WICKLIFFE
VETERINARY PHARMACY

Wickliffe, LLC

4340 Georgetown Road, Lexington, KY 40511

(859) 389-7470 (888) 934-5678

October 5, 2023

[VIA ELECTRONIC MAIL TO ORAPHARM3_RESPONSES@fda.hhs.gov]

Jeffrey Meng
Program Division Director
Office of Pharmaceutical Quality Operations
Division 3
U.S. Food & Drug Administration

FEI Number:
3002992930

Subject: Authorization to Publish Wickliffe LLC Response dated October 5, 2023 to FDA Form 483

On behalf of Wickliffe LLC, I authorize the United States Food and Drug Administration ("FDA") to publicly disclose the information described below on FDA's website. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. § 1905, 21 U.S.C.§ 331(y)(2), and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold FDA harmless for any injury caused by FDA's sharing of the information with the public.

Information to be disclosed: Wickliffe LLC 's response letter dated October 5, 2023 excluding attachments/exhibits, which responds to FDA's Form 483 dated September 15, 2023.

Authorization is given to FDA to disclose the above-mentioned information which may include confidential commercial, financial, or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of Wickliffe LLC . My full name, title, address, telephone number, and facsimile number is set out below for verification.

Sincerely,

Nicholas R. Kirkpatrick,
Pharmacist in Charge
Wickliffe LLC
4340 Georgetown Road
Lexington, KY 40511

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Cincinnati District Office
Food and Drug Administration
550 Main St. Suite 4-930
Cincinnati, OH 45202

ORAPHARM3_RESPONSES@fda.hhs.gov

FEI Number 3002992930

Re: Wickliffe Veterinary Pharmacy Response to FDA Form 483 Observation Issued on September 15, 2023

Wickliffe Veterinary Pharmacy ("Wickliffe") is committed to providing quality compounded animal drugs to fulfill unmet needs and believes the response provided below and the documentation enclosed will signal the enhancement Wickliffe has made in comprehensively addressing the Agency's observations. Wickliffe appreciates the diligence and professionalism of the FDA inspection team and the opportunities provided to further improve Wickliffe's quality system.

Background

Wickliffe is a state-licensed pharmacy that operates in compliance with Kentucky law, the applicable laws in other states where Wickliffe is licensed, and United States Pharmacopeia (USP) General Chapters <795> and <797> to prepare and dispense compounded animal medications to individually identified patients and licensed veterinarians pursuant to state laws and regulations.[1] Further, Wickliffe maintains accreditation with the Pharmacy Compounding

[1] Wickliffe compounds animal drugs in compliance with state pharmacy laws and regulations. Wickliffe's response to FDA's Form 483 observations of potential noncompliance with current good manufacturing practices (21 C.F.R. Part 211) are not an indication that Wickliffe believes its business is subject to 21 C.F.R. Part 211. Wickliffe reserves all rights and the responses herein illustrate Wickliffe's commitment to quality.

Accreditation Board, an independent accreditation board requiring all accredited pharmacies to comply with USP <795> and <797>.

Corrective and Preventative Action

Wickliffe has taken a comprehensive review of the observations and has taken appropriate and prompt corrective action to address each observation. Wickliffe will continue implementing further steps to prevent recurrence. In addition to the observations, Wickliffe appreciates the comments and recommendations provided by the investigators.

The enclosed responses demonstrate Wickliffe's sincere and comprehensive focus on continuous improvement. Wickliffe is fully committed to providing patients with the highest quality compounded preparations pursuant to state law and regulation. We trust that this response meets the expectations of the FDA for a state-licensed pharmacy and addresses the Agency's concerns.

Wickliffe will provide periodic updates to the FDA. These updates will summarize the progress of Wickliffe's corrections, preventions, enhancements, and commitments. We will provide monthly updates for the first three months starting on November 15, 2023.

Concurrently, we request a meeting with the Agency to provide any additional information or clarification related to the actions described in the enclosed response.

We look forward to the close-out of this inspection and issuance of an EIR.

Please let us know if we can provide any additional information or clarification.

