DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738 Industry Information: www.fda.gov/oc/industry	7/27/2017-8/4/2017* FEI NUMBER 3004610460

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Dr. Jacqueline A. Kunzler, Global Head of Quality

FIRM NAME	STREET ADDRESS
Claris Injectables Limited	Chacharwadi Vasna
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382213 - India	TYPE ESTABLISHMENT INSPECTED Terminally Sterilized Pharmaceutical Manufacturer

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

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Electronic records do not support the authenticity of environmental monitoring:

a. (b) (4) data does not support documentation of environmental monitoring. Specifically, data in the (b) (4) system that registers entry into classified areas by (b) (4) access does not support the integrity or accuracy of paper based environmental monitoring reports. For example, per (b) (4) data the following individuals were absent from rooms where environmental monitoring purportedly occurred:

Item	Date	Operator	Line	(b) (4) Affected Batch
i	January 4, 2017	(b) (6)	Line (b) (4)	(b) (4)
ii	January 4, 2017		Line	
iii	January 6, 2017		Line	N/A
iv	January 1, 2017		Line	(b) (4)
v	January 9, 2017		Line	
vi	January 10, 2017		Line	

(vii) Document "Report of Environment Monitoring By Settle Plate for (b) (4) Line" capturing the environmental monitoring of Line (b) (4) for January 6, 2017 specifies that operator (b) (6) conducted environmental monitoring for (b) (4). However, the (b) (4) system fails to support that this operator entered the room during those times. Specifically, the (b) (4) data indicates (b) (6) entered the (b) (4) line at (b) (4) on January 6, 2017, however, the environmental monitoring documentation reports they were there throughout the 17:00 hour.

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Similar examples in June 2017 were noted, as evidenced by "Report of Environment Monitoring By Settle Plate" documents dated June 14, 18, 22 and 29.

Further, operator (b) (6) has no history in the (b) (4) system to support that they ever entered these areas to conduct environmental monitoring. Similarly, operator (b) (6) who is documented as conducting environmental monitoring in June 2017 has no history in the (b) (4) system.

A written statement was provided that explained "as of today that there are inconsistencies in the recording of (b) (4) controls in the 'Environmental Monitoring' area of the Claris Facility to the existing physical log books."

b. Electronic attendance records to support employee entrance to the facilities fail to support environmental monitoring. Specifically, environmental monitoring records indicate that environmental monitoring was conducted by personnel who were not denoted as present by this attendance system. Examples follow:

Date	Operator	Line (b) (4)	Affected Batch
January 9, 2017	(b) (6)	Line (b) (4)	(b) (4)
January 10, 2017		Line	
		Line	
January 12, 2017		Line	
		Line	N/A
January 13, 2017		Line	N/A
January 15, 2017		Line	(b) (4)
		Line	N/A

The Senior Manager – Quality Assurance and Junior Manager – Microbiologist confirmed the discrepancies between the electronic attendance records versus the environmental monitoring records.

Firm management provided a paper based "Attendance Sheet for the month of Jan'2017" to explain the aforementioned inconsistencies between the attendance and environmental monitoring records. The Associate Vice President – Human Resource Management acknowledged that the

paper based records exhibits inconsistencies with the electronic system. On July 29, 2017, the "Attendance Sheet for the month of June'2017" was obtained and appears incomplete.

Note: (b) (4) data does not support that individuals noted in the table above were on the premise during the purported environmental monitoring. Rather, (b) (4) data supports the attendance record that the individuals were not present.

c. The Senior Microbiologist is responsible for observation of Environmental Monitoring (EM) plates. On July 31, 2017, Senior Microbiologist was provided with various "Environmental Monitoring By Settle Plate" forms with multiple variations of signatures documenting the same person. The Senior Microbiologist explained all of these signatures were his, but was unable to sign in a manner consistent with what was captured in all of the documents. The Vice President, Corporate Quality Assurance identified this individual as the person who signs with "three different names [signatures]" in environmental monitoring records.

