSTEM

OBSERVATION 1

Test procedures relative to appropriate laboratory testing for sterility and pyrogens are not written and followed.

Specifically, the results of sterility test sample and media fill vial interpretation for microbial contamination cannot be verified. Sterility testing was performed at JHS for at least the following products: 3mL and 10mL sterile empty vials (b) (4)), (b) (4) ((b) (b) (4)), (b) (4) (b) (b) (4)), (b) (4) (b) (b) (4)), (b) (4) (b) (b) (4)), (b) (4) ((b) (b) (4)), (b) (4): ((b) (b) (4)), (b) (4) (NDA (b) (4)), (b) (4) ((b) (b) (4)), (b) (4) (b) (b) (4)), (b) (4) ((b) (b) (4)), (b) (4) ((b) (b) (4)), (b) (4) (b) (b) (4)), and (b) (4) (b) (4) (b) (4)). Performance Qualification media fills were executed on aseptic filling (b) (4) to mimic commercial production of sterile injectable drug products.

A) An unauthorized method, SOP 405.21 (b) (4) ", R-6 issued 2/14/11, was the only test method used to determine if sterility test samples and media fill vials identified as "visual abnormalities", "questionable possible growth", and "precipitate" were contaminated with microbial growth. SOP 405.21 was not included as a test method for the determination of microbial contamination in SOP 404.22 "Sterility Test Failure Investigation", R-10 issued 10/17/11; or in SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13; or SOP 404.20 "Media Fill Master Plan for Qualification of Aseptic Processing", R-25 issued 12/5/13. SOP 405.21 was not included as a test method in the Product Specifications, section Test, Sterility Test. There was no documented validation to demonstrate SOP 405.21, R-6, Attachment 4 " (b) (4) of Samples from Sterility Test" was suitable to determine microbial contamination in Soybean-Casein Digest Medium (SCD) or Fluid Thioglycollate Medium (FTM) by Gram stain evaluation. Under SOP 405.21, R-6, Attachment 4, (b) (4) (b) (4) then no further testings are required, the test results are concluded as negative (no growth). The sterility test samples and media fill vials with suspected microbial

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contamination were discarded after the results were interpreted.

B) Sterility test technicians failed to permanently document the sterility test sample and media fill vial observations for units with "visual abnormalities", "questionable possible growth", and "precipitate". (b) (4) sterility test technicians interviewed said unusual sterility test samples and media fill vials detected during the incubation period were not considered to be positive for contamination because per management instructions the units would continue to be incubated until (b) (4) They described unusual sterility test samples and media fill vials with "a fog" or "a mound" in the bottom, a "cottony" mass, a "fibrous" strand, "chunks" that didn't appear to be bits of stopper, and "flakes".

1) Sterility test technicians were directed to mark culture canisters and vials, and notify a supervisor when they observed visual abnormalities during sterility test and media fill vial incubation. SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13, Attachment 1 section 4.3 reads in part:

a) "*** When performing (b) (4) if visual abnormalities are observed mark culture canister/bottle with short description initial and date ***". The culture canisters and vials were discarded, and the marked information was not otherwise retained as a permanent record. As a practice, no visual abnormality (suspected contamination) observations were documented on the testing worksheets. The SOP 404.40 documentation instructions are in conflict with SOP 102.94 "Standards for Recording Data on a Controlled Document", R-12 issued 10/29/12, which reads in part "*** Standards are necessary for collecting, recording and correcting data on controlled documents to ensure accuracy, integrity and traceability of all data pertinent to a manufactured batch of product ***".

b) "*** Any bottle of questionable possible growth will be checked by one of the Microbiologists or MQC Supervisor ***". Sterility test technicians interviewed stated they were instructed to notify the supervisor or MQC Manager by phone to come and check the questionable units. There was no documentation a Microbiologist, the MQC Supervisor or MQC Manager were notified of the need to check suspect units. There was no documentation the suspect units were checked.

2) As a practice, when sterility test samples or media fill vials display visual abnormalities at the first check and mid check, the worksheets were stamped with a date stamp in (b) (4) to indicate no growth. SOP 404.40 Attachment 4 step 1.4 reads in part "*** A date stamp in (b) (4) is used to denote a negative (no growth) Sterility Test result (negative growth stamp) ***". The sterility test technicians interviewed said they put a date stamp in (b) (4) on sterility test and media fill worksheets after they observed units with visual abnormalities per management instructions, and because the units would continue to be incubated until (b) (4)

C) Internal sample custody was not maintained for sterility test samples and media fill vials designated "turbid", "visual abnormalities", "questionable possible growth", and "precipitate" in accordance with SOP 303.87 "Receipt and Handling of Samples in the Jubilant HollisterStier Reference and Sample Storage Area", R-11 issued 3/19/12. SOP 303.87 section 1.2 reads in part "*** control of samples *** is necessary to ensure the integrity and usability of these samples ***". SOP 303.87 section 3.2 reads in part "*** Internal test samples *** includes samples generated during the execution of any HS SOP, protocol or engineering study ***". The transfer of custody for turbid and abnormal sterility test samples and media fill vials from Room (b) (4) where the samples were interpreted by sterility test technicians to the Microbiology Lab Room (b) (4)

where they were to be further tested by microbiologists was not documented in the SOP 303.87 Attachment 3 - CRSS Internal Sample Receipt Log. The CRSS (central references and standards storage) room is where the test sample tracking log is maintained. The practice of not tracking turbid or suspected growth sterility test samples and media fill vials is in contrast to the media fill growth promotion vials that require CRSS sample tracking in accordance with SOP 404.20 "Media Fill Master Plan for Qualification of Aseptic Processing", R-25 issued 12/5/13, Attachment 9 for the same sample custody transfer.

OBSERVATION 2

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

Specifically,

A) There are no assurances that the aseptic media fill simulations conducted by the firm are reliable. From March 2012 to March 2014, the firm conducted approximately (b) (4) media fill simulations for Aseptic filling Lines: (b) (4) to demonstrate the sterility of released sterile CDER products. No growth/ (zero) were documented for all of the media fill simulations. The review of the firm's media fill simulations disclosed the following significant objectionable conditions:

1) Lack of simulations of the hold times of the bulk products used in the simulations of the media fills to demonstrate worst case conditions. The fill Drug Substance batches during the normal filling processes can be held for up to (b) (4) hours before (b) (4) (b) (4) and aseptic fill. However, the media fill bulks used in the media fill simulations are held before fill for less than ≤ (b) (hours.

2) There are no assurances that media fill interventions were actually performed by the media fill operators. Media fill interventions are listed in media fill SOPs for (b) (4) areas, however, the requirements for the documentations that media fills are performed is the notations of the operators initials next to the referenced SOPs intervention numbers on a page included in the media fill batch record.