Sincerely,

Nicholas Kirkpatrick
Pharmacist-in-Charge
Wickliffe Veterinary Pharmacy

Attachment: Wickliffe Veterinary Pharmacy's 483 Response

Wickliffe Pharmacy's Responses to FDA's Inspection Observations

Inspection Dates: 8/21-8/24, 9/6-9/7, 9/15/2023

FEI Number: 3002992930

FDA Observation # 1

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

1. **Personnel were observed conducting aseptic manipulations where the movement of "first air" in the ISO 5 area is blocked or disrupted. On 8/22/2023, in the sterile filling hood, your technician was producing Pentosan Glucosamine batch 520880. During aseptic filling your technician and/or pharmacist was observed blocking first pass air:**
    a. **Your technician stored the .2 micron filter on a cloth sprayed with sterile IPA between the glove ports within the hood. First pass air over the tip of this filter was blocked throughout the aseptic filling operation Additionally, during aseptic filling the sterile filter was held below the technician's hands on several occasions blocking first pass air.**
    b. **Your technician had an ISO 5 sterile glove break during aseptic filling. The technician proceeded to replace the sterile glove while open vials were sitting on the benchtop of the ISO-5 environment. These vials were then filled, capped, and sealed. According to the technician, glove changes occur as often as daily for some batches of gloves and rarely for others. Your firm does not document glove replacement for the ISO-5 gloves.**
    c. **Your pharmacist reached over approximately 20 empty vials to reach a spray bottle located in the back of the hood. These vials were then filled and capped.**
    d. **Your technician handled sterile forceps below their gloved hand, blocking first pass air, while manipulating sterile stoppers. The opened bag of sterile stoppers was approached from above frequently resulting in first pass air being blocked.**
2. **Personnel infrequently sanitized gloves to prevent contamination. On 8/22/23, during aseptic filling of Pentosan Glucosamine batch 520880, your technician used an auto pump to fill vials to the correct volume. The technician had to reset/manipulate the auto pump outside of the ISO-5 hood and then return to aseptic filling throughout the filling process. Your technician did not re-sanitize gloves upon re-entry into the ISO-5 glove port every time. The manipulation of the auto pump occurred as often as 3 times in 8 minutes without re-sanitizing with sterile IPA. During the filling of this batch the left ISO-5 glove, which was the hand used to manipulate the auto pump, was changed due to a break.**

<u>Wickliffe Pharmacy response to Observation 1:</u>

Observation 1 – Bullet 1 – Sub bullets A, C, and D response.

Wickliffe Veterinary Pharmacy recognizes the importance of observing proper aseptic technique, including the importance of strategic placement of materials within the ISO 5 environment, and is committed to compliance with USP 797 regarding the proper movement of personnel and materials within this environment. This observed batch of pentosan Glucosamine lot 520880 was quarantined and destroyed prior to sterility testing.

Wickliffe Veterinary Pharmacy would like to add clarity to what was being observed. This observation occurred inside of a containment aseptic isolator. Regarding observation 1c, the pharmacist was observed inside of the second set of gauntlet sleeves and was performing the final step of sealing the vials with a crimper. The vials the pharmacist reached over had been stoppered and thus no longer had any critical sites exposed.

The observations regarding blocking first pass air are not consistent with our SOP "Aseptic Processing". Relevant excerpts of our standard operating procedure "Aseptic Processing" are highlighted below:

- "*Materials used throughout compounding shall be logically and thoughtfully organized to minimize movement and allow for ease of aseptic manipulations and maintenance of unidirectional airflow/first air to all critical sites*
- *Critical sites may include: filter outlets, vial openings, transfer needles, container closures, stoppers, sterile tools used for manipulations, etc.*
- *All manipulations shall be approached with the concept of unidirectional airflow/first air to critical sites.*
    - *Smooth, deliberate motions*
    - *Avoidance of blocking first air to critical site*
    - *Maintenance of critical sites within the direct compounding area"*

All aseptic compounding personnel must undergo a comprehensive training program including a competency assessment both initially and semi-annually demonstrating proficiency and understanding of aseptic technique.

Wickliffe Veterinary Pharmacy has taken the following immediate corrective actions:

- Corrective Action 1: All aseptic compounding personnel have completed retraining on principles of first air, particularly when staging, filling, and stoppering vials. Documentation of this training is attached as exhibit 1A.
- Corrective Action 2: Observation of this technician has been completed on 4 separate occasions on 9/20, 9/26, 10/2, and 10/3 demonstrating adherence to this procedure, with particular attention given to maintaining first air to critical sites throughout the compounding process. Documentation of training has been attached as exhibit 1B and observation forms have been attached as exhibit 1E.

Wickliffe Veterinary Pharmacy conducted a thorough review of all sterility results, environmental monitoring, complaints, and Quality Related Event (QRE) records for all sterile preparations for the previous 12 months. The review resulted in the following facts:

- All sterile batches are quarantined until sterility and endotoxin testing is performed and passed by a third-party FDA registered analytical laboratory.

- A total of 92 batches were produced using filter sterilization over the past 12 months. There have been no sterility failures associated with any of these batches.
- No environmental monitoring excursions noted for any batches produced.
- No customer complaints indicated quality or sterility issues with any batches produced.
- The records review showed no evidence to suggest any sterility concerns for past batches produced by this technician.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy will implement the following preventative actions:

Preventative Action 1: Wickliffe Veterinary Pharmacy will enhance our current SOP by 11/01/2023 to include random audits of aseptic filling technique to be performed by the pharmacist-in-charge or sterile compounding supervisor and documented on at least a weekly basis for operators to ensure adherence to aseptic procedures.