OBSERVATION 2

Controlled documents are not appropriately controlled:

a. On July 27, 2017, Operator (b) (6) was observed backdating the Quality Assurance "Visual Inspection Test For (b) (4) Line" for (b) (4) Injection USP batch (b) (4) in the production area of the firm's facility. For example:

a.1 - Section D titled "Manual VIT at the time of Loading" indicates a visual inspection test was completed on July 26, 2017, however, the corresponding data is missing. On July 27, 2017, Operator (b) (6) was observed completing this document.

a.2 - Section E titled "Visual Inspection Record For (b) (4) Machine (Automatic Visual Inspection Machine)" indicates a visual inspection was completed on July 26, 2017 that was signed as "Checked by Packaging", however, the corresponding data is missing. On July 27, 2017, Operator (b) (6) was observed completing this document.

When asked about these discrepancies, the Deputy General Manager stated "I don't know".

SOP CF/CQA/003 titled "Good Documentation Practice" stipulates that "Back date entries are never permitted."

b. On July 28, 2017, official, original documentation were observed in the "scrap" area of the (b) (4) (b) (4) building (the area used for the manufacture of US products):

b.1 - Regarding a manually torn document with an original signed "Checked By" section, the Vice President, Quality stated that the document appears to be a quality investigation. No additional information regarding the signature or contents of the torn document was provided.

b.2 - In addition, there were manually torn pages with unexplained calculations and lot information.

c. On August 2, 2017, the Senior Manager of Quality Assurance provided identical versions of endotoxin testing reports for lot (b) (4) and (b) (4) (both at time 3:26:03PM) containing unique signatures and writing styles. The dating and timing on both versions is purported to be identical.

d. A paper shredder is maintained in the Quality Assurance area of the (b) (4) building (the area used for the manufacture of US products). The Senior Vice President – Manufacturing & Operations stated this shredder is utilized for "labels" and "printer errors". However, upon reviewing the paper shreds, we identified writing and stamps on the documents. Documentation supporting the content and reconciliation of destroyed documents was not available.

e. There are (b) (4) paper shredders located in the following departments / locations i.e., packing department, QA/IPQA department, QA laboratory, in-coming materials warehouse and in the Corporate QA department. The Deputy General Manager Compliance confirmed that the departments do not register and/or maintain a record of all of the documents and paper records that are shredded.

OBSERVATION 3

Complaint follow-up is deficient:

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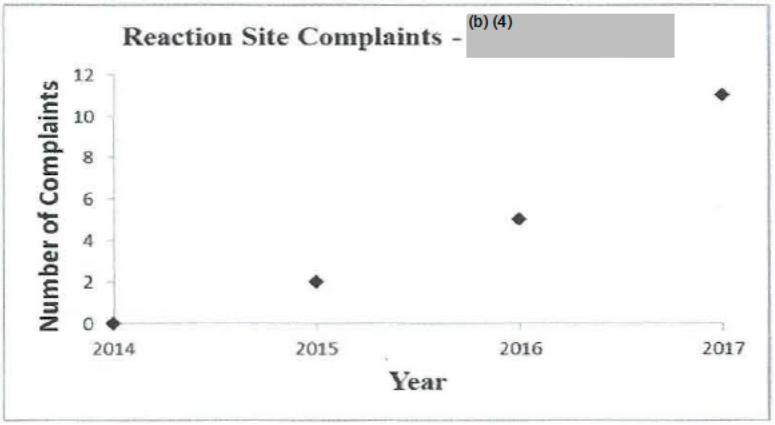
In 2017, complaints were opened for (b) (4) Injection USP (b) (4) mg/ml for injection site reactions such that the veins became red. For example, these complaints were attributed to "administration procedure" with no requisite for corrective or preventative actions.

Complaint	Product	Number of Affected Patients
C1/PCR/2017/013	(b) (4) Injection	6 (2 with batch (b) (4)
C1/PCR/2017/028	Injection	1 (batch (b) (4)
C1/PCR/2017/029	Injection	1 (batch (b) (4)

The General Manager of Corporate Quality Assurance explained that these site reactions may be attributed to drug product not being pyrogen free (presence of bacterial endotoxin). The complaint investigation relied on additional product testing without further follow-up. The Senior Manager of Quality Assurance elaborated that endotoxin levels are homogenous ("throughout") a batch and it would be expected for an endotoxin contamination to be ubiquitous throughout the batch.