3) There are no assurances that media fill interventions are performed accurately and that they adequately simulate normal aseptic vials filling conditions, in that media fill interventions end times are not documented in the batch record. Only media fill start times are recorded, except for rare instances that interventions are required per the SOP to be performed, i.e., for not less than (b) (4) minutes.

4) There is no documentation of the review of the commercial aseptic filling batch records for unusual occurrences to consider the unusual occurrences for inclusion in to media fill simulations. For example, to consider unusual occurrences that are not included in the media fill SOP to be performed and/or to extend media fill interventions that are currently performed but were noted to be longer in commercial production than are currently simulated.

5) Media fill vials were not adequately inspected for microbial contamination on day (b) (4) of the incubation. SOP 404.20, R 25, "Media Fill Master Plan for Qualification of Aseptic Processing", is deficient in providing adequate

written instructions on how to conduct media fill vials inspection. SOP 404.20, Attachment 1, section 14 and 15 specify media fill containers are checked for clarity on day (b)(4) of the incubation at (b) and on day (b) of the incubation at (b) During the inspection, we discovered that on day (b)(4) of the incubation individual vials were not removed from trays for inspections. Vials in trays were only visually "scanned" for microbial contaminations. Specifically, sterility technicians performing media fill vials inspections were verbally instructed by the management to visually "scan" vials in trays on day (b)(4) Only on day (b) of the incubation vials were removed in groups from each tray for visual inspection of microbial contaminations.

Additionally, media fill inspection results were not adequately recorded on the worksheets. SOP 404.20, Attachment 9, "Media Fill Sterility Test Incubation Results", lacks adequately designated worksheet spaces for technicians to record results. For example, media fill Batch record # D1400058 contained a total of (b) (4) acceptable vials collected in (b)(4) trays for incubation. Attachment 9 provides only one data entry field for each category "Contaminated Acceptable Containers" and "Contaminated Incubated Rejects" at (b) (4) . There is no designated space to document individual vial inspection; there is no designated space to document, by trays, to indicate where in the batch the suspected contaminated unit was found. Without adequately inspecting and recording media fill vial inspections for microbial contamination, your firm lacks assurance that the aseptic processing is capable of manufacturing sterile drug products.

B) The Environmental Monitoring program had the following deficiencies:

1) No diagrams are used for EM sample collections. The environmental monitoring procedure has only descriptions of general locations that could be variously interpreted by different personnel.

2) The EM sample locations are not based on risk assessments to determine if the locations are representative of worst case sample points. The EM sample types were not validated to represent the surface being sampled. For example, the (b) (4) touch plate used to sample (b) (4) that were used for interventions on the filling line appeared to make minimal contact with one side of (b) (4) .

3) There is a lack of passive viable air sampling in ISO classified areas. Specifically, during (b) (b) set up and filling operation on 04/02/2014 and 04/03/2014, (b) settling plate was used during pump connection in ISO5 area. Also, (b) settling plate was used in ISO6 area during aseptic set up. Additionally, no settling plates were used in ISO5 and ISO6 areas during filling operations.

4) Operators hands still wet from (b) (4) were sampled by contact plates.

5) Personnel monitoring (including gloves) by TSA-80 (b) (4) contact plates were not deliberate and controlled. Contact time and coverage did not appear to be sufficient.

6) There was no documented calibrations or monitoring of (b) (4) active air samplers used in ISO 5 classified areas where injectable drug products are aseptically filled.

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OBSERVATION 3

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Electronic records are used, but they do not meet systems validation, system access limitation, audit trail, and signature to record linking requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.

Specifically, appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

A) Analysts share a common user logon with administrator permissions (delete, modify, read, and write data, and change other users' permissions) for the computers used to operate, obtain testing results, and store testing results obtained from the (b) (4) The (b) (4) are used for endotoxin testing of (b) (4) drug products.

B) Analysts have user permissions including delete, modify, read, and write data on the computer used to operate, obtain testing results, and store testing results obtained from the (b) (4) instrument. The (b) (4) instrument is used for (b) (4) testing of (b) (4) drug products and (b) (4) testing of (b) (4) drug products.

C) Analysts have user permissions including delete, modify, read, and write data on the computer used to operate, obtain testing results, and store testing results obtained from the (b) (4) instrument. The (b) (4) instrument is used for testing of (b) (4) drug products.

OBSERVATION 4

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

Specifically, sterility test technicians failed to permanently document the sterility test sample and media fill vial observations for units with "visual abnormalities", "questionable possible growth", and "precipitate". (b) (4) sterility test technicians interviewed said unusual sterility test samples and media fill vials detected during the incubation period were not considered to be positive (growth) because the units would continue to be incubated until (b) (4). They described unusual sterility test samples and media fill vials with "a fog" or "a mound" in the bottom, a "cottony" mass, a "fibrous" strand, "chunks" that didn't appear to be bits of stopper, and "flakes". SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13, Attachment 1 section 4.3 reads in part:

> a) "*** When performing (b) (4) if visual abnormalities are observed mark culture canister/bottle with short description initial and date ***". The culture canisters and vials were discarded, and the marked information was not otherwise retained as a permanent record. As a practice, no visual abnormality (suspected contamination) observations were documented on the testing worksheets. The SOP 404.40 documentation instructions are in

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conflict with SOP 102.94 "Standards for Recording Data on a Controlled Document", R-12 issued 10/29/12, which reads in part "*** Standards are necessary for collecting, recording and correcting data on controlled documents to ensure accuracy, integrity and traceability of all data pertinent to a manufactured batch of product ***".

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OBSERVATION 5

Drug product samples are not representative of the entire batch.

Specifically,

A) The final release tests performed to release Sterile Drug Product batches into the US commerce are not representative of the final released batches. The in-process sampling and testing of the vials for the release of the final Drug Products are performed immediately following the filling of a product batch; sterilized product batch and/or unloading of a lyophilized product batch. The in-process sampling and testing of the vials for the release of the final Drug Products are performed immediately following the filling; sterilization and unloading of the lyophilizer. Although additional handling of the sterile Drug Product batches are performed, such as: storage of the batch for up to (b)(4) days before the vials are inspected and/or re-inspected by the Manufacturing Unit; AQL sampling by QA Auditors; and vial labeling and packaging. No additional testing of the batches is conducted before the batches are release by the firm. Per memo dated April 09, 2014 provided by the firm's management, this practice of in-process sampling to release manufactured sterile Drug Product batches has been in place since 1980 and is the current practice. For example:

1) The final releases of the following sterile Drug Product batches are based on in-process testing, no additional tests are performed before the batches are released: (b) (4) and (b) (4).

2) In process samples of the manufactured Products that are not representative of the final release batches are sent by the firm (JHS), to clients or clients' analytical laboratories per the contract agreements for the final Drug Product batch release testing, for example: (b) (4) (b) (4) (b) (4).