Observation 1 – Bullet 1 – Sub bullet B response.

The observation of an ISO 5 glove break is acknowledged but allowed per the manufacturer's SOP "2.4 Emergency CAI Glove Change Procedure" attached as Exhibit 1C. Wickliffe Veterinary Pharmacy would like to add clarity to what was being observed. This observation occurred inside of a containment aseptic isolator.

Three sterile gloves are donned when using a containment aseptic isolator.

- Sterile Glove 1 is donned directly over the hands of the sterile technician.
- Sterile Glove 2 is donned over the containment aseptic isolator gauntlet sleeves and changed daily prior to compounding.
- Sterile Glove 3 is donned over Sterile Glove 2 in the ISO-5 area and changed between batches.

A sterile glove break for Sterile Glove 3 does not compromise the sterility of the environment.

Wickliffe Veterinary Pharmacy has taken the following immediate corrective action:

- Corrective Action 3: All aseptic compounding personnel have completed retraining on requirements for identifying and reporting any in-process abnormalities, including but not limited to glove breaks. Documentation of this training is attached as Exhibit 1B.

Wickliffe Veterinary Pharmacy conducted a thorough investigation of the frequency of glove breaks in the compounding aseptic isolator. The investigation resulted in the following facts:

- An interview of all aseptic compounding personnel revealed that glove breaks do not occur daily.
- No reported differences in quantity of glove breaks using different compounding aseptic isolators for any aseptic compounding personnel.
- The same Halyard manufactured gloves have been used in the compounding aseptic isolator for at least the last 12 months with no reported trends in quality or integrity from any aseptic compounding personnel.

- Aseptic compounding personnel have collected and documented the number and frequency of glove breaks over the previous 14 days to establish a facility baseline for ISO 5 glove breaks. There have been no glove breaks during the last 14 days.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy has or will implement the following preventative actions:

- Preventative Action 2: An enhanced SOP has been implemented regarding identification and reporting of any in-process abnormalities. This enhanced SOP is attached as Exhibit 1D.
- Preventative Action 3: Glove breaks are now being documented by batch and trended quarterly to identify any adverse trends in glove integrity.

Observation 1 – Bullet 2 response.

Wickliffe Veterinary Pharmacy acknowledges the observation but disagrees with the conclusion regarding infrequent sanitization of gloves. This observation occurred inside of a containment aseptic isolator, not an ISO-5 hood.

Three sterile gloves are donned when using a containment aseptic isolator.

- Sterile Glove 1 is donned directly over the hands of the sterile technician.
- Sterile Glove 2 is donned over the containment aseptic isolator gauntlet sleeves and changed daily prior to compounding.
- Sterile Glove 3 is donned over Sterile Glove 2 in the ISO-5 area and changed between batches.

Sterile Glove 2 and Sterile Glove 3 never leave the ISO-5 area and sterility is not impacted by the technician entering or exiting the containment aseptic isolator gauntlet sleeves. Sterile Glove 1 never enters the ISO-5 area. Sterile Glove 1 was the sterile glove observed not being sanitized prior to entry into the ISO-5 glove port.

Wickliffe Veterinary Pharmacy conducted a thorough review of all sterility results, environmental monitoring, complaints, and QRE records for all sterile preparations for the previous 12 months. The review resulted in the following facts:

- All sterile batches are quarantined until sterility and endotoxin testing is performed and passed by a third-party FDA registered analytical laboratory.
- A total of 92 batches were produced using filter sterilization over the past 12 months. There have been no sterility failures associated with any of these batches.
- No environmental monitoring excursions noted for any batches produced.
- No customer complaints indicated quality or sterility issues with any batches produced.
- The records review showed no evidence to suggest any sterility concerns for past batches produced by this technician.

However, in the spirit of continuous improvement, Wickliffe Veterinary Pharmacy has implemented the following preventative action:

- Preventative Action 4: An enhanced SOP has been implemented to include sanitization of sterile gloves prior to entering containment aseptic isolators. This enhanced SOP is attached as Exhibit 1D.