Incidents related to injection site reactions for (b) (4) have been increasing as summarized below:



OBSERVATION 4

Out-of-Specification (OOS) results are invalidated without an adequate justification:

OOS results pertaining to the US market are frequently invalidated and described below:

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Year	Valid OOS	Invalid OOS	% Invalidated
2016	41	9	82
2017	58	9	87

a. The following OOS results for stability samples were invalidated due to "column efficiency". No chromatographic errors were discerned, including retention times, theoretical plates and tailing factor. Nevertheless, the OOS results were invalidated and passing retest results were reported. When asked if these results would have been invalidated should they have yielded passing result, the Deputy Manager of Stability Studies stated "never".

OOS	Product	Batch	Analysis
OOS/2017/CF/004	(b) (4) Injection	(b) (4)	(b) (4) Assay
OOS/2017/CF/007	Injection	(b) (4) & (b) (4)	Assay

b. 9 of 16 invalid OOSs pertaining to stability samples were invalidated due to dilution/ pipetting errors. Despite 56% of OOS results invalidated due to dilution/ pipetting errors, no comprehensive CAPA has been opened (b) (4) trainings regarding sample preparation are reported in the past two years). The following include examples of invalidated OOSs without adequate justification:

b.1 - The following OOSs for (b) (4) content of (b) (4) Injection were invalidated due to an assignable cause of standard solution contaminating the sample solution in the pipette. The OOS results were above specification. However, the standard solution yielded a lower peak area than the sample. It is unclear how a solution of lower (b) (4) content contaminating the sample would yield an OOS above the specification. The OOS results were invalidated and passing retest results were reported.

OOS	Product	Batch	Result (Specification (b) (4) – (b) (4) mg)
OOS/2017/CF/002	(b) (4) Injection	(b) (4)	(b) (4) mg
OOS/2017/CF/027	Injection		mg
OOS/2017/CF/020	Injection	Various	(b) (4) – (b) (4) mg

b.2 - OOS report OOS/2017/CF/035 for (b) (4) injection (batch (b) (4) was invalidated due to identification (via interview) of a dilution/ pipetting error. The analyst that ran the chromatographic sequence was interviewed; the interview did not include the analyst who performed the pipetting and dilution for generating the sample. The OOS results were invalidated on the interview of the analyst that performed the chromatography.

c. OOS report OOS/2017/CF/018 pertaining to stability samples for (b) (4) permeability of (b) (4) Injection (batches (b) (4) and (b) (4) were invalidated with "assignable root cause could not be identified". The failing results for batches (b) (4) and (b) (4) of (b) (4) % and (b) (4) %, respectively, were invalidated and passing retest results were reported.

OBSERVATION 5

During a walkthrough of the facility we observed within the personnel corridor (Note: corridor leads into the personnel entryways that lead into the controlled classified manufacturing areas) approximately 27-28 separate areas in the ceiling where water was either dripping, seeped and/or soaked through the building structural material. This is evident, for example, by water dripping from the ceiling, a small accumulation of water on the personnel corridor floor and varied water stains on the walls of the personnel corridor. In addition;

a. In the personnel corridor there is an approximate 15.24cm (h) x 12.7cm (w) breakage of the building wall structure material;
b. There is a ceiling panel over the personnel corridor lighting fixture that is open (not sealed) such that it allows the ingress of air from the building's plenum and location of the air handling units (Note: by touch the ceiling material appeared to be a bit damp);
c. There is a ceiling panel and opening (approximate 45.72cm x 5.05cm) over the (b) (4) sterilizer that allows the ingress of air from the building's plenum into the post sterilization area.

