DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	
8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913)495-5100 Fax:(913)495-5115	8/13-17, 20-24, 09/12-14/2018 FEI NUMBER 3004839646

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

Micahiah (Mia) M. McCombs Quality Assurance Manager

FIRM NAME	STREET ADDRESS
JCB Laboratories LLC	7335 W. 33rd St. North
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Wichita, KS 67205	Outsourcing Facility

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

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is no testing to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use. Also, there are no written testing programs designed to assess the stability characteristics of drug products.

Specifically,

A. Your firm lacked valid analytical and stability data to support the 60, 90, and 180-day beyond use-date (BUD) expiration date assigned to all of your products such as Vancomycin, Sodium Thiosulfate, and Ephedrine Sulfate.

B. While you began to develop stability protocols for some of your product you fail to have stability data for (b) (4) batches of products in accordance to the protocols you have written. This failure extends to all of your products as you do not have stability data for a representative number of batches for any of your marketed and distributed products. In addition, you do not have an on-going stability program for your products.

C. Your firm has incomplete methods and methods validations for the following products:

1. Bevacizumab (Avastin) Injection Solution-no method validation for potency, and no potency testing is performed.

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2. Sodium Thiosulfate 25% PF Injection Solution – no method validation for potency, sterility, and endotoxin.
3. EDTA (edetate disodium) Topical Ophthalmic Injection Solution - no method validation for potency, sterility, and endotoxin.
4. Tropicamide 1%, Cyclopentolate 1%, Phenylephrine 2.5%, Ketorolac 0.4%, Proparcaine 0.1 % Ophthalmic Solution– no antimicrobial effectiveness testing (USP <51>).
5. Iohexal (Omnipaque) Injection Solution- no method validation for potency, sterility, and endotoxin.
6. Calcium Chloride PF injection Solution - no method validation for potency, sterility, and endotoxin.

Repeat Observation from 02/12-21/13 and 11/16-12/3/15 EI inspections

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OBSERVATION 2

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

Specifically,

A. The smoke study is deficient as it does not continuously show that the air is moving unidirectionally as the smoke is either too faint and/or the smoke source is depleted and there is no smoke present. In addition, the smoke study was not conducted while simulating your current manufacturing and operating processes of (b) (4) laminar flow hoods at the same time which represents your normal processing operations.

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B. The media fill performed is inadequate as it does not simulate the complete sterile operations for your manufacturing processes as follows:

You currently qualify your aseptic operators through your media fill operations but you do not mimic the worst-case manufacturing operations which occur during your aseptic processing operations. For example, (but not limited to):

1. You do not simulate the maximum number of activities which occur during your manufacturing operations.
2. You do not simulate the worst-case activities during your manufacturing operations.
3. You do not simulate the maximum number of people which are involved in the aseptic operations and/or are in the environment during your media fill operations.

C. On 8/14/18, I observed your cleaning practice and found you do not follow your SOP no. 3.3010 "Cleaning of the Cleanroom Facility". You failed to use aseptic cleaning techniques as you did not mop the floors, starting in a position that allows the Technician to mop in a uniform manner covering all floor surfaces from the back of the room to the exit. Your Technician stepped over onto the cleaned area after mopping it and they did not always clean from the inside out, or from the top downward.

D. During your room qualification activities and evaluation of the HEPA filters you do not evaluate the air velocity at the work surface in your ISO-5 laminar flow hoods. In addition, you do not have a system in place to track the repairs made to your HEPA filters which are evaluated during your (b) (4) evaluations of these filters.

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E. We identified hold times for your Sodium Thiosulfate 25% PF Injection for Solution for up to (b) (4) You do not have bioburden data for this product to support the end hold times used.

F. You do not have an SOP which addresses the quality oversight of gowning used during the manufacturing operations and the Quality Unit does not perform oversight of these items used during processing operations for your sterile injectable products. This includes your sleeve covers, coveralls, hoods, and boots.