FDA Observation # 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic or sterilization process. Specifically,

1. **Your media fills do not include any high-risk challenges and are performed during "routine" operations**
    a. **On 8/22/23, during aseptic filling of Pentosan Glucosamine batch 520880, your technician changed out a glove on the ISO-5 glove port, however, glove changes are not documented during media fills or reflected in the batch record. According to your technician these glove changes can occur frequently (Daily). It is unknown if your firm has ever changed a glove during media fills.**
    b. **Your technician overfilled a vial of pentosan Glucosamine batch 520880 and proceeded to pour that vial's contents into another vial that was later filled and sealed. This task is not recorded during media fills.**
2. **Your firm's sterilization cycle for your ovens and autoclaves, that is used to render several injectable drug products sterile, has not been validated**
    a. **Your firm has not validated the Autoclave cycles used for moist heat sterilization used in the sterilization of several drug products including Stanozolol in water for Injection 50mg/mL, Prednisolone Acetate Injectable 50mg/mL, and Estrone Injectable 5mg/mL. Validation of the cycles includes determining appropriate loading patterns and temperature mapping of the cycle to determine worst case locations for biological indicator placement.**
    b. **Your firm has not validated the oven cycles used for dry heat sterilization of several drug products including Estradiol Cypionate Injectable 10mg/mL, Iodine in Almond Oil Injectable 2%, and Altrenogest Injectable 110mg/mL. Validation of the cycles includes determining appropriate loading patterns and temperature mapping of the cycle to determine worst case locations for biological indicator placement.**
3. **Visual inspection limits are not based on defect criticality. An overarching 10% reject threshold is set for all sterile injectable batches with no consideration for defect types that would impact sterility such as turbidity, container integrity, and extrinsic particulates, such as hair. Defect criticality has not been determined and defects found are not recorded during visual inspection. Additionally, the visual inspectors are not qualified to perform visual inspection, demonstrating that they can correctly and accurately identify know defects.**

<u>Wickliffe Pharmacy response to Observation 2:</u>

Wickliffe Veterinary Pharmacy understands the importance of and has in place processes and procedures necessary to achieve and maintain the sterility of compounded sterile preparations as required of a state-licensed pharmacy by the Kentucky Board of Pharmacy and USP Chapter 797. With this observation the FDA appears to be expecting Wickliffe to meet a cGMP standard associated with

process validation, a standard that is applicable to FDA-registered entities such as outsourcing facilities and drug manufacturers. Notwithstanding the inapplicability of cGMP standards to a state-licensed pharmacy, Wickliffe Veterinary Pharmacy recognizes the importance of continuously improving processes used to achieve and maintain sterility.

Observation 2 – Bullet 1 – Sub bullet A response.

Wickliffe Veterinary Pharmacy acknowledges the observation but would like to add clarity to what was being observed. Wickliffe Veterinary Pharmacy performs high risk media fill challenges semi-annually that incorporate daily routine operations as well as high risk aseptic challenges by being completed at the end of the shift. Glove changes are not considered part of daily routine operations nor a high-risk challenge. As described in observation 1, this observation occurred inside of a containment aseptic isolator.

Three sterile gloves are donned when using a containment aseptic isolator.

- Sterile Glove 1 is donned directly over the hands of the sterile technician.
- Sterile Glove 2 is donned over the containment aseptic isolator gauntlet sleeves and changed daily prior to compounding.
- Sterile Glove 3 is donned over Sterile Glove 2 in the ISO-5 area and changed between batches.

The procedure used during the donning of Sterile Glove 1 as outlined in SOP "Aseptic Processing":

- "Donning of Sterile Glove- Aseptic processing requires sterile gloves to be worn over the gauntlet gloves of the isolator. Sterile gloves shall be donned immediately prior to the start of aseptic processing."

Wickliffe Veterinary Pharmacy has taken the following immediate corrective action:

- Corrective Action 3: All aseptic compounding personnel have completed retraining on requirements for identifying and reporting any in-process abnormalities, including but not limited to glove breaks as detailed in response to observation 1 bullet 1 sub bullet b. Documentation of this training is attached as Exhibit 1B.

Wickliffe Veterinary Pharmacy conducted a thorough investigation of the frequency of glove breaks in the compounding aseptic isolator. The investigation resulted in the following facts:

- An interview of all aseptic compounding personnel revealed that glove breaks do not occur on a daily basis.
- No reported difference in quantity of glove breaks using different compounding aseptic isolators for any aseptic compounding personnel.
- The same Halyard manufactured gloves have been used in the compounding aseptic isolator for at least the last 12 months with no reported trends in quality or integrity from any aseptic compounding personnel.
- Aseptic compounding personnel have collected and documented the number and frequency of glove breaks over the previous 14 days to establish a facility baseline for ISO 5 glove breaks. There have been no glove breaks during the last 14 days.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy has or will implement the following preventative actions:

- Preventative Action 2: An enhanced SOP has been implemented regarding identification and reporting of any in-process abnormalities as detailed in response to observation 1 bullet 1 sub bullet B. This enhanced SOP is attached as Exhibit 1D.
- Preventative Action 3: Glove breaks are now being documented by batch and trended quarterly to identify any adverse trends in glove integrity as detailed in response to observation 1 bullet 1 sub bullet B.