B) The following deficiencies are noted in the Inspection of final sterile Drug Products vials:

1) There are no assurances that the batches of final sterile Drug Product vials inspection reject rates that are

documented for each inspected sterile Drug Product batches are representative of the final released batches. For example: rejected vials that are found during the QA Auditors inspections of the beginning, middle and end of batch production samples are sent to the firm's (JHS) QC laboratory for final container testing and release, and/or vials sent to Clients or Clients contract laboratories for final testing and release are noted on Attachment #2 to the SOP 209 series, titled "Vial/Closure/Contents Inspection Record for QC Samples", after which the vials are discarded. However, there is no documentation that these rejected vials are included in the batch records final tallies of rejected vials that are used for the determinations of the final dispositions of these batches. Furthermore, per the QA Auditor, the rejected vials are discarded by him in a drum located in the warehouse, which he showed to us and discarded vials were confirmed in the drum by the inspection team.

2) No re-inspection of finished vials batches are conducted by the Manufacturing Unit regardless of the defective vials reject rate or if the rejected vials are classified as critical or major to assure that all defective vials are culled out before release. Re-inspections of product vials are only conducted by manufacturing if the batch fails AQL inspection by Quality Assurance per SOP #209 series, titled: QA Final Container Sampling and Visual Inspection Instruction. For example:

a) Per INC20130103 dated June 05, 2012, an excursion to the reject limit rate per SOP 1830.1 occurred during the inspection of (b) (4) , batch (b) (4) ((b) (4)). The batch exceeded the allowable (b) (4)% number of critical rejects rate with reject rate of (b) (4). Also, the batch exceeded the allowable (b) (4)% number for major vials reject rate with result of (b) . Additionally, the batch record exceeded the allowable (b) (4)% for number of inspection rejects with result of (b) . The majority of the rejects of (b) (4) vials that were culled out for the batch was for product between the stopper and neck of vials and the majority of major rejects of the (b) (4) vials that were culled out was for product on the shoulder of vials. There was no documentation that the batch was re-inspected by the Manufacturing Unit before it was released for packaging.

b) Per INC20130283 dated August 19, 2013, (b) (4) batch (b) (4) ((b) (4)) dated July 09, 2013, exceeded the (b) (4)% allowable vials reject limit for critical rejects. Out of the (b) (4) vials that were inspected, (b) (4) vials were rejected for critical defects with (b) (4) vials rejected for product between stopper and neck. There was no documentation that the batch was re-inspected by Manufacturing Unit before it was released for packaging.

c) Per INC20130389 dated November 01, 2013, (b) (4) batch # (b) (4) dated October 25, 2013 (b) (4)) exceeded the (b) (4)% reject rate for critical rejects. Out of (b) (4) vials that were inspected, (b) (4) were rejected as critical rejects and (b) (4) of the rejected vials were for product between the vials neck and stopper with reject percent rate of (b) . There was no documentation that the batch was re-inspected by the Manufacturing Unit before it was released for packaging.

3) There is no documentation that when inspected sterile Drug Product vials failed to meet more than one AQL defects acceptance criteria per the inspection 209 SOP series, titled: Vial/Closure/Contents Inspection Record for QC Samples, for critical or major defects that the final batches are re-inspected for all the failed defects before the

batches are released. For example per SOP # 209.40, Revision #6, "If more than (b) defect is found in a vial, record the defect (b) (4) to the product only. Record other defects in the "Comments" section for information purposes". Per the QA Auditor, if [redacted] different sterile vial defects are found during AQL vial inspection, only the defect (b) (4) to the product is recorded for re-inspection.

4) The AQL re-inspection of all manufactured sterile Drug Products vial batches by the QA Unit is not conducted at tighter AQL level. For example, per SOP 209.2 Revision 17 Section #8, "(b) (4) [redacted]", this according to the SOP is the latest revision of the ANSI/ASQ Normal, Single General Level 1.

OBSERVATION 6

Samples taken of drug products for determination of conformance to written specifications are not representative.

Specifically, there are no assurances that the requirements to randomly select sterile Drug Product vials from the (b) [redacted] (b) (4) for in-process final release sampling and testing immediately following vials filling; sterilization and/or after unloading of the lyophilizer and final batch vials inspection are representative of the entire batch. For example:

A) Although over (b) (4) product vials are filled per batch of product manufactured, product vials sampling (b) (4) [redacted] that are sent to the firm's (JHS) QC laboratory, Clients or the Client's laboratories for final product release testing or for AQL, QA vials inspection are not conducted continuously throughout the process. Per the firm's QA Auditor, all of the samples for the (b) (4) [redacted] of the manufacturing process are collected by the QA Auditor at the same time from the vials collection table as long as it is within the (b) (4) [redacted] of the required process time frames.

B) There is no procedure in place that adequately describes QA random selections of the (b) (4) [redacted] selections of sterile Drug Product vials.

OBSERVATION 7

Laboratory records do not include a record of all calculations performed in connection with the test.

Specifically,

A) There was no assurance that the endotoxin turbidimetric testing results are accurate and reliable because the firm's (b) (4) [redacted] records do not include raw data that show calculations of test samples dilutions. SOP 401.35, R 11, (b) (4) [redacted]" is used to detect endotoxin levels in raw materials, water for injection (WFI) samples, components, in-process samples, and finished products. The firm's analysts stated that sample dilution calculations were noted on the test tubes but not in the laboratory notebooks, worksheets, or test reports. Without raw data, the accuracy of sample serial dilution calculations cannot be verified for routine assays as well as in OOS investigations. For example, all Lots of (b) (4) are

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tested at (b) (4) serial dilutions. However, (b) (4) endotoxin test records did not contain raw data showing how (b) (4) serial dilutions were calculated and carried out. Additionally, endotoxin detection of (b) (4) Lots (b) (4) (fill date 07/10/2013), (b) (4) (fill date 07/18/2013), (b) (4) (fill date 11/19/2013), and (b) (4) Lots (b) (4) (fill date 04/10/2013), and (b) (4) (fill date 08/15/2013) required multiple repeat testings due to one or more of the following: standard curve failures, low spike recovery, delayed onsets, or software early terminations. Without raw data review and verification, the validity of the test results and justification for repeat testing cannot be confirmed.

B) SOP 401.35 R 11 is deficient in allowing unlimited repeat testings without management review or investigation.

C) There is a lack of adequate justification in changing software default of (b) (4) % Coefficient of Variation (CV) to (b) (4) % CV. The % CV value entered and flagged in the analysis software becomes the acceptance requirement for standard and sample replicates. SOP 401.35, R 11 (b) (4) ", is silent regarding % CV criteria. Without applying adequately justified % CV criteria, the firm has no assurance the endotoxin testing results are accurate and reliable.