OBSERVATION 6

Media fill records are false:

a. The most recent media fill for Line (b) (4) (batch (b) (4) completed in December 2016) is false. Senior Executive - Microbiologist acknowledged that microbiology completed the media fill batch record.

The batch record was signed by Senior Executive Microbiologist on December 4, 2016. However, the Senior Executive Microbiologist was off on this date.

The reconciliation for media fill vials for batch (b) (4) exceeds 100%. Specifically, the document entitled "Summary of Process Simulation Study" (document C1/MFIL/TERMINAL) indicates that (b) (4) containers had been filled with (b) (4) containers incubated. However, the batch record documents 7 vials had been rejected. Furthermore, the number of rejects between the "Summary of Process Simulation Study" and the "Batch Manufacturing Record" for batch (b) (4) is irreconcilable.

b. The most recent media fill for Line (b) (4) (batch (b) (4) completed in December 2016) is false. The Senior Microbiologist confirmed that microbiology department completed the media fill batch record.

The Senior Executive Microbiologist completed the batch record on December 30, 2016 after 08:54. However, the attendance records document that they completed the (b) (4) at 08:54 on this day. For example, the Batch Manufacturing Record for batch (b) (4) documents that the record was completed in the afternoon of December 30, 2016. The Senior Executive Microbiologist acknowledged writing this page despite not being present on the premise during these times. The reconciliation for media fill vials for batch (b) (4) exceeds 100%. The "Record of Observation for Incubated Containers" (form SF/C1/MFIL/SVP/013) indicates that (b) (4) containers had been observed after incubation). However, per the Batch Manufacturing Record and "Summary of process simulation Testing (Media fills trial)" (document (C1/MFIL/SVP) indicates that only (b) (4) containers had been subject to incubation.

c. Regarding personnel movement in fill line (b) (4) the layout of the fill equipment, design of the ISO-5 area within the ISO-7 room requires gowned personnel to go (b) (4) the fill line conveyor belt; a similar concern and personnel movement occurs in the vial capping line.

OBSERVATION 7

Aseptic technique is deficient:

During the manual intervention the fill room operator was observed manually placed the lid of the EM settle plate covering the (b) (4) *petri dish, which precludes from obtaining a representative EM sample during the manual intervention.*

a. The EM personnel was observed placing their gloved hand under the RABs barrier and into the ISO-5 fill zone while positioning the NVP probe in order to conduct the NVP measurements.

b. During NVP measurements a leak from a filling (b) (4) was observed on the fill line with an accumulation of liquid in the ISO-5 fill zone.

c. After the NVP measurements were taken the fill room operator conducted a manual intervention to replace the fill (b) (4) the RABs access (b) (4) was opened throughout a period of (b) (4) During this time, the operator's (b) (4) was observed within the ISO-5 fill zone, which included frequently contacting the RAB's

d. Subsequent the aforementioned activities noted above the (b) (4) and the area surrounding the fill (b) (4) were not subject to cleaning/ sanitization.

OBSERVATION 8

The air flow pattern evaluations (aka smoke studies) are performed to "demonstrate and assure that the LAFs" in the (b) (4) ine and (b) (4) line "are capable enough to provide Unidirectional Air flow to the work station and there are not turbulence observed and/or any non-unidirectional movement of the air observed so as to maintain the laminarity of the air flow with the LAF work station." Similar air flow pattern considerations and evaluation principles have been performed in support of the area qualification for the (b) (4) Line. A review of the air flow pattern videos document the following concerns e.g.;

a. There are a number of instances documented in the videos where there is no smoke placed over the personnel manual interventions in order to visualize the impact upon the unidirectional flow of air within the ISO-5 area;

b. There is no simulation regarding opening and closing of RABs access (b) (4) or of the (b) (4) barrier (b) (4) to demonstrate that the unidirectional flow of air is not compromised during routine operations;

c. There are a number of instances when personnel perform some form of manual interventions within the ISO-5 area. However, due to the position of the fill room personnel, their position blocks the video camera and prevented the ability to observed the manual intervention and the impact upon the unidirectional air flow;

d. Fill room personnel perform a manual intervention (b) (4) the conveyor that transfers the glass vials from the fill equipment to the vial capping station. The manual intervention requires opening the (b) (4) of the conveyor enclosure, at which time the conveyor's ISO-5 interior is exposed to the ISO-7 environment;

e. During the above manual intervention noted above, personnel are performing the task within an ISO-7 environment. There is no physical partition to separates and control the ISO-5 from the ISO-7 environment.