Observation 2 – Bullet 1 – Sub bullet B response.

The observation of using an overfilled vial to continue filling would be a deviation and considered an in-process abnormality as described in SOP "Aseptic Processing."

Wickliffe Veterinary Pharmacy has taken the following immediate corrective action:

- Corrective Action 4: All aseptic compounding personnel have completed retraining on requirements for identifying and reporting any in-process abnormalities, including but not limited to overfilled vials. Documentation of this training is attached as Exhibit 1B.

Wickliffe Veterinary Pharmacy conducted a thorough review of all sterility results, environmental monitoring, complaints, and QRE records for all sterile preparations for the previous 12 months. The review resulted in the following facts:

- All sterile batches are quarantined until sterility and endotoxin testing is performed and passed by a third-party FDA registered analytical laboratory.
- A total of 92 batches were produced using filter sterilization over the past 12 months. There have been no sterility failures associated with any of these batches.
- No environmental monitoring excursions noted for any batches produced.
- No customer complaints indicated quality or sterility issues with any batches produced and dispensed.
- The records review showed no evidence to suggest any sterility concerns for past batches produced by this technician.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy has or will implement the following preventative action:

- Preventative Action 2: An enhanced SOP has been implemented regarding the identification and reporting of any in-process abnormalities as detailed in response to observation 1 bullet 1 sub bullet B. This enhanced SOP is attached as Exhibit 1D.

Observation 2 – Bullet 2 response.

Wickliffe Veterinary Pharmacy acknowledges FDA's observation, however the standard of practice FDA appears to be expecting – validation of sterilization equipment and processes – is a cGMP standard not

applicable to a state-licensed pharmacy. Wickliffe has in place procedures and policies required of a state-licensed pharmacy to verify the operation of the autoclaves and ovens. Self-contained biological indicators are added to each terminal sterilization cycle to evaluate whether the sterilization cycle was adequate, as required by USP Chapter 797. Sufficient space is left between materials to allow for circulation of air during terminal sterilization

In the spirit of continuous quality improvement, Wickliffe Veterinary Pharmacy has or will implement the following preventative action:

- Preventative Action 5: Wickliffe Veterinary Pharmacy will assess its current oven and autoclave verification procedures to determine what, if any, changes need to be made. Wickliffe Veterinary Pharmacy expects to have this analysis completed by 12/01/2023.

Observation 2 – Bullet 3 response.

Wickliffe Veterinary Pharmacy acknowledges your observation but disagrees with your conclusion. Wickliffe has appropriate procedures and policies for the visual inspection process. Wickliffe Veterinary Pharmacy does qualify inspectors to perform visual inspections for final preparation release. Visual inspectors are trained on SOP "Visual/Physical Inspection of CSPs" which includes:

- *Particulate matter inspection under a high intensity light under both black and white background*
- *Container closure inspection*
- *Other apparent defects inspection*

Wickliffe Veterinary Pharmacy conducted a thorough review of all sterility results, environmental monitoring, complaints, and QRE records for all sterile preparations for the previous 12 months. The review resulted in the following facts:

- All sterile batches are quarantined until sterility and endotoxin testing is performed and passed by a third-party FDA registered analytical laboratory.
- A total of 147 batches were produced and released after passing sterility and endotoxin testing over the past 12 months. One batch was destroyed prior to any units being dispensed due to a positive sterility test result. The expanded investigation into that result is ongoing.
- No customer complaints indicated quality or sterility issues with any batches produced and dispensed.
- The records review showed no evidence to suggest any sterility concerns for past batches inspected by trained pharmacists.

However, in the spirit of continuous improvement, Wickliffe Veterinary Pharmacy has or will implement the following preventative actions:

- Preventative Action 6: An enhanced SOP has been implemented to identify and document defect reason by batch produced. This enhanced SOP is attached as Exhibit 2A.
- Preventative Action 7: Defect reasons will be tracked and trended quarterly to identify trends associated with API, vial size, or method of sterilization.

FDA Observation # 3

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

On 9/7/2023, during aseptic filling of Reserpine 2.5mg/mL, brown residue was wiped off the bottom of the vials that were introduced to the sterile hood for filling. Reserpine is a clear/yellow liquid. More than 9 vials were discarded due to the brown residue. Filling, capping, and sealing of the batch was completed.

The last 3 batches of the 30mL vials being filled were Altrenogest lot 517601 on 8/4/2023, Stanozolol lot 517465 on 8/7/23, and Altrenogest lot 520197 on 8/18/2023. Altrenogest is a terminally sterilized oil-based product and has an orangish/brown color when dry according to the Pharmacist in Charge. The batch of Altrenogest on 8/4/2023 was rejected due to overfilling and the seals popping off during oven sterilization. Following the rejected Altrenogest oven cycle, a lot of 30mL vials was loaded into the oven for depyrogenation. Similarly, following the Altrenogest lot of 8/18/2023, a lot of 30mL vials was loaded into the oven for depyrogenation. These 30mL vials are then run through an autoclave cycle for sterilization and use in other 30mL vial batches.

