DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 N. Central Expressway, #300 Dallas, TX 75204 214-253-5200 Industry Information: www.fda.gov/oc/industry	08/08/2018-09/13/2018
	FEI NUMBER 30112866349

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Shaun P. Riney, CEO and Managing Partner

FIRM NAME	STREET ADDRESS
Qualgen LLC	14844 Bristol Park Blvd.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Edmond, OK 73013	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 (I) (WE) OBSERVED:

OBSERVATION 1

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 or not the batch has been already distributed.

Specifically,

a) Since May 2017, your firm has had six (6) sterility failures reported to you by your contract testing facility (Lot #C085 Estradiol 12.5mg; Lot #C231 Testosterone 200mg; Lot #D030 Testosterone 200mg; Lot #D046 Testosterone 200mg; Lot #D065 Testosterone 200mg; and Lot #D074 Testosterone 25mg). Your investigations into the last five (5) sterility failures are still open and some lack complete documentation of the contract testing lab's investigation. Moreover, your investigations do not always include a documented review of all potential items that may have contributed to these failures, for example environmental and personnel monitoring, engineering controls, inadequate cleaning procedures and the use of non-validated processes.

This is a repeat observation from the 8/24/15-9/17/15 and 4/17/17-5/10/17 inspections.

b) From April 2017 through July 2018, your firm had at least eight (8) action level excursions for environmental monitoring (viable air, settle plates and/or surface samples) in the ISO 5 hoods. Three (3) excursions occurred in the ISO 5 Biological Safety Cabinet (BSC) where the Testosterone pellets are vialed and five (5) excursions occurred in the ISO 5 BSC where the Estradiol pellets are vialed. Your investigations into these excursions did not identify a root cause and do not include a documented review of all potential items that may have contributed to these failures.

This is a repeat observation from the 4/17/17-5/10/17 inspection.

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	lisawhitt	Margaret M. Annes, CSO Lisa Whitt, CSO	09/13/2018

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c) On April 23, 2018, your firm had an action level environmental monitoring excursion on the surface of the table in the ISO 7 (b) (4) Lab ((b) (4)). Too Numerous to Count (TNTC) CFUs were found. The isolates were not sent out for identification and no investigation was conducted. Your firm made Estradiol Granulation lot #s DGE804 & DGE805 on this date.

d) Lot D048 of Testosterone 100mg pellets made on February 27, 2018, was rejected. The batch record states the pellets were of "poor quality" but does not elaborate. Your firm did not initiate an investigation into the rejected lot.

e) On May 3, 2018, Technician (b) (6) ailed the (b) (4) gowning qualification. No investigation was conducted and the isolates were not sent out for identification.

f) Lot #B032 of Estradiol 6mg pellets was placed on stability under Stability Study Protocol #AMI-1369-V1 Estradiol Pellet (b) (4) Stability Study Protocol – Qualgen (cGMP), implemented 08/05/2016. The lot failed in-process test for pellet uniformity by weight variation. No investigation was initiated by your firm.

OBSERVATION 2

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

Specifically, your firm has an inadequate change control process. SOP QG-1129 Validation Change Control, requires that all changes to GMP processes, equipment and procedures be reviewed and evaluated by the Quality Unit prior to approval. Your firm does not always document review and approval of changes prior to implementation. For example,

a) In September 2017, your firm installed a new ISO 5 hood in the ISO 7 (b) (4) lab ((b) (4)). Your firm had to remove a Plexiglas wall in the ISO 7 cleanroom to bring the hood into the room. The change control does not include any documentation of how the hood was to be brought into the room, how cleaning and decontamination of the hood would be performed and by whom, and does not include documentation of what was done during and after installation to ensure the cleanroom and hood were properly qualified/certified and the production area had

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been returned to a state of control prior to resumption of operations.

b) In May 2018, your firm changed the contract testing laboratory who performs your finished product sterility testing. No change control was created to review and evaluate this change to ensure that all tasks that needed to be completed, such as method suitability, were performed and that the change to the sample preparation method was appropriate.

c) During the current inspection, your firm made changes to the (b) (4) cleanrooms without creating a change control and having the changes reviewed and evaluated to ensure the changes were adequate and appropriate. Changes made include adding stainless steel sheets to the inside of the (b) (4), applying weather stripping to replace the (b) (4) seals around the (b) (4) and replacing the rusted handles to the (b) (4) with the same type of handle that had been there before (chrome plated).

d) In March 2017, your firm changed the supplier of the stoppers used by your firm and they are now received in bulk. This change resulted in your firm re-packaging the stoppers into smaller plastic bags in the unclassified area of the warehouse. Your firm did not initiate a change control and has not reviewed and assessed the impact to the cleaning, sterilization and depyrogenation process for the stoppers. In addition, the re-packaging of stoppers into smaller plastic bags is not included in a written procedure.