OBSERVATION 9

The "Clean Room Monitoring" document #C1/QAD/004 establishes "two methods of environmental monitoring" i.e., physical and microbial monitoring. "Microbial monitoring aims at obtaining representative estimation of bio-burden of the environment and detecting an adverse drift in trend of microbiological conditions, in a timely manner, which would allow for meaningful and effective actions." Regarding the microbial alert and actions limits, the environmental monitoring (EM) program establishes, for example, (b) (4) - (b) (4) cfu (alert/action) for the ISO-7 and (b) (4) - (b) (4) cfu (alert/action) for the ISO-8 manufacturing controlled areas. The EM data for the last three years document microbiological counts, dependent of the ISO classification of the manufacturing area (within a range from (b) (4) - (b) (4) cfu), are well below the current microbial limits. The EM microbial alert and action limits are not established or based on the historical performance that is documented in the EM data. In addition,

a. The microbial alert and action limits for the (b) (4) Line was initially established from Sept. 18, 2011 to Feb. 01, 2012, for the (b) (4) Line on Jan. 01, 2008 and for the (b) (4) Line on Feb. 04, 2008. The EM data obtained and established from the aforementioned previous years continues as the microbiological foundation in support of the current EM program microbial limits. There are a number of discrepancies with respect to the current EM sampling and data that have a direct impact upon the microbial alert and action limits. For example, there are current EM sampling locations that do not correspond to the initial EM sampling locations, there are current

sampling areas that are a modification of the original sample site and/or EM sampling is no longer taken from areas that was initially sampled;

b. The Senior Manager of Quality Assurance provided a verbal explanation regarding a variety of considerations and details that were used with respect to the rationale that assisted with establishing the EM sampling locations. However, the specific microbiological considerations and/or explicit details are not part of, or described in, the current "Rationale for Environmental Monitoring Locations" document #Ex/C1/QAD/004.15;

c. The "Clean Room Monitoring" document #C1/QAD/004 establishes "…procedures and methods to be used for monitoring Physical parameters…and microbial parameters." Regarding microbial contaminants the procedure instructs to "Incubate the plates…at 20-25°C for 3 days (72 hours). After completion 3 days of incubation transfer the plates to incubates at 30-35°C for 2 days (48 hours)." There is an inconsistent set of instructions with regards to the length of incubation for the bacteria and mycological microorganisms, in that, the "Media Preparation" procedure (document #C1/QAD/043) establishes an incubation period of 3 and (b) (4), respectively. And, the "Media verification report for Ready to Use Plates" procedure (document #SF/C1/QAD/038.01" instruct to "*Perform observation for Bacteria on 3rd day and for yeast/mold on (b) (4);

d. The "Trend Management" document #C1/QAD/012 define and establish "the procedures to be used for trending of Critical Quality Attributes of the product for ongoing monitoring and establishment of trend limits and investigating out-of-trend (OOT) or questionable results observed." This would include the use of the '(b) (4) Monitoring" and "Clean Room Monitoring" procedures. The "Clean Room Monitoring" procedure contains language that provides specify instructions regarding the preparation of a (b) (4) summary report that is based on (b) (4) observations of the EM data i.e., NVP, passive microbial plate counts and active microbial air sampling. However, the procedure is silent with respect to the inclusion and assessment of the personnel monitoring data.