OBSERVATION 8

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

Specifically,

A) Test procedures to qualify cleaning performance of manufacturing equipment are used outside of validated ranges and at levels that do not adequately evaluate cleaning performance. Cleaning performance of product contact manufacturing equipment is not qualified. For example:

1) A (b) (4) is verified to detect carbon content in the linear range of (b) (4) parts per billion to (b) (4) parts per billion. The (b) (4) is used to evaluate the performance of cleaning (b) (4) manufacturing equipment at a concentration of approximately (b) (4) parts per million (b) (4) parts per billion) which is outside the verified linear range.

2) Recovery of (b) (4) from equipment surfaces for the purpose of Cleaning Performance Qualification is demonstrated at a concentration of approximately (b) (4) parts per billion. The specified limit of (b) (4) on manufacturing equipment surfaces after cleaning is (b) (4) parts per billion. The recovery of (b) (4) at a concentration of approximately (b) (4) parts per billion is not adequate to qualify cleaning procedures specified to meet a criterion of less than (b) (4) parts per billion (b) (4) remaining on equipment surfaces after cleaning.

3) Due to the lack of an adequate concentration to demonstrate recovery of (b) (4), cleaning performance of (b) (4) manufacturing equipment is not qualified.

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B) Analytical Method transfers do not include specific criteria and do not document review of method validations.

1) The qualification of a (b) (4) analytical method, "Qualification of Analytical Testing for (b) (4) (b) (4))," Acceptance Report 06-120-A-1, specifies an acceptance criterion of a "(b) (4) " of data without an explanation of how the review will be conducted or what will make the data "(b) (4) "

2) There is no documented review by the firm of the method validation for test procedure " (b) (4) (b) (4) " described in SOP 303.196 for the analytical testing of (b) (4) drug product.

3) There is no documented review by the firm of the method validation for test procedure " (b) (4) " described in SOP 303.196 for the analytical testing of (b) (4) drug product.

C) There is no validation of (b) (4) incubation of TSA-32 ml plates used in the viable environmental monitoring (EM) of ISO classified areas. The firm has no assurance that (b) (4) incubation can support the optimal recovery of yeast and mold species that otherwise thrive at ambient temperature.

D) In-house environmental isolates are not routinely included in the media fill growth promotion of Soybean Casein Digest (SCD) broth after (b) (4) of media fill incubation. Per SOP 404.3, R-27 "Growth Promotion Testing", Attachment 1, (b) (4) .

E) In-house environmental isolates were not included in the growth promotion of TSA-32ml and TSA-80 (b) (4) plates. Per SOP 404.3, R-27 "Growth Promotion Testing", Attachment 2, TSA-32ml and TSA-80 (b) (4) are used in the recovery and enumeration of viable environmental microorganisms present in ISO classified clean rooms.

OBSERVATION 9

Written procedures are lacking which describe in sufficient detail the receipt, storage, handling, testing, approval, and rejection of components.

Specifically, the firm has no assurance that materials, reagents, and accessories purchased and utilized in the Microbiology QC Laboratory are qualified, tracked, and suitable for the intended use. There is no written procedure in place for the receiving and handling of reagents, media, reference isolates, and accessories used in the Microbiology QC Laboratory (MQC). The MQC responsibilities include but are not limited to the quality testing and release of in-process and final drug products.

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Rajesh Kapoor, Ph.D., Global Head, Quality

FIRM NAME	STREET ADDRESS
Jubilant HollisterStier, LLC	3525 N Regal St
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Spokane, WA 99207-5788	Contract drug manufacturer

OBSERVATION 10

Laboratory written procedures are not followed to ensure that the lab equipment is routinely calibrated.

Specifically, the dedicated Microbiology Quality Control pH meter (pH Meter 62) was routinely used while out of calibration for testing of microbiological media, endotoxin reagents, and (b) (4) reagents (Microbial Identification) between 07/03/2013 and 03/25/2014. All testing of microbiological media, endotoxin reagents, and (b) (4) reagents at the site during the specified timeframe would be affected.

OBSERVATION 11

Laboratory records do not include the date(s) the tests were performed.

Specifically, the firm cannot assure the integrity and validity of data generated by the firm's QC Laboratory. During inspection of the Microbiology Laboratory on 03/28/2014, we found SOP 402.15, R 16, Attachment 5-General Bacterial Isolate Identification Data Sheet lacked a run date in an information field for sample CRSS#: 1S14-3919 that was being analyzed by the (b) (4) instrument and requested a copy of the deficient document. On 03/31/2014, a copy of the document was provided to us with the run date, "3·27·14" entered into the previous blank information field. There were no initials, date, or explanation on the document to show when/why/by whom the information was entered into the blank field. Without accurate documentation, data generated by the firm's QC Laboratory are **not reliable.**

OBSERVATION 12

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, the firm cannot assure total aerobic microbial count (TAMC) and total yeast and mold count (TYMC) of component raw materials are reliable and accurate. SOP 401.16, R 17 governs the firm's Microbial Limits Test for TAMC and TYMC of component raw materials. SOP 401.16, R 17 references USP <61>, Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests. However, the firm fails to follow growth promotion (GP) criteria per USP <61> for Trypticase Soy Agar (TSA) and Sabouraud Dextrose Agar (SAB) used in microbial limits testing. Per USP <61>, growth obtained on solid media must not differ by a factor greater than 2 from the calculated value for a standardized inoculum. The firm's GP acceptance criteria for TSA and SAB are uniformly defined as < (b) (4) CFU of the standardized inoculum. Without proper GP of the test media, the firm cannot assure TAMC and TYMC of component raw materials are reliable and accurate.

QUALITY CONTROL SYSTEM

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OBSERVATION 13

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

Specifically,

A) Product-contact-surface equipment cleaning validations were not based on product specific or component specific risk assessments for why the evaluation methods were used or the acceptance limits were chosen. There is no routine or periodic monitoring of the adequacy of the product-contact-surface equipment cleaning procedures. A written statement "Product-Contact Cleaning" dated 4/9/14 reads in part "*** At this time, none of these products have cleaning verification analytical samples pulled on a routine or requalification basis ***".

1) A written statement "Product Dedicated Cleaning Validation Overview", dated 4/11/14, reads in part "*** ((b) (4) ***". A written statement "Product-Contact Cleaning" dated 4/9/14 reads in part "***(b) (4) ***. The 4/9/14 and 4/11/14 statements list the following products as being manufactured in dedicated equipment: (b) (4) (b) (b) (4)); (b) (4) (b) (b) (4)); (b) (4) (b) (b) (4)); (b) (4) (b) (b) (4) (BLA (b) (4)); (b) (4) (NDA(b) (4)); (b) (4) ((b) (b) (4)); (b) (4) (BLA (b) (4)); (b) (4) (b) (b) (4)); (b) (4) (b) (b) (4)); (b) (4) i(b) (4) (b) (4)); and (b) (4) (b) (b) (4)).