OBSERVATION 3

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

Specifically,

a) In September of 2017, your firm installed a new ISO 5 Biological Safety Cabinet (BSC) in the ISO 7 (b) (4) Lab to be used for the vialing of the Testosterone/Anastrazole pellets. Your firm has no documentation to show that a smoke study was performed under dynamic conditions after the installation of this hood. The June 2018 smoke study video for this hood is short, of poor quality and does not demonstrate the

airflow pattern under dynamic conditions. Moreover, the report accompanying the hood certification does not state that the smoke study was performed under dynamic conditions. Your firm has made approximately (b) (4) lots of Testosterone 200mg/Anastrazole 20mg pellets from the time of installation in September 2017 until June 2018.

b) Your firm did not have adequate contact time for the (b) (4) for use as a sporicidal agent. On August 16, 2018, I observed your technician spray the solution onto the surface of the ISO 5 hood and then (b) (4) minutes later wipe is away. Your Director of Quality stated that you follow the manufacturer's recommended dwell times. The manufacturer recommended dwell time for (b) (4) is (b) (4) minutes.

c) On August 14, 2018, we observed the vialing of lot #D184 of Testosterone 100mg pellets. The technician who was working at the pellet press was observed inappropriately handling (b) (4) used to remove pellets from the press and to perform weight checks. For example, the technician held the (b) (4) in one hand while leaning against a table and held them so they were near and almost touching his gowned legs while sitting down. There is no designated receptacle to place the (b) (4) when not in use, and the technician would place them on the table or ledge of the (b) (4) hood or pellet press.

d) On August 14, 2018, we observed the vialing of lot #D184 of Testosterone 100mg pellets. Several of the items in the ISO 5 hood used during vialing were pushed against the exhaust vent at the back of the hood. The items included the tray with the depyrogenated vials and the trays with the stoppered vials.

e) For the last re-validation in April/May 2018 of the (b) (4) used to sterilize stoppers and utensils, your firm failed to document the lot number of the biological indicator (BI) used, the incubation temperature for the BI, the duration of the incubation and who reported the results.

OBSERVATION 4

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically,

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a) Air could also be felt coming out near the top of a Plexiglass panel between the ISO 7 (b) (4) Room (b) (4) (b) (4) and the unclassified PIC's office. This is the same panel that was removed to bring the new laminar flow hood into the room in September 2017.

b) The ceiling of the ISO 7 cleanrooms, the ISO 8 Prep Room and ISO 8 Ante Room is constructed of plastic coated drywall panels with connecting seams. Panels are equipped with a (b) (4) seal that sits upon the support railing. The (b) (4) seal has begun to deteriorate and/or the panel is not fully seated onto the support railing on some panels in the ISO 7 (b) (4) Room (b) (4)), ISO 7 (b) (4) Room (b) (4) and the ISO 8 Prep Room. This allows for the collection of production dust and airborne particulates. Also, the seals do not totally enclose the circumference of each ceiling tile, allowing open access directly into the ISO 8 Prep Room from the adjoining unclassified areas. Additionally, there is a damaged ceiling tile in the ISO 8 Prep Room near the corner by the door opening, where the coating is coming off.

c) The surface of the (b) (4) ISO 8 Ante Room into the ISO 7 (b) (4) (b) (4) and from the ISO 8 Prep Room to the ISO 7 (b) (4) is constructed of laminated pressed wood. Moreover, the laminate surface of the (b) (4) ISO 8 Ante Room into the ISO 7 (b) (4) is coming off, thus exposing the wood surface.

d) The seal around each of the (b) (4) is constructed of a foam like substance that has begun to deteriorate.

e) The floor trim below the sink in the ISO 8 Prep Room is coming away from the wall.

f) Rust could be seen on the door handles for the (b) (4) ISO 8 Ante Room into the ISO 7 (b) (4) and from the ISO 8 Prep Room into the ISO 7 (b) (4)

g) Stickers could be seen on the support rails near the HEPA filters in all rooms. In the ISO 7 (b) (4) Room (b) (4) one of the stickers could be seen peeling away from the support rail.

h) The panel on the air return in the ISO 8 Prep Room had a screw coming away from the panel and part of the panel is not flush with the air return.

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i) There was a hole in the light cover near the door of the ISO 8 Prep Room.

This is a repeat observation from the 8/24/15-9/17/15 inspection.