Repeat Observation from 02/12-21/13 EI inspections

OBSERVATION 3

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

A. While you document a visual inspection of your Povidone-Iodine (Betadine) 5% Ophthalmic Solution 1 mL syringe product is being performed, you do not perform a visual inspection of this amber colored product which is packaged in amber syringes. In addition, your SOP for Visual Inspections does not cover a visual inspection process for this product.

B. During our review of your visual inspection process on 8/15/18 Employees (b) (6) , and (b) (6) were observed performing visual inspections of Omnipaque Injectable Repack Vials lot no.

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C274-000006332. Your visual inspection process was inadequate because we observed they did not evaluate the units for at least (b) (4) in accordance to your SOP.

OBSERVATION 4

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether the batch has been already distributed.

Specifically,

A. You failed to respond timely to the aberrant test results which later tested as OOS test results for your Cefuroxime Ophthalmic Solution for Injection, Lot no. C274-000002528. On 10/17/17, this lot was tested for potency and received test results of 90.4% (specifications are (b) (4) This lot was retested in triplicate on 11/16/17 and the results reviewed on 11/20/17 with OOS results of 82.5%, 83.5% and 83.8%. Deviation no. 2017-2017-080 initiated 1/18/18 summarizes these results including a review of the original BUD information which found two of the three BUD studies performed in 2014 indicates the potency of Cefuroxime drops significantly over a short period (b) (4) days)". DEV-2018-004 initiated on 1/18/18 documents Quality Assurance performed a review of DEV-2017-080 on 1/8/2018. Your Risk Assessment was not approved until 1/12/18, almost 2 months after confirmed OOS test results were received; you initiated NOE 2018-023 on 1/17/28 for Quality Assurance review on 1/8/2018 for stability failure and

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questionable BUD date approval. Your Health Hazard Evaluation was not approved until 1/26/18 and your Recall notification was dated 1/24/18.

B. Deviation no. DEV-2017-071, discovered 10/4/17, documents a complaint received on 8/21/17 for Mitomycin Solution for Injection, 0.2 mg/mL, 1 mL Single Use Syringe (ophthalmic use only) for lot no. C2724-000001703. The report was for three (3) patients who experienced reactions on their eye(s) following the use of this product. As a part of the investigation for this complaint retain samples were evaluated including retain samples from other lots. During the review of the retain samples lot no. C274-00000165 was found to have particulates in four units. You failed, however, to test these retain units to identify what the particulates were. During your visual inspection process, your SOP no. 9.200 "Visual Inspection and Defect Recognition" it gives instructions for you to "note any heavy particulates". In addition, you have not identified what these particulates might be and collected information on inherent, intrinsic, and extrinsic particulates which have appeared historically in your product which are identified through training in your visual inspection process.

C. Customer Complaint no. 0118-029 was initiated on 19-Jan-2018 for Mitomycin 0.2mg/mL, lot no. C274-000003188. The complaint was for the presence of a black particle found from your Mitomycin solution. Additional follow-up information was requested for this complaint which you stated the records were unavailable as you could not find the records for our review. This complaint had not been closed and you initiated an NOE and Deviation Report as a result of this event.

D. Customer Complaint 0118-017 was initiated 15-Jan-2018 for Cefuroxime lot C274-000003077 and Lidocaine/Phenylephrine lot C274-000002851. The complaint was for patients which had

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possible TASS or endopthalmitis. During your investigation of this complaint you failed to perform a complete investigation as you did not evaluate your retain samples.

E. DEV-2017-054 was initiated on 7/19/2017 after failing sterility results were received for Avastin Solution for Injection, 2.5mg/0.1 mL. 0.11mL Fill Lot C274-000001585. Your investigation identified Paenibacillus taichungensis in the (b) (4) media and a Paenibacillus species in your (b) (4) media for this product. You failed to include environmental monitoring information in your investigation where you found this organism in your environment on 06/16/17 and 06/21/17. In addition, you did not initiate corrective and preventive actions as a response to this event.

Repeat Observation from 02/12-21/13 and 11/16-12/3/15 EI inspections

OBSERVATION 5

Drug products are not stored under appropriate conditions of temperature so that their identity, strength, quality, and purity are not affected.