2) A written statement "(b) (4) Cleaning Validation Overview" dated 4/11/14 reads in part "*** The product-contact equipment ((b) (4) Filling Pumps and Product Vessel) used to manufacture (b) (4) are shared between these (b) products at the customer's request ***(b) (4) ***". A written statement "Product-Contact Cleaning" dated 4/9/14 reads in part "*** The product-contact equipment (Filling Pumps and Product Vessel) used to manufacture (b) (4) are shared between these (b) products at the customer's request *** At this time, none of these products have cleaning verification analytical samples pulled on a routine or requalfication basis ***".

3) A written statement "Diluent Dedicated (b) (4) Cleaning Validation Overview" dated 4/11/14 reads in part "***(b) (4) ***(b) (4) ***". The following(b) (4) and(b) (4) are representative examples relevant to tank (b) (4) from the written statement "Product-Contact Cleaning" dated 4/9/14: (b) (4) (b) (b) (4) ; (b) (4) (b) (b) (4)),(b) (b) (4)

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(b) (4));(b) (4) (b) (4)); (b) (4) (b) (b) (4)); and (b) (4) (b) (4) (b) (4)

B) Performance Qualification# 09-077-P-0, titled: Mixing/Holding Verification for (b) (4) dated September 29, 2009 executed record 09-077-P-2 dated April 11, 2011 for the volume increase in (b) (4) batch size from volume of (b) (4) manufactured in a (b) (4) to volume of (b) (4) manufactured in a new (b) (4) is inadequate. Total of (b) (4) batches of (b) (4) volume have been manufactured since the qualification, (b) (4) of which have been released: (b) (4) ; (b) (4) (b) (4)) dated (b) (4) (b) (4) . (b) (4) batches manufactured were rejected: batch # (b) (4) dated July 09, 2013 is currently on hold/to be rejected for OOS peak (b) (4) mpurities Index and (b) (4) dated November 06, 2013 was rejected due to multiple excursions, i.e., product leakage during filling on (b) (4) For example:

1) There are no mixing studies that include the qualifications of different mixing times, temperatures, speed and the determination of the optimum mixing times, temperatures and speed for each of the critical mixing times noted in the (b) (4) batch record for the excipients. Only a combined mixing time of (b) (4) (b) (4) were demonstrated on (b) (4) batches of (b) (4) using only excipients and containing no (b) (4) API) and (b) batch mixing study was conducted with (b) (4) API in tank (b) (4) . No justification was provided for the use of (b) (4) (b) (4) instead of the mixing times provided in the various sections of the used (b) (4) Manufacturing Batch Record #1830.1 R15 dated October 11, 2013.

2) Although there was a change in manufacturing of the (b) (4) batch, such as: equipment; weight of the (b) (4) API used in the manufacture of (b) (4) was increased from (b) (4) mg (b) (4) (to (b) (4) (b) (b) (4) (b) and increases in all of the quantities of (b) (4) compounding excipients, however, all of the process times for the currently used (b) (4) in the manufacture of (b) (4) including mixing times indications of only NLT (Not Less Than) in the batch record remained the same for the increased batch size (b) (4) as the previously manufactured (b) (4) batch size. There is no documentation with justifiable equivalencies and/or comparisons between these (b) (b) (4) manufacturing sizes for the use of the same manufacturing (b) (4) in the batch record.

3) Although the above Performance Qualification #09-077-P-0 dated September 29, 2009 mixing study, was to demonstrate the homogeneity of (b) (4) excipients solution prior to adding (b) (4) (b) (4) in the (b) (4) the referenced sampling instructions in the protocol: SOP 101.103 R1, dated October 03, 2011, titled: Sampling of Bulk Product Vessels, failed to specify all of the sampling locations of the tank that the (b) (4) samples ranging from (b) (b to (b) (4) (b will be pulled for testing from the (b) (4) (b) (4) of the mixing process with justifications provided to assure consistency in the sampling process by the firm's personnel.

adequate CVO 4/15/2014

C) There is no credible data or study to support the decision not to cull out (b) (4) product vials with product on the vial shoulders. Per (b) (4) Manufacturing SOP 1830.1 Revision 15 dated October 11, 2013, "Product on the vial shoulder is an acceptable vial and should not be rejected". For example: Incidence (INC) Report #20130287 dated August 16, 2013 for

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(b) (4) batch # (b) (4) dated July 18, 2013 ((b) (4)), noted that product on shoulders of vials is caused by improper product dispensing from the nozzles and conveyance issues in that, product can dispense on the vial wall or product can splash into the neck of the vial as a result of slight shaking of the conveyance belt. However, the firm failed to institute adequate corrective and preventive actions and instead chose to remove the vials with product on shoulders as a "Major" vial defect. So far (b) (4) batches ((b) (4) (b) (4) have been released with revision #15 to the above SOP, which considers the defective vials acceptable. The following are examples of deficiencies noted in the study, which was used to make the decision not to cull out products on (b) (4) vial shoulder:

1) Study dated August 01 2013, titled: (b) (4) Lot (b) (4) Potency, Dosage Uniformity and Container/Closure Integrity for Samples Exhibiting (b) Visual Inspection Defects, protocol lacks enough documentation as to how the study will be conducted including the interpretations and acceptance of the test results.

2) There are no statistical justifications for the use of (b) (4) product batch for the study.

3) The numbers of vials used for the study are not representative of the numbers of vials manufactured per batch of (b) (4) and no statistical rationale was provided. For example, (b) (4) vials of (b) (4) batch # (b) (4) ((b) (4)) dated February 27, 2013 were manufactured, however, potency, purity and dosage uniformity testing was performed on total of (b) (4) vials out of the (b) (4) vials inspected.

4) The numbers of rejected vials used for the study are not representative of the numbers of vials rejected and no statistical justification was provided. Total of (b) (4) rejected vials were culled out for product on shoulder of vials and (b) (4) rejected vials were culled out for product between shoulder and neck of vials for (b) (4) batch (b) (4). However, potency, purity and dosage uniformity testing was performed on total of (b) (4) vials that were rejected for product on the shoulder of the vials and (b) (4) vials that were rejected for product between the stopper and the neck of the vials.

D) There is no procedure in place specific to the documentation of Change Control for manufacturing process changes that includes, risk assessments and the determination if validation or verification will be appropriate for the changes made to manufacturing processes. Per the firm's management, changes to manufacturing processes are made using procedural changes. For example:

1) There is no documentation of Change Control for the increase in (b) (4) batch volume size from (b) (4) manufactured in a (b) (4) to volume of (b) (4) manufactured in a new (b) (4) (b) (4) Changes to the increase in (b) (4) manufacturing volume from (b) (4) To (b) (4) was documented under Procedural Change Document Control #1830.1, R 15, dated October 11, 2013.

2) There is no documentation of change control for the change made to (b) (4) to consider Product on the vial shoulder as an acceptable vial that should not be rejected, per the (b) (4) Manufacturing SOP 1830.1 Revision 15, dated October 11, 2013.