OBSERVATION 10

The "Validation Master Plan" (VMP) document #VM/QA01 establishes that '(b) (4) shall also be frequently monitored to cover all the (b) (4) variations and to have history of data that will prove the consistent (b) (4) quality required for parenteral preparation." Regarding the (b) (4) there

are a total of (b) (4) point of use (POU) locations (b) (4) of the POU locations include hoses/pipes that are connected to the filling machine and varied (b) (4) equipment that are used for the manufacturing operations. The hoses/pipes range from (b) (4) to (b) (4) in length with an inside diameter of (b) (4) The sampling consists of removing the equipment hoses/pipes from the POU sites and connecting a depyrogenated (b) (4) sampling device; the sampling of the (b) (4) does not include the production equipment hoses/pipes. In addition,

a. The sampling does not accurately reflect the manner with which the (b) (4) is conveyed/ obtained from the POU site for routine manufacturing operations;

b. There is no microbiological monitoring data regarding the (b) (4) POU (b) (4) sites and the (b) (4) to (b) (4) length hoses/pipes.

OBSERVATION 11

Nonviable monitoring is deficient:

Non-viable particle (NVP) monitoring is deficient in that there is no record to support the effectiveness regarding the manual method that is used to obtain the NVP measurements:

a. The manner with which manual measurements are obtained is not defined. Specifically, the procedures governing NVP monitoring, "Air Particulate Counter" procedure C1/QAD/060 and "Clean Room Monitoring" procedure C1/QAD/004 are silent with regards to the manner to conduct the measurement i.e. (b) (4) of holding the probe, distance of the probe within the Class A area, etc.

b. On 07/27/2017, we observed NVP monitoring is performed under static conditions. Further, the probe to the device is not held consistently (b) (4) to the surface to ensure accuracy; rather the NVP probe was observed being held at an (b) (4) towards the (b) (4) barrier of the filling line. There is no dynamic NVP monitoring performed and no assurance that the ISO-5 fill zones are appropriately maintained during the dynamic filling process.

c. The Senior Manager – Quality Assurance and Junior Manager – Microbiologist, stated that there is no record to substantiate that the manual measurements conducted in the manner described above are capable of accurately quantitating non-viable particulates.

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OBSERVATION 12

The (b) (4) inspection equipment is used to detect pinholes (b) (4) in (b) (4) and Non- (b) (4) bags of finished drug products. The basic principle consists of (b) (4) which detects a defective bag by (b) (4) (b) (4) in the intact bag. There is a lower and upper (b) (4) et point that establishes the range when testing the filled bags for leaks. The Assistant General Manager – Engineer Services explained that they do not calibrate the equipment. The lack of calibration brings into question the accuracy of the upper and lower set points that are used to reject leaking bags. In addition,

a. The PQ includes a (b) (4) test of the filled bags, which consists of (b) (4) (b) (4) . The (b) (4) test is performed via the use of an in-house fabricated (b) (4) device. The Assistant General Manager-Engineering Services confirmed that there is no written procedure to describe and establish the manner with which the (b) (4) test is performed;

b. The Process Performance Qualification (PPQ) of the pinhole inspector dated 4/16/17 includes a leak test challenge performed at the (b) (4) (b) (4) of a typical filling process. The leak test challenge consists of using (b) (4) bags with known (b) (4) pinholes. The Assistant General Manager – Engineer Services and Senior Manager Quality Assurance explained that they do not perform random pinhole leak test challenges during the PPQ process. Rather, the leak test challenge is performed at the aforementioned established time periods, which is not reflective of normal operations;

c. Production personnel perform a visual inspection of the filled bags (b) (4) manually loading the filled bags into the (b) (4) The inspection includes for example checking for "leakage, printing, improper closure and other rejections". The General Manager – Training & Development confirmed that the visual inspection training does not consist of, for example, visuals aids that assists to illustrate the specific bag related anomalies or written descriptions of the quality attributes that the visual inspection personnel are required to inspect.