There is no documentation for daily or weekly cleaning of Oven G which is used for depyrogenation of vials as well as terminal sterilization for oil-based drug products such as Altrenogest 110mg/mL injectable, Estradiol Cypionate Injectable 10mg/mL, Estradiol Cypionate Injectable 2mg/mL, and Iodine in Almone Oil Injectable 2%. Additionally, a white residue was seen along each of the walls and back of Oven G on 8/23/23.

<u>Wickliffe Pharmacy response to Observation 3:</u>

Wickliffe Veterinary Pharmacy recognizes the importance of maintaining, cleaning, and sanitizing equipment and utensils used in the production of drug products.

Wickliffe Veterinary Pharmacy conducted a thorough investigation into the root cause of the source of brown residue. The root cause analysis identified the most likely source of brown residue as altrenogest residue on an oven tray which was dry heat sterilized on 08/04/2023. This batch was quarantined and discarded.

Wickliffe Veterinary Pharmacy has taken the following immediate corrective actions:

- Corrective Action 5: All vials processed from 08/07/2023 - 09/07/2023 were removed for visual inspection. No residue was noted on any of these vials. These vials were destroyed out of an abundance of caution.
- Corrective Action 6: All oven trays have been removed and replaced with new trays designated for either depyrogenation or dry heat sterilization only as of 09/11/2023
- Corrective Action 7: Inside of oven cleaned on 09/11/2023 to remove observed white residue, which was most likely excess cleaner residue. This residue would not come into contact with any equipment or material in the oven. Oven cleaning added to daily aseptic cleaning tasks.

Wickliffe Veterinary Pharmacy hired an outside expert to conduct Health Hazard Evaluation to evaluate microbiological contamination risk and cross-contamination risk associated with this observation. A total of 5 batches were produced that were potentially affected. Four of those batches are fully quarantined and have not been dispensed to any patients. The other batch had a total of 16 vials dispensed after passing sterility and endotoxin testing prior to this observation. Based on the results of the Health Hazard Evaluation, no patient risk was identified. The Health Hazard Evaluation is attached as Exhibit 3E.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy has or will implement the following preventative actions:

- Preventative Action 8: Wickliffe Veterinary Pharmacy will assess purchasing depyrogenated, sterilized vials from a reputable supplier with a certificate of analysis by 12/01/2023.
- Preventative Action 9: An enhanced SOP has been implemented to designate oven trays for a specific use of either depyrogenation or dry heat sterilization only. This enhanced SOP is attached as Exhibit 3A.
- Preventative Action 10: An enhanced SOP has been implemented to include a monthly formalized inspection of all reusable cleanroom materials by sterile compounding supervisor. This enhanced SOP is attached as Exhibit 3B.
- Preventative Action 11: An enhanced SOP has been implemented to include daily oven cleaning. This enhanced SOP is attached as Exhibit 3C.
- Preventative Action 12: All aseptic compounding personnel have been trained to enhanced SOP. Documentation of trainings is attached as Exhibit 3D.

FDA Observation # 4

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release. Specifically,

Your firm only tests potency of a product the first time it is compounded. Once the first batch is successfully produced for potency then all subsequent batches are not tested for potency. On 5/24/2023, your firm received passing potency results for Estrone Injectable 5mg/mL, lot 499797. Since then, your firm has produced and released 3 additional lots of Estrone Injectable 5mg/mL with no additional potency testing performed. One additional batch of Estrone 5mg/mL, lot 504414, was produced after initial potency but was not released due to a sterility failure.

Wickliffe Pharmacy response to Observation 4:

Wickliffe Veterinary Pharmacy recognizes the importance of producing drug products that meet labeling specifications. To clarify this observation, initial potency testing is done for each formula. Subsequent potency tests are completed annually for any aseptic compounders. There is no requirement by the Kentucky Board of Pharmacy or recommendation in USP 797 to potency test each subsequent batch.

While Wickliffe Veterinary Pharmacy meets USP requirements, in order to continuously improve, Wickliffe Veterinary Pharmacy has or will implement the following preventative action:

- Preventative Action 13: Wickliffe Veterinary Pharmacy will engage an outside independent consultant to analyze Wickliffe Veterinary Pharmacy's current potency testing practices to determine what, if any, changes to potency testing frequency Wickliffe Veterinary Pharmacy should implement. Wickliffe Veterinary Pharmacy expects to have reviewed any recommendations made by this independent consultant by 12/31/2023.