3) There are no documented change controls for changes made to sterile Drug Products Manufacturing batch records. For example: no documentations of change controls for the revisions #1-16 made to (b) (4) Manufacturing Batch Record 1830.1; for revisions #1-3 made to (b) (4) Manufacturing Batch Record 1855.1 and change controls for revisions #1-8 made to (b) (4) Manufacturing Batch Record 1833.1.

OBSERVATION 14

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

Specifically,

A) Internal audits failed to detect deficiencies in the QC Microbiology laboratory (MQC). SOP 303.203 "QC Laboratory Internal Audit Program", R-3 issued 12/22/11, which was used to review safety, general laboratory housekeeping and organization, and compliance with cGMP was not sufficient in scope to self-audit the deficiencies detected in the MQC laboratory. SOP 102.9 "Internal Audit Program", R-19 issued 10/14/13, used to ensure continued compliance with cGMPs, failed to detect the following MQC laboratory deficiencies:

1) An unauthorized method, SOP 405.21 (b) (4) ", R-6 issued 2/14/11, was the only test method used to determine if sterility test samples and media fill vials identified as "visual abnormalities", "questionable possible growth", and "precipitate" were contaminated with microbial growth. SOP 405.21 was not included as a test method for the determination of microbial contamination in SOP 404.22 "Sterility Test Failure Investigation", R-10 issued 10/17/11; or in SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13; or SOP 404.20 "Media Fill Master Plan for Qualification of Aseptic Processing", R-25 issued 12/5/13. SOP 405.21 was not included as a test method in the Product Specifications, section Test, Sterility Test. There was no documented validation to demonstrate SOP 405.21, R-6, Attachment 4 "(b) (4) of Samples from Sterility Test" was suitable to determine microbial contamination in Soybean-Casein Digest Medium (SCD) or Fluid Thioglycollate Medium (FTM) by Gram stain evaluation. Under SOP 405.21, R-6, Attachment 4, (b) (4) The sterility test samples and media fill vials with suspected microbial contamination were discarded after the results were interpreted.

2) Internal sample custody was not maintained for sterility test samples and media fill vials designated "turbid", "visual abnormalities", "questionable possible growth", and "precipitate" in accordance with SOP 303.87 "Receipt and Handling of Samples in the Jubilant HollisterStier Reference and Sample Storage Area", R-11 issued 3/19/12. SOP 303.87 section 1.2 reads in part "*** control of samples *** is necessary to ensure the integrity and usability of these samples ***". SOP 303.87 section 3.2 reads in part "*** Internal test samples *** includes samples generated during the execution of any HS SOP, protocol or engineering study ***". The transfer of custody for turbid and abnormal sterility test samples and media fill vials from Room (b) (4) where the samples were interpreted by sterility test technicians to the Microbiology Lab Room (b) (4) where they were to be further tested by microbiologists was not

documented in the SOP 303.87 Attachment 3 - CRSS Internal Sample Receipt Log. The CRSS (central references and standards storage) room is where the test sample tracking log is maintained. The practice of not tracking turbid or suspected growth sterility test samples and media fill vials is in contrast to the media fill growth promotion vials that require CRSS sample tracking in accordance with SOP 404.20 "Media Fill Master Plan for Qualification of Aseptic Processing", R-25 issued 12/5/13, Attachment 9 for the same sample custody transfer.

3) SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13 provides directions to document suspect microbial contamination in ways that are not part of the permanent testing record. As a practice, the firm documents visual abnormalities on a disposable container. The culture canisters and vials are discarded, and the marked information is not otherwise retained as a permanent record. As a practice, no visual abnormality observations were documented on the worksheets. SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13, Attachment 1 section 4.3 reads in part:

a) "*** When performing (b) (4) s if visual abnormalities are observed mark culture canister/bottle with short description initial and date ***". The SOP 404.40 documentation instructions are in conflict with SOP 102.94 "Standards for Recording Data on a Controlled Document", R-12 issued 10/29/12, which reads in part "*** Standards are necessary for collecting, recording and correcting data on controlled documents to ensure accuracy, integrity and traceability of all data pertinent to a manufactured batch of product ***".

b) "*** Any bottle of questionable possible growth will be checked by one of the Microbiologists or MQC Supervisor ***". Sterility test technicians interviewed stated they were instructed to notify the supervisor or MQC Manager by phone to come and check the questionable units. There was no documentation a Microbiologist, the MQC Supervisor or MQC Manager were notified of the need to check suspect units. There was no documentation the suspect units were checked.

B) The document "Hiring Process", without version control and undated, does not have documented quality unit review and approval. There is no written procedure for quality unit review and approval of job position qualifications and job descriptions for personnel to ensure personnel will have the education and experience required to successfully perform GMP operations.

C) The quality unit failed to establish approved procedures for the management of contract service providers with access to GMP areas. There is no documented quality unit oversight for (b) (4) contracted to supply cleanroom garments (sterile gowns) to ensure there is no impact to GMP areas. Sterile gowns are used in all aseptic processing areas. (b) (4) provides On-Site Coordinators to deliver garments to gowning rooms. No documentation could be provided to show when contracted employees were on site or their designated reporting relationship to someone at JHS.

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OBSERVATION 15

The quality control unit lacks authority to review production records to assure that no errors have occurred.

[REPEAT OBSERVATION, 5/10/13 Observation 2]
Specifically,

A) The 12/19/13 Jubilant HollisterStier Warning Letter response included a "Facility Impact Assessment" with "Table 1. Media Fill History at JHS-Spokane from Jan 2012 to Nov 2013" followed by a statement which reads in part "*** There have been no failures in process simulations ***".

1) Table 1 includes container closure integrity studies which are not designed to simulate aseptic commercial production. SOP 404.20 "Media Fill Master Plan for Qualification of Aseptic Processing", R-25 issued 12/5/13, Attachment 1 section Media Fill Types reads in part "***(b) (4) ***". SOP 404.20 Attachment 1 section Media Fill Types reads in part "*** (b) (4) ***(b) (4) ***".