OBSERVATION 13

Regarding (b) (4) sterilization process for the (b) (4) sterilizers (b) (4) ea.) the process performance qualification (PPQ) is subject to an (b) (4) revalidation. The Senior Manager Quality Assurance confirmed that

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there is no written procedure to define and establish the manner of how to place the (b) (4) (b) (4) within the sterilizer's interior chamber. In addition,

a. The (b) (4) studies include the use of (b) (4) biological indicators (BI) challenge with a 10 to the 6th concentration of spores, which is used to ensure the sterilization process provides at least a 6-log reduction. The Senior Manager of Quality Assurance explained that there is no written procedure to define and establish the manner of preparing the BI spore suspensions that are used for the (b) (4) evaluations that in turn support the PPQ;

b. There are (b) (4) different load configurations for the various finished drug products, e.g., filled (b) (4) and Non (b) (4) bags (range from (b) (4) ml to (b) (4) ml), that are subject to the (b) (4) sterilization cycles. The unique load configurations illustrate the required placement of the different products in a defined number of (b) (4) in the sterilizer's (b) (4) With a retinue of senior managers (e.g., Senior Vice President Manufacturing & Operations, Deputy General Manager of Compliance, Senior Manager Quality Assurance, Assistant General Manager Engineering Services) we observed (b) (4) separate individuals, including an IPQA representative, that work in the sterilizer loading area as they unsuccessfully attempted to locate a copy of the (b) (4) different load configurations from (b) (4) different document wall display stands and (b) (4) separate (b) (4) tubs. The load configuration and diagrams are not readily displayed such that the production operators can reference the sterilization load patterns.

OBSERVATION 14

Analytical method validation for endotoxin testing via a kinetic turbidimetric method is deficient:

There is no procedure for conducting analytical method validation pertaining to microbiological test methods.

a. The Validation Master Plan (VMQA/01) establishes a supplier based qualification when "the adequacy of the document(s) shall be ensured before their approval and considered for use." However, instrument qualification for a kinetic turbidimetric method for endotoxin testing was conducted under to "WinKQCL 5 Qualification Manual" provided by the vendor with no accompanying demonstration that the adequacy of the documentation had been ensured.

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b. Analytical method validations for the kinetic turbidimetric analysis of endotoxins (protocol PPQ/C1/IND/21) fail to provide objective criteria to ensure method reproducibility and accuracy. During the validation of (b) (4) Injection (b) (4) (from October 24 – 26, 2016) (b) (4) tests were conducted, 6 failing to meet acceptance criteria of the test. However, the validation report is silent with regards to (b) (4) of the bacterial endotoxin tests being "DISREGARDED".

c. Of (b) (4) assays utilizing this kinetic turbidimetric method, there have been 39 OOS incidents and 6 laboratory error reports (approximately (b) (4) % of all tests). During kinetic turbidimetric bacterial endotoxin testing, gel clot analysis was performed simultaneously. During this time, 7 tests for endotoxin testing via the kinetic turbidimetric bacterial endotoxin testing failed to meet the acceptance criteria. However, these failures were not evaluated to determine root cause and the passing results reported were from the gel clot tests.

OBSERVATION 15

The (b) (4) microbiological identification system is used to identify the microbiological contaminants that are recovered via the EM program, USP Sterility Tests, (b) (4) Sampling program and/or other microbiological analyses. The I/OQ and Performance Qualification (PQ) was performed in June and August 2016. The PQ established an identification challenge (Phase I) with five separate microorganisms (ATCC genus and species) to include *Bacillus subtilis* and a separate EM microbiological isolate. The challenge included Phase II reproducibility and ruggedness tests. Of the challenge microorganisms, the *Bacillus subtilis* was not successfully identified (% Probability). In addition,

a. In the event that the (b) (4) does not identify an unknown microbe to a high level percentage of probability, the unknown microbe's biochemical/ biopattern results can be added to the identification library via the (b) (4) Regarding the unsuccessful identification of the Bacillus species challenge noted above, the biopattern was added via the (b) (4) addition; the (b) (4) was then able to successfully identify the *Bacillus subtilis* ATCC microbial standard. The PQ protocol does not include language that allows for the (b) (4) addition of biochemical/biopattern results for microorganisms that are not successfully identified by the (b) (4) System;

b. The (b) (4) system is a computer controlled system that captures and records varied (b) (4) alarmed conditions that may occur during the microbial identification process. The Senior Man-