OBSERVATION 5

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, your firm receives non-sterile active pharmaceutical ingredients (API) from multiple API manufacturers. Method Suitability, as required by USP <71>, was not conducted for sterility testing of the finished drug products made with said API received from all manufacturers. For example,

In May 2018, Method Suitability was not performed for testosterone pellets made with the API supplied by the manufacturer from (b) (4) using the new sample preparation method of (b) (4) .

In May 2017, your firm acquired a new manufacturer of Estradiol USP. The manufacturer was changed again in September 2017. Your firm produced estradiol implantable hormone pellets using API from both manufacturers from May 2017 through May 2018. However, method suitability was not conducted by the contract laboratory performing the sterility testing on these finished estradiol pellets.

OBSERVATION 6

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically, your firm does not supervise/monitor aseptic practices as outlined in your procedure, QG-1096, Aseptic Processing.

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SOP QG-1096 states that your firm's PIC (Pharmacist in Charge) or designated pharmacist will supervise production personnel working in the ISO 7 (b) (4) , ISO 7 (b) (4) and ISO 5 Biological Safety Cabinets on days of production. This supervision is to be documented on form QG-1096.

In addition, according to SOP QG-1096, specific production activities performed by personnel working in the ISO 7 (b) (4) , ISO 7 (b) (4) and ISO 5 Biological Safety Cabinets are to be supervised/monitored for specific times during production. These activities include:

a) Gowning for a minimum of (b) (4) minutes

b) Dispensing for a minimum of (b) (4) minutes

c) Pressing for a minimum of (b) (4) minutes

d) Packaging vials for a minimum of (b) (4) minutes

Review of the completed QG-1096-A forms from October 2017 – August 2018 revealed the following:

a) Your firm's Quality Department failed to review the forms completed from May – August 2018.

b) Your firm's pharmacists and PICs failed to supervise/monitor required activities during each day of production.

c) Your firm's pharmacist, (b) (6) noted "Found one unsigned Batch Record" on 5/17/2018. This form was not reviewed by the Quality Department. When I asked your Director of Quality about this statement, he stated this event should have been investigated and an Investigation Report (IR) should have been initiated.

d) Your firm's pharmacists and PICs failed to supervise/monitor each activity each day. A '1' with a circle around it denoted "N/A (Not Applicable) or Not Observed" is used on every form. However, it is not clear on the form whether each activity was Not Applicable or Not Observed. Examples where a '1' with a circle around it was used include Gowning (b) (4) minutes), Dispensing (b) (4) minutes), Compounding Techniques, Pressing Process (b) (4)

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minutes) and Packaging and Vialing (b) (4) minutes). Your Director of Quality stated a '1' with a circle around it should not denote both Not Applicable or Not Observed since they are completely different explanations.

e) Your firm failed to control Form QG-1096-A. Your pharmacists currently use two different QG-1096-A forms; both with no revision number and effective date 4/18/2018. One form is titled, Pharmacist in Charge (b) (4) Checklist, and the other is titled, Pharmacist (b) (4) Checklist. Your Director of Quality stated he did not know why your firm was using two different QG-1096-A forms.

OBSERVATION 7

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, from December 2016 until April 2018, your firm used an unqualified pellet press to make the Testosterone 200mg/Anastrazole 20mg pellets. This includes lots that were made for stability and process validation. A deviation/investigation was not opened to address this matter.

OBSERVATION 8

The separate or defined areas and control systems necessary to prevent contamination or mix-ups are deficient.

Specifically,

a) On August 9, 2018, I observed rust on the base of several chairs being used inside of the ISO 7 (b) (4) Room (b) (4) and the ISO 7 (b) (4) Room (b) (4) On August 10, 2018, I observed rust on the bolts in the area under the deck of the ISO 5 BSC where the vialing of testosterone pellets occurs. Rust is difficult to clean.

b) Your firm did not document pressure differential readings between the ISO 8 Ante Room where gowning occurs and the ISO 7 (b) (4) from (b) (4) . The following lots were made during that time:

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Lot #D173, Estradiol 6mg Pellets, made on 8/2/2018; Lot #D177, Estradiol 15mg Pellets, made on 8/7/2018; Lot #D179, Estradiol 15mg Pellets, made on 8/8/2018; and Lot #D181, Estradiol 10mg Pellets, made on 8/9/2018.

This is a repeat observation from the 4/17/17-5/10/17 inspection.

OBSERVATION 9

Equipment and utensils are not maintained at appropriate intervals to prevent malfunctions that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, from June 1, 2018 until August 22, 2018, your firm did not document the temperature in the incubators where the environmental and personnel monitoring samples are incubated.

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

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

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

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

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