October 16, 2023

[VIA ELECTRONIC MAIL TO ORAPHARM4_RESPONSES@fda.hhs.gov]

Steven Porter
Program Division Director
Office of Pharmaceutical Quality Operations
Division 4
U.S. Food & Drug Administration

FEI Number:
3005698544

Subject: Authorization to Publish Precision Equine LLC Response dated October 16, 2023 to FDA Form 483

On behalf of Precision Equine 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: Precision Equine LLC's response letter dated October 16, 2023 excluding attachments/exhibits, which responds to FDA's Amended Form 483 dated September 26, 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 Precision Equine LLC. My full name, title, address, telephone number, and facsimile number are set out below for verification.

Sincerely,

Shauna Doherty,
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Precision Equine's Responses to FDA's Inspection Observations

Inspection Dates: 8/23/23-8/25/23, 8/28/23-9/1/23, 9/22/23

FEI Number: 3005698544

Observation 1:

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

Specifically,

A) *Your environmental monitoring (EM) of the ISO 5 Laminar Airflow Hood (LAFH) in Sterile Non-Hazardous Drug Suite and the ISO 5 Biological Safety Cabinet (BSC) in Sterile Hazardous Drug Suite is not performed on a frequent basis to demonstrate that the ISO 5 environment is adequate for the production of sterile drugs. EM was conducted on a monthly basis including viable air sampling and surface sampling. For example, your firm performed EM in Sterile Hazardous Drug Suite on 6/21/23 and 7/18/23 and in Sterile Non-Hazardous Drug Suite on 6/14/23 and 7/14/23. Non-viable air monitoring is conducted biannually during qualification of ISO classified area. For example, the two most recent certifications of LAFH were issued on 3/15/23 and 9/14/22; however, no EM was conducted during manufacturing of each batch. During the period of 7/24/23 to 8/23/23, your firm received 701 prescription orders for sterile compounded drug products. For example, your firm produced Atipamezole Hydrochloride @ 20mg/ml injection, Lot# 04252023@19 on 4/25/2023 and Lot# 05252023@2 on 5/25/2023. No EM was performed during aseptic compounding process for these batches.*

Observation 1A Response:

Precision Equine understands the importance of and has in place processes and procedures necessary to ensure its ISO 5 environments are in a state of control. With this observation the FDA appears to be expecting Precision to meet a cGMP standard associated with sterile production environmental monitoring, a standard that is applicable to FDA-registered entities such as outsourcing facilities and drug manufacturers. As a state-licensed pharmacy, Precision meets or exceeds the environmental monitoring requirements of the California Board of Pharmacy and USP Chapter 797.

According to current USP <797>; "environmental sampling shall occur as part of a comprehensive quality management program and shall occur minimally under any of the following conditions:
• as part of the commissioning and certification of new facilities and equipment;
• following any servicing of facilities and equipment;
• as part of the re-certification of facilities and equipment (i.e., every 6 months);
• in response to identified problems with end products or staff technique; or
• in response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection)."

Additionally, according to California Code of Regulations Section 1751.4 (j), "viable surface sampling shall be done at least every six months for all sterile-to-sterile compounding and quarterly for all non-

sterile-to-sterile compounding." As Precision only performs, non-sterile to sterile compounding, viable surface sampling is only required to be on a quarterly basis.

Precision Equine performs in-house viable sampling on a monthly basis, which is a more frequent basis than required, according to SOP 3.030 "Environmental Monitoring of the Clean Room Facilities". In-house EM includes sampling surfaces and collecting viable air samples utilizing a volumetric air sampler. We would like to correct the EM sampling dates stated above. EM was performed on 6/21/23 and 7/19/23 in the hazardous clean room with no resulting action level. Monthly EM was performed again in the hazardous clean room on 8/16/23 with no resulting action level. In the non-hazardous clean room, EM was performed on 6/14/23 and 7/12/23 with no resulting action level. Monthly EM was performed again in the non-hazardous clean room on 8/9/23 with no resulting action level.

Preventative Action 1: As a continuous improvement, Precision has updated SOP 3.030, Environmental Monitoring of the Clean Room Facilities, and will be implementing newly revised USP <797> sampling standards prior to the November 1, 2023 (Exhibit 1A). Newly revised USP standards for Category 3 compounded sterile preparations (CSPs) require dynamic viable air sampling on a monthly basis in all classified areas using a volumetric impaction air sampling device, as we are currently practicing. In addition, dynamic surface sampling will be required on a weekly basis in all classified areas and pass-throughs. Surface sampling must also occur at the conclusion of each batch in the Primary Engineering Control (PEC) before cleaning occurs.