ager Quality Assurance confirmed that there is no record to document a review of the alarmed events, which would ensure that the alarmed events do not negatively impact upon the microbiological identifications;

c. The (b) (4) System automatically performs a (b) (4) backup of the database (e.g., all microbiological identifications, personnel access of the system, audit trails, and alarmed events), which includes an ability of supported backup methods via external hard drive. The Senior Manager Quality Assurance confirmed that the practice of performing the supported backup method is no longer performed and the external hard drive has been removed. And, while the "Change Management System – Corporate Functions" document #CF/CQA/034 defines and establishes the procedures for management changes and its documentation e.g., "procedural steps for change request, review, risk and impact assessment, approval implementation and verification of effectiveness of the changes/s requested", the Senior Manager Quality Assurance confirmed that there is no record to document the aforementioned change regarding the external hard drive.

OBSERVATION 16

The Validation Master Plan (VMP) document #VM/QA/01 establishes the Installation and Operational Qualifications (I/OQ) requirements (i.e., "build and installed in compliance with their design specifications". The (b) (4) an automatic (computer control and high resolution camera) colony counter that is used to count microbiological colonies, characterize the microbiological contaminants and record the color photographs of contaminants from the environmental monitoring microbial (b) (4) media. The Senior Manager of Quality Assurance explained that they (Claris) did not perform an I/OQ of the (b) (4) (b) (4) microbiological colony counting system. Rather, a two page checklist was provided by the vendor with respect to the I/OQ. There is no record to support that the I/OQ was reviewed and approved by the Quality Unit to ensure that the (b) (4) was "build and installed in compliance with their design specifications".

OBSERVATION 17

The "Functions and Roles & Responsibilities" document #CF/HRM/001 establishes and "…defined methodology for preparing functions, operational roles & responsibilities and organization operational structure of the departments." This would include but not limited to, for example, "…ensure implementation and maintenance of Current Good Manufacturing Practices (cGMP) standards and all applicable international quality standards in the plant." Despite the establishment of the aforementioned responsi-

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10903 New Hampshire Ave,Bldg 51,Rm 4225 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738 Industry Information: www.fda.gov/oc/industry	7/27/2017-8/4/2017* FEI NUMBER 3004610460

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Dr. Jacqueline A. Kunzler, Global Head of Quality

FIRM NAME	STREET ADDRESS
Claris Injectables Limited	Chacharwadi Vasna
CITY, STATE, ZIP CODE, COUNTRY Ahmedabad, Gujarat, 382213 - India	TYPE ESTABLISHMENT INSPECTED Terminally Sterilized Pharmaceutical Manufacturer

bilities the Senior Executive Human Resources Management confirmed that there is no individual who is responsible for, or in charge of, overall Quality Assurance during the manufacturing operations that occur during the (b) (4) production (b) (4)

OBSERVATION 18

The "Continued Process Verification Program" (CPVP) document #CF/QA/028 establishes an "ongoing assurance that the process remains in a state of control (the validated state) during commercial manufacture." "The purpose of this procedure is to identify and summarize the current systems within Claris Injectables Limited which are implemented to evaluate the performance process, identify potential problems and determine whether action must be taken to correct, anticipate, and prevent problems so that the process remains in a state of control throughout the lifecycle." The implementation of the CPVP "will ensure adherence to the CGMP requirements (specifically, the collection and evaluation of information and data about the performance of the process) and will promote detection and remediation of undesired process variability." The list of objectionable conditions document a number of instances where the Quality Unit has not effectively "evaluate the performance process, identify potential problems and determine whether action must be taken to correct, anticipate, and prevent problems so that the process remains in a state of control throughout the lifecycle."

*DATES OF INSPECTION

7/27/2017(Thu),7/28/2017(Fri),7/29/2017(Sat),7/31/2017(Mon),8/01/2017(Tue),8/02/2017(Wed),8/03/2017(Thu),8/04/2017(Fri)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Thomas J. Arista, Investigator Massoud Motamed, Investigator	DATE ISSUED 08/04/2017