FDA Observation # 5

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product or other drug products that may have been associated with the specific failure or discrepancy, Specifically,

1. **Your firm did not determine a root cause or investigate batches that failed during visual inspection for leaking vials due to excessive seals popping off during dry heat terminal sterilization. Your firm has rejected two batches in the past year due to seals leaking. On 7/5/23, Estradiol 2mg/mL lot 511677 was rejected due to excessive vial seals popping off. On 8/4/23, Altrenogest 110mg/mL lot 517601 was rejected due to excessive vial seals popping off.**
2. **Your firm produced Estrone injectable 5mg/mL batch 497879 that failed potency at 83% with a specification of 90-110%. This batch was discarded. The investigation into batch 497879 concluded that "not setting the steering [sic] plates on the proper rotating velocity ended up with some vials filled with less Estrone concentration than 5mg/mL." The following Estrone 5mg/mL production, bath 499797, was produced using the same batch instructions and no documented retraining. Appropriate preventative actions were not implemented to assure that this product and other similar products consistently meet potency specifications.**
3. **Your firm did not expand the investigation of a sterility failure of Estrone Injectable 5mg/mL lot 504414 to other batches of aseptically filled products from around the same period. The investigation corrective actions included running biological indicators to verify cycle efficiency and running an additional clean cycle on each autoclave. According to the investigation "Follow up was done with the following batch and shall be done with successive batches each time", however actions for follow up were not identified nor recorded in the investigation.**

<u>Wickliffe Pharmacy response to Observation 5:</u>

Wickliffe Veterinary Pharmacy acknowledges this observation and recognizes the importance of conducting robust investigations into batches or any components of batches that are out of its specifications. In-depth investigations of the observed batch failures have been initiated.

Observation 5 – Bullet 1 response.

Wickliffe Veterinary Pharmacy acknowledges this observation and recognizes the importance of the aseptic process. The investigation into this observation is currently ongoing. Wickliffe Veterinary Pharmacy will provide an update on 12/01/2023.

Observation 5 – bullet 2 response.

Wickliffe Veterinary Pharmacy acknowledges this observation. We reviewed and expanded our investigation. The detailed investigation report is attached as Exhibit 5B. Our expanded investigation revealed no other OOS for low potency on any estrone batches as well as any other sterile products. All information recorded in the Compounding Record for Estrone Lot 497879 was reviewed and found to be within specification. However, our investigation revealed there is not a specified speed setting for mixing the product throughout the filling process. This process improvement has been added to the Estrone Injectable 5mg/mL Master Formula and is attached as exhibit 5C. Wickliffe Veterinary Pharmacy will implement the following preventative actions:

- Preventative Action 14: All master formulas for sterile suspensions have been updated to specify a spin speed to be maintained throughout the filling process.
- Preventative Action 13: Wickliffe Veterinary Pharmacy will engage an outside independent consultant to analyze Wickliffe Veterinary Pharmacy's current potency testing practices to determine what, if any, changes to potency testing frequency Wickliffe Veterinary Pharmacy should implement as detailed in response to observation 4. Wickliffe Veterinary Pharmacy expects to have reviewed any recommendations made by this independent consultant by 12/31/2023.

Observations 5 – bullet 3 response.

Wickliffe Veterinary Pharmacy acknowledges this observation and recognizes the importance of the aseptic process. We have reviewed and expanded our initial investigation. This investigation is currently ongoing. Wickliffe Veterinary Pharmacy will provide an update on 12/01/2023.

FDA Observation # 6

There is no written testing program designed to assess the stability characteristics of drug products. Specifically,

Batches are not put on stability that have been prescribed for office stock. Products prescribed for office stock include Doxycycline Hyclate in Oil Suspension 500mg/mL and Methimazole Suspension 2.5mg/mL. Potency over time or forced degradation is tested for new sterile products, however, other drug quality attributes are not evaluated under long term storage conditions such as impurities formed over time. No stability testing has been performed for non-sterile products.

Wickliffe Pharmacy response to Observation 6:

Wickliffe Veterinary Pharmacy acknowledges this observation. However, Wickliffe Veterinary Pharmacy follows the requirements set forth by the Kentucky Board of Pharmacy and USP 795 in reference to establishing beyond use dates for compounded nonsterile preparations. Wickliffe Veterinary Pharmacy would like to note that both doxycycline hyclate in oil suspension 500mg/mL and methimazole suspension 2.5mg/mL are compounded non-sterile preparations, and as such are tested under different requirements than those listed above for sterile drug preparations. The potency over time testing required by USP 795 was provided for methimazole suspension 2.5mg/mL at the time of the visit. The potency over time testing for doxycycline hyclate in oil suspension 500mg/ml is attached as Exhibit 6A. This testing was conducted by a third-party FDA registered analytical laboratory.