Preventative Action 2: All sterile compounding personnel will be required to read and undergo applicable training pertaining to new procedures in SOP 3.030, Environmental Monitoring of the Clean Room Facilities, Version 18, by 10/31/23.

Observation 1B:

B) *Personnel monitoring does not follow your procedure. According to your SOP 3.030, Environmental Monitoring of the Clean Room Facilities, Version Number 17.0, personal gloves shall be sampled at least monthly, including when sterile compounding personnel complete, a semi-annual sterile compounding media fill, after garbing and prior to disinfecting gloves; however, your firm sampled personal gloves for microbiological testing only during media fill but not on a monthly basis per your SOP requirement. For example, Technician CH sampled gloved on 1/20/23 and 7/5/23 during media fill for sterile non-hazardous compounded drugs, but there was no monthly sampling conducted in 2023. Also, personnel monitoring is not performed during the manufacturing of each batch.*

Observation 1B Response:

We acknowledge the observation. During the COVID state of emergency, Precision wrote a memo modifying our current policy per SOP 1.010, Policies and Procedures, requiring monthly glove tests due to PPE shortages experienced during the pandemic. According to SOP 1.010, a memo may be used to document pending changes to an SOP prior to a formal SOP review. The memo is signed by all parties involved in the SOP change, then filed with the SOP. The memo stated, "monthly glove tests will be suspended until further notice" and was effective 3/27/20 to last the duration of the state of emergency. Although California ended their state of emergency on 2/28/23 and the federal state of emergency ended 5/11/23, this SOP is required to be reviewed on an annual basis. It was last reviewed during the state of emergency in October 2022, making it due for review October 2023 (Exhibit 1B)

Compliance with USP <797> does not require per batch testing. According to current USP <797>; "After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel for this competency shall occur at least annually for personnel who compound low- and medium-risk level CSPs and semi-annually for personnel who compound high-risk level CSPs using one or more sample collections during any media-fill test procedure before they are allowed to continue compounding CSPs for human use." Precision followed USP since glove tests continued to be performed every six months during media fill assessments throughout the entire pandemic.

Corrective Action 1: Precision has since updated the SOPs 3.030 "Environmental Monitoring of the Clean Room Facilities", Version 18, and 9.130 "Sterile Compounding Process Validations (Media Fills), Version 16, to align with newly revised USP <797> requirements for Category 3 compounded sterile preparations requiring glove tests to be performed every 3 months for compounding personnel directly involved in sterile compounding. SOPs effective 10/10/23 and 10/11/23, respectively. See Exhibits 1A and 1C.

Correction Action 2: All sterile compounding personnel will be required to read and undergo applicable training pertaining to new procedures in SOP 3.030, Environmental Monitoring of the Clean Room Facilities, Version 18, by 10/31/23. Sterile compounding personnel will also be required to read and document understanding of SOP 9.130, Sterile Compounding Process Validations (Media Fills) by 10/31/23.

Observation 1C

C) *On 8/23/23, during the compounding of Acetyl-D-Glucosamine in water for injection 200mg/ml injectable, Lot #08232023@5 in the sterile non-hazardous suite, it was observed sealed double layer bags containing vials, stoppers or utensils placed on a movable cart in the ISO 7 buffer room were introduced into the ISO 5 LAFH one at a time by technician RM, and then the outer layer of each bag was removed by technician GH; however, surfaces of each outer later bag were not sanitized with 70% sterile Isopropyl Alcohol prior to be introduced into the ISO 5 LAFH by technician RM.*

Observation 1C Response:

We acknowledge the observation but would like to clarify the description of events on 8/23/23. Supplies that are double bagged are sanitized before entering the buffer room and remain on carts prior to use. This step was not observed at the time of inspection. When the filtering technician is ready, the assisting technician will open the first bag at the edge of the ISO 5 area while the processing technician inside the Primary Engineering Control (PEC) pulls out the inner sterile bag to be staged in the direct compounding area within the PEC. The processing technician does not touch the outer autoclave bag. According to Precision's SOP 1.060, General Aseptic Technique, "containers shall be wiped down with sterile IPA prior to placement in the PEC to prevent possible contamination." Since these bags were not placed in the PEC, Precision was adhering to its policies. This same practice is done with all media fills to mimic the procedures done with compounded preparations. There have been no failed media fills over the past 12 months. Precision also has passing sterility tests for all compounded sterile batches within the assigned beyond use date utilizing this technique in the non-hazardous clean room.
Additionally, we are compliant with USP <797>. According to newly revised USP <797> Section 8.2, this practice is acceptable and specifically described: "When sterile items are received in sealed containers designed to keep them sterile until opening, the sterile items may be removed from the covering as the

supplies are introduced into the ISO Class 5 PEC without the need to wipe the individual sterile supply items with sterile 70% IPA (isopropyl alcohol).