2) Table 1 includes at least (b) media fill process simulations which were conducted before shutdown of the aseptic filling lines and cannot be relied on to represent aseptic process control after shutdown. Commercial production resumed after shutdown and there was a period of time before the next performance qualification media fills were run. The following are only representative examples of the sequence for aseptic filling line shutdown, the manufacture of commercial batches after the shutdown, and the next performance qualification media fills on the aseptic filling lines used to manufacture CDER-regulated products.

a) The (b) (4) performance qualification media fill batch C1200102 shows a media fill start date of 4/5/12, the Spring 2012 shutdown was 4/7/12 to 4/16/12, (b) (4) batch (b) (4) was aseptically filled on 4/25/12, and the next performance qualification media fill batch C1200279 shows a media fill start date of 10/18/12.

b) The (b) (4) performance qualification media fill batch D1200046 shows a media fill start date of 3/31/12, the Spring 2012 shutdown was 4/2/12 to 4/12/12, (b) (4) (b) (4) batch (b) (4) was fill date 4/24/12, and the next performance qualification media fill batch D1200111 shows a media fill start date of 7/26/12.

c) The (b) (4) performance qualification media fill batch E1200574 shows a media fill start date of 2/16/12, the (b) (4) Spring 2012 shutdown was 4/7/12 to 4/10/12, (b) (4) batch (b) (4) was fill date 4/18/12, and

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the next performance qualification media fill batch E1202590 shows a media fill start date of 6/6/12.

d) The (b) (4) performance qualification media fill batch E1202590 shows a media fill start date of 6/6/12, the (b) (4) Fall 2012 shutdown was 10/20/12 to 10/27/12, (b) (4) batch (b) (4) was fill date 11/14/2012, and the next performance qualification media fill batch A1300007 shows a media fill start date of 1/11/13.

B) Sterility test technicians reported the practice of documenting a no growth stamp (b) (4) date stamp) on sterility test worksheets or media fill interpretation records when a sterility test sample or media fill vial was visually abnormal. SOP 404.40 "Sterility Test: Reading, Recording, and Release", R-12 issued 1/21/13, Attachment 4 step 1.4 reads in part "*** A date stamp (b) (4) is used to denote a negative (no growth) Sterility Test result (negative growth stamp) ***". The sterility test technicians interviewed said they put a date stamp (b) (4) on sterility test and media fill worksheets after they observed units with visual abnormalities per management instructions, and because the units would continue to be incubated until (b) (4). Further, sterility test technicians reported a practice of being notified by a supervisor or microbiologist to document a passing notation (b) (4) date stamp) on sterility test worksheets after abnormal sterility test samples or media fill vials were reviewed and reportedly determined to be negative.

C) There were discrepancies in the information reported to FDA during the inspection. On 4/11/14 about mid-day a memo "Sterility Test Canisters/Bottles" was provided to FDA CSOs which reads in part "*** Jubilant HollisterStier uses the (b) (4) ***". The CSOs requested a copy of BAM R32, found that the test procedure was intended to be used for food samples, and requested documentation that BAM R32 was validated as suitable for the intended use to determine if pharmaceutical sterility test samples and media fill units were contaminated with microbial growth. At the end of the day, a second memo "Sterility Test Canisters/Bottles" was provided to FDA CSOs which omitted the statement for the use of BAM R32 and included a section reading in part "*** SOP 405.21 (b) (4) *** contains instructions [redacted] are housed in SOP 402.15 *** The SOP is not cross referenced in SOPs 404.40, 404.22 nor 402.15 ***".

D) The firm cannot assure the integrity and validity of data generated by the firm's QC Laboratory. During inspection of the Microbiology Laboratory on 03/28/2014, we found SOP 402.15, R 16, Attachment 5-General Bacterial Isolate Identification Data Sheet lacked a run date in an information field for sample CRSS#: 1S14-3919 that was being analyzed by the (b) (4) instrument. A copy request was made for the deficient document. On 03/31/2014, a copy of the document was provided with the run date "3·27·14" entered into the previous blank information field. There were no initials, date, or explanation on the document to show when, why, by whom the information was entered into the blank field. Without concurrent documentation and good documentation practices, data generated by the firm's QC Laboratory are not reliable.

OBSERVATION 16

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

Specifically, the firm failed to document the sterility test technicians and their supervisor were adequately trained for their job

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role to detect contaminated sterility test samples and media fill vials. The Job Description Form MQC Sterility Test Technician (QL1292) requires a high school diploma or equivalent and 1 to 5 years of related experience. The Job Description form QL1292 is silent on minimal requirements for education or experience to interpret microbial contamination in sterility test samples and media fill units. QL1292 reads in part "*** This position requires 1 to 5 years of aseptic processing experience. Experience must include aseptic technique, clean room gowning practices, and cGMP based documentation skills. ***". QL1292 accountability reads in part "*** Incumbent will perform the sterility test, read the sterility tests at set incubation periods (check for contamination) and enter results ***".

A) Sterility test technician training documentation was deficient for personnel currently interpreting sterility test samples and media fill vials.

1) One sterility test technician had no documented initial comprehensive training for the practical aspects of sterility testing, detecting contamination in sterility test samples and media fill vials, and the demonstration of proper viewing technique for unit assessment as required by SOP 404.2 "MQC Sterility Testing and Inspection Training Outlines", R-6 issued 9/12/06.

2) (b) (4) sterility test technicians had no documented attendance for an observation session to view growth of different microorganisms in FTM and SCD with a MQC Microbiologist as required by SOP 404.2 section 3.b.1.

3) (b) sterility test technician who interpreted media fill vials failed to have documented supervisor approval for SOP 404.2 Attachment 6 section e. Reading and Release: sterile media fills.

B) There is no written SOP to describe specifically what microorganisms to use for microbiological training demonstrations or how to prepare the examples of microbial growth used to train sterility test technicians with minimal or no formal education in microbiology. The microbiological training sets are required by SOP 404.2 section 3 b Microbiology Training and SOP 404.2 Attachment 7 - Training Documentation Media Turbidity Test. The microbiological training sets were not prepared using a written procedure to ensure the training sets were:

1) appropriate to demonstrate the variety of physical characteristics displayed by microorganisms isolated from within the aseptic filling environments.

2) representative of the commercial production test conditions.

C) The QC laboratory failed to review and approve QC laboratory trainers to assure the trainers are qualified to detect contaminated sterility test samples and media fill vials or demonstrate proper viewing technique for unit assessment. The Microbiology QC laboratory SOP 404.2 "MQC Sterility Testing and Inspection Training Outlines", R-6 issued 9/12/06, Attachment 1 step 2 reads in part "*** Training is to be conducted by a currently trained and experienced technician, and/or by MQC Supervisor ***". The QC laboratory SOP 302.122 "Laboratory Training Program", R-7 issued 2/24/14, section 3.1 reads in part "*** Qualified Trainers - Persons who are knowledgeable in and regularly perform the procedures in which they instruct others ***". The Microbiology QC Manager and the QC Director confirmed there is no review and approval process for QC laboratory trainers.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Barbara J. Breithaupt, M.A., Consumer Safety Officer Omotunde O. Osunsanmi, Consumer Safety Officer Andrew J. Idzior, Chemist Eileen A. Liu, Microbiologist Mark W. Babbitt, Consumer Safety Officer	BJB EL MWB OO 04/15/2014

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
22215 26th Ave SE Suite 210 Bothell, WA 98021 (425) 302-0340 Fax:(425) 302-0404 Industry Information: www.fda.gov/oc/industry	03/26/2014 - 04/15/2014 FEI NUMBER 3010477

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Rajesh Kapoor, Ph.D., Global Head, Quality

FIRM NAME	STREET ADDRESS
Jubilant HollisterStier, LLC	3525 N Regal St
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Spokane, WA 99207-5788	Contract drug manufacturer

PRODUCTION SYSTEM

OBSERVATION 17

The in process control procedures were deficient in that they did not include an examination of the adequacy of mixing to assure uniformity and homogeneity.