Specifically,

A. API drug products were observed on 8/14/18 in an area of your warehouse where there is no temperature monitoring performed. The following products were observed locked up in your quarantine area in the receiving area of your warehouse and include the following:

1. Gentamicin Injectable, USP, lot (b) (4), the label reads "store at USP controlled room temperature 20-25°C (66-77°F). This API product is used in your Sodium Citrate 4% product.

2. Omipaque, lot (b) (4) . This is a product you repackage and the label reads store at 20-25°C (59-80°F).
3. Phenol Liquid 90%, lot no. (b) (4) label read "Store at Room Temperature".

B. Temperature mapping studies have not been performed in the areas where raw materials and finished drug products are stored.

OBSERVATION 6

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

Specifically,

The floor in aseptic core is not cured properly and appears dirty in several areas throughout the aseptic core. On 8/13/18, we observed areas around the bottom of carts which appeared to be rust. We were told "cleaners are used which are caustic and they erode the metal".

OBSERVATION 7

Batch production and control records do not include complete labeling control records, including specimens or copies of all labeling used for each batch of drug product produced.

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The retain samples for this product along with all finished product do not contain the same labels as finished products. The use of other labels prevents your complete review of your distributed product including labeling.

OBSERVATION 8

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

Specifically,

1. You failed to follow your SOP No. 6.020 "Label Control" when you made changes to your labels. You did not do it via change control procedures.

2. You did not follow your SOP No. 1.030 "Change Control" when a change was made to cease manufacturing operations for your Tropicamide 0.2% Cyclopentolate 0.2% Phenylephrine 0.5% Ketoralac 0.1% Lidocaine Jelly 0.4%. Your NOE 2018-659, initiated on 9/12/17, identified the decision to cease manufacturing operations for this product occurred on 4/4/17, but no documentation was generated to support this decision.

3. You failed to follow your SOP no. 5.020 "Customer Complaints" where you did not conduct an investigation for Complaint no. 0118-029, initiated on 1/19/2018 for Mitomycin lot no. C274-000003188, for the presence of a black particle.

4. You did not follow your SOP No. 9.200 "Visual Inspection and Defect Recognition" for Avastin 2.5mg/0.1 mL Ophthalmic Solution lot no. C274-000004947. You did not perform a visual

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inspection of your retain samples and did not include a review of these samples as a part of the investigation reported in DEV-2018-042 initiated on 6/27/18.

5. You did not follow your SOP no. 5.110 "Adverse Drug Experiences" as you did not submit adverse drug experience reports for unexpected adverse drug experiences received for your compounded sterile drug products.

6. You did not follow your SOP No. 1.030 "Change Control" when you made changes to the manufacturing codes affected as a result of your change to the (b) (4) software system in April 2017. This change affected a number of things (to include but not limited to) such as the format of the batch records, finish product labels, and the invoice layout for JCB invoices to the customer.

OBSERVATION 9

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

Specifically,

In your environmental monitoring program, your SOP no. 3.020 "Environmental Monitoring" does not include information on all the equipment located in your sterile core. In your Environmental monitoring program, you do not account for all equipment in your aseptic core to assure appropriate monitoring is performed.

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Repeat Observation from 11/16-12/3/15 EI inspections

OBSERVATION 10

The labels used on your compounded drug products are incorrect as follows:

Specifically,

A. Currently the label states "FDA.gov/medwatch or 1-800-FDA-1088" which is not the web address given in section 503B(a) (10) (B)(ii) …and does not take the user directly to FDA's MedWatch page.

B. Currently the label states "sterile solution for injection" or "solution for injection" and does not include the type of injection (e.g., "epidural" for betamethasone sodium phosphate injection, dexamethasone sodium phosphate injection, methylprednisolone acetate injection, and triamcinolone acetonide injection; "retrobulbar" for bupivacaine/lidocaine injection; "intraocular" for epinephrine injection and lidocaine/phenylephrine injection; "IV" for sodium citrate containing gentamicin injection, sodium citrate injection, and sodium thiosulfate injection).

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