Wickliffe Veterinary Pharmacy no longer dispenses either doxycycline hyclate in oil 500mg/ml suspension or methimazole 2.5mg/ml suspension for office use as they are not on the "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals" or "Bulk Substances Currently Under Review."

Wickliffe Veterinary Pharmacy conducted a thorough review of all customer complaints, adverse event reports and Quality Related Event (QRE) records related to these two preparations for the previous 12 months. The review resulted in the following facts:

- No customer complaints relating to quality issues with any batches produced of these preparations.
- No adverse events reported with any batches produced of these preparations.
- No quality related events reported with any batches produced of these preparations.

New USP 795 standards will become official on 11/01/2023. The new recommendations for establishing beyond use dates introduced the concept of "water activity" to assess the susceptibility of a nonsterile preparation to microbial contamination and the potential for degradation due to hydrolysis. The water activity for an oral oil-based solution such as doxycycline hyclate in oil suspension 500mg/ml is estimated to be < 0.60. Therefore, the beyond use date for this formulation would remain unchanged under the new standards. The water activity for a preserved oral water-based suspension such as methimazole suspension 2.5mg/ml is estimated to be > 0.60. Therefore, the beyond use date for this formulation would be shortened under the new standards.

FDA Observation # 7

Your firm failed to establish adequate written procedures for production and process controls designed to assure that drug products have been identity, strength, purity, and quality that they are purported or represented to possess. Specifically,

1. **On 9/6/2023, during non-sterile observation of Doxycycline (as Hyclate) Powder 5gm/TBSP lot 521872, your firm hand mixed the batch and weighed out scoops to determine if adequate mixing had occurred. Your scoop weights did not meet specification (8.0-9.1 g) during initial weighing of approximately 30 scoops. The batch was hand mixed and an additional 60 scoops were weighed to verify scoop weight was met. The 60 scoops were within the tolerance of 90% of scoops weighing within specification. The initial 30 scoops were weighed out by a different technician than the following 60 scoops.**

This process is manual and has not been validated to assure that each operator can successfully perform adequate mixing and weighing. Processing instructions state to mix by geometric dilution in an appropriately sized bucket/mortar and to mix thoroughly. Mix times and mixing technique are not described.

Scoops weights are used to assure that each scoop contains the desired amount of active ingredient and ingredient adjustments to the formulation are made when scoops weights are not being met. Additionally, the firm did not keep the 30 scoop weight data and only reported the 60 scoops that passed specification in the compounding record,

<u>Wickliffe Pharmacy response to Observation 7:</u>

Wickliffe Veterinary Pharmacy acknowledges the observation and recognizes the importance of written procedures and process controls to assure drug products meet labeled specifications.

Before describing the actions to be taken to address this observation, Wickliffe Veterinary Pharmacy would like to provide a more detailed explanation into the process that was being observed. Each ingredient for this compound is weighed inside of a powder containment hood prior to being mixed via geometric dilution under the immediate supervision of a pharmacist. The combined powders are mixed thoroughly, and scoops are weighed to ensure an even distribution of all ingredients. All scoop weights obtained shall be within +/- 7% of the theoretical scoop weight of the batch, as per SOP "Finished Preparation Assessments, Tests and Quality Assurance". This is a conservative range based on the +/- 10% allowable range noted in USP Chapter 795. The theoretical scoop weight is determined by dividing the total weight of powder in the batch by total number of scoops in the batch. For this observation, initial scoop weights obtained by a compounding technician were out of range. The batch was remixed and again the scoop weights were out of range. The compounding technician was visibly nervous during this process and was sent to break. The compounding pharmacist supervising this batch assessed the 3 previous batches for this compound and observed that all scoop weights were well within the accepted range of +/- 7%. These batches were compounded using the same API manufacturer and same inactive ingredients as the batch that was observed. The pharmacist concluded that the same materials and procedure were followed as previous batches which resulted in acceptable scoop weights. After returning from break and being visibly less nervous, the compounding technician was observed obtaining scoop weights within range. Scoop weights are used as a measure of quality assurance. The compounding pharmacist concluded the inconsistent scoop weights could be attributed to observation bias and nerves and were not a reflection of the quality of this batch. This was based on the powder already being thoroughly mixed twice and the review of the previous batches of the same compound. These scoop weights were discarded based on this determination by the compounding pharmacist.

To prevent future recurrence of this observation, Wickliffe Veterinary Pharmacy has or will implement the following preventative actions:

- Preventative Action 15: All pharmacists and technicians will be retrained to maintain record of all measured scoop weights regardless of investigational outcomes by 10/15/2023.
- Preventative Action 16: Wickliffe Veterinary Pharmacy has retrained the observed technician on how to appropriately collect scoop weights. Documentation is provided as Exhibit 7A.