Specifically, the following deficiencies were noted in the manufacturing process controls for sterile Drug Products:

A) Minimum and/or maximum mixing times are not indicated in the (b) (4) Manufacturing Batch Record #1803.1, Revision #16 dated October 11, 2013 for critical formulation steps of (b) (4) , a (b) (4) used for (b) (4) (b) (4) , manufacturing process:

1) There is no maximum time in the batch record that (b) (4) API) can be (b) (4) and placed in (b) (4) ((b) (4) before use. Only minimum time of Not Less Than (NLT) (b) (4) is indicated in the batch record Attachment 27, Procedure #34.

2) There is no maximum time in the batch record, Procedure #25 for the "Addition of (b) (4) API), (b) (4) "; only minimum mixing time of NLT (b) (4) minutes is provided, no maximum mixing time is indicated.

3) There is no minimum time in the batch record for the additional mixing step #47 and 48 to assure that the formulated (b) (4) batch solution is essentially free of (b) (4) . Only maximum mixing time of Not More Than (NMT) (b) (4) is indicated.

4) There are no minimum and maximum mixing times defined for several of the (b) (4) critical manufacturing/formulation steps. For example, Attachment #27, Procedure #15, 16, 17 and 18.

5) There is no maximum time defined in (b) (4) batch record, Procedure #35, (b) (4) : only minimum (b) (4) start time and (b) (4) End Time of NLT (b) (4) minutes is indicated.

B) There are no documented data to support the mixing times, speed and temperature indicated in the batch record for (b) (4) several manufacturing steps including the mixing of (b) (4) API (b) (4) with excipients during the manufacture of (b) (4) , item # (b) (4) , currently used Batch Record #1833.1, Revision #8 dated February 10, 2014.

C) There are no documented data in the batch record to support the mixing times, speed and temperatures indicated for the several manufacturing steps including the mixing of the (b) (4) API (b) (4) with (b) (4) in the currently used (b) (4) Material Part # (b) (4) , Batch Record #1855.1 Revision #3, dated December 16, 2013, a (b) (4)

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(b) (4) indicated for use (b) (4) (b) (4) for the (b) (4) of (b) (4) (b) (4).

D) There are no documented data in the current (b) (4) Material # (b) (4) Batch Record 1852.2 Revision 1, dated July 30, 2012 to adequately support the mixing times, speed and temperatures indicated for the several manufacturing steps including the mixing of the (b) (4) during the manufacture of sterile (b) (4), which is indicated for use as (b) (4) (b) (4). In addition, there are no maximum times indicated in the batch record for the several mixing steps, only minimum mixing time of NLT are provided. The review of the conformance batches revealed the indications of both minimum (NLT) and maximum (NMT) mixing times. However, the review of the process validations of the conformance batches disclosed the lack of data to justify the maximum mixing times, temperatures and speed indicated in the conformance lots batch records.

OBSERVATION 18

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

Specifically,

A) [REPEAT OBSERVATION, 5/10/13 Observation 4(a)] SOP 101.74 "General Cleaning, Sanitization and Disinfection of Aseptic and Controlled Areas" used to clean the ISO 5 and ISO 6 areas before set-up of the aseptic filling lines lacks adequate detail to sequence cleaning tasks, provide instruction for wiping contours of the equipment in the ISO 5 aseptic filling area, and manage cleaning supplies. On 4/2/14, we observed the area cleaning of (b) (4) prior to setup for aseptic filling of (b) (4) (b) (4) solution Lot (b) (4). We observed the following deficiencies:

1) Aseptic process technicians walked over the wet mopped floor in the ISO 6 area to wipe surfaces inside the ISO 5 areas.

2) Non-sterile buckets were used to contain (b) (4) for the cleaning of ISO5 critical manufacturing areas. There was no documentation to verify the buckets had either been disinfected, or sanitized, or cleaned prior to addition of (b) (4). Further, the bucket of cleaning solution, previously in the ISO 6 area, was placed on the ISO 5 outfeed accumulator table while the operator was cleaning ISO 5 surfaces.

3) Aseptic process technicians were observed topically wiping contoured surfaces by laying a wipe flat in the hand and making a single pass with no apparent effort to clean concave surfaces.

4) A sterile mop pad used to clean internal ISO5 rigid barrier panels was seen consistently returning back to the same bucket containing (b) (4) after cleaning each section of the ridged barrier panels.

B) Procedures used to control aseptic processes are deficient in that there are no operator directions to minimize the time

rigid barrier doors are open. On 4/2/14, we observed aseptic process technicians cleaning (b) (4) prior to setup for aseptic filling of (b) (4) solution Lot (b) (4) (b) different aseptic process technicians were observed to walk away from the filling line leaving the rigid barrier doors open when no operations were being performed in the ISO 5 area. During the inspection, the firm reviewed their SOPs and proposed the following SOPs; however none of these procedures included instructions to close the rigid barriers around the ISO 5 areas as soon as practical or when not working in the ISO 5 area:

1) SOP 101.66 "Aseptic Technique", R-20 issued 12/23/13.

2) SOP 706.17 "Filling and Stoppering Equipment for (b) (4) ", R-67 issued 3/5/14.

3) SOP 707.2 "Loading and Un-loading of the (b) (4) Commercial Lyophilizers", R-18 issued 9/16/13.

C) Surfaces within ISO 6 areas containing ISO 5 areas are only cleaned upon request. SOP 101.74 "General Cleaning, Sanitization and Disinfection of Aseptic and Controlled Areas", R-43 issued 3/24/14, Attachment 4 section 1.2.5 reads in part "*** Ceilings are cleaned (b) (4) under SOP 402.12 ***". A statement "Review for Cleaning of Ceilings in ISO6/ISO7 Rooms Containing ISO 5 Areas" dated 4/4/14 reads in part "*** There is no documented re(b) for sanitization/disinfection of the ceilings containing (b) (4) ***". Diagrams (b) (4) show (b) (4) ceilings are located in the following ISO 6 rooms which contain ISO 5 areas (b) (4) ((b) (4) (b) (4) ((b) (4) and (b) (4) ((b) (4)

D) On 4/2/14 (b) (4) was set up for aseptic filling of (b) (4) (b) (4) batch (b) (4) . Management said the aseptic filling operations would be delayed; however there was no validated hold time for the period after (b) (4) was cleaned and set up for aseptic filling and before aseptic filling operations could be initiated for (b) (4) (b) (4). This is a representative example; an exhaustive determination for the lack of a stated duration after cleaning and filling line setup and before aseptic filling operations are initiated.