We would also like to clarify, Precision does not have a technician with the initials, "GH".

Preventative Action 3: In an effort for continuous quality improvement, Precision will perform a reinforcement of current practice of the sterile compounding technicians on proper procedures of disinfection and staging supplies according to SOP 9.130, Attachment 2, "USP Assessment – 797: Aseptic Technique and Related Practices of Compounding Personnel (Media Fills)". Additionally, more specific language will be added to SOP 1.060, General Aseptic Technique, outlining the staging process to harmonize current practice with the acceptable procedures outlined in newly revised USP <797>, Section 8.2. Along with reinforcement of current practice, technicians will be randomly audited by a sterile compounding supervising pharmacist three times to ensure compliance starting early November 2023. They will also be audited quarterly with scheduled media fill assessments, thereafter.

Observation 1D:

D) *During aseptic compounding of Acetyl-D-Glucosamine in water for injection, 200mg/ml injectable, Lot #08232023@5 in the sterile non-hazardous suite on 8/23/23 and Histrelin (Histrelin Acetate) @ 0.5mg/ml injection, Lot #08252023@1 in the sterile hazardous drug suite on 8/25/23, it was observed on both occasions technicians forehead was not fully covered by a hairnet and hair on the back of neck was exposed.*

Observation 1D Response:

Precision acknowledges your observation and understands the significance of proper garbing to reduce the risk of contamination when compounding sterile preparations. With this observation, FDA appears to expect garbing standards according to cGMP. As Precision is a state-licensed pharmacy, forehead and neck coverings are not required for sterile compounding according to current USP <797> and California Board of Pharmacy laws and regulations. Precision is in compliance with the current "head covering" (hairnet) requirement.

According to current USP <797>; "Personnel shall don the following PPE in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs."

Additionally, according to California Code of Regulations Section 1751.5(a)(1); "Personal protective equipment consisting of a non-shedding gown, head cover, face mask, facial hair covers (if applicable), and shoe covers must be worn inside the designated area at all times. For hazardous compounding double shoe covers are required."

Preventative Action 4: Precision will update SOP 9.120, "Required Garb for Clean Room Facility Access", by 11/1/23 to be compliant with newly revised USP <797> which will require forehead and neck coverings to compound Category 3 CSPs. Employee training on proper garbing procedures according to SOP 9.120 will be completed before 11/1/23.

Observation 1E:

E) There is no air return vent in the Sterile Non-Hazardous Drug Suite. The return air blows out from the ISO 7 cleanroom directly into the unclassified non-sterile drug production area through an air filter taped on from the outside on all four sides of the cleanroom suite.

Observation 1E Response:

We acknowledge the observation but disagree with the findings that the facility design does not prevent microbial contamination.

According to current USP <797>, clean room facility design shall be as follows: "HEPA-filtered supply air shall be introduced at the ceiling, and returns should be mounted low on the wall, creating a general top-down dilution of area air with HEPA-filtered make-up air." Precision is in compliance with this facility design for the non-hazardous clean room. HEPA-filtered air comes from the ceiling in the ISO 7 buffer room and exits through returns mounted low on the wall. Since this room is positive pressure relative to adjacent spaces, air flows to the general pharmacy. The air is then gathered from the general pharmacy through an intake on top of the clean room and re-filtered through HEPA filters before entering the non-hazardous clean room.

The non-hazardous clean room maintains an environment preventing microbial contamination as evident by the semi-annual certification according to CETA guidelines and consistent with appropriate ISO classifications. There have been no environmental monitoring action levels for any compounded sterile preparations processed in this area within their beyond use date.

Preventative Action 5: While we believe our facility and practice meets current regulatory requirements, we are committed to continuously improving our quality processes and as such plan on modifying the design of this clean room by directly ducting return air to the clean room intake. The anticipated remodel date is 10/24/23.

Observation 1F:

F) Your firm has not established and/or validated a hold time for supplies after depyrogenation. Your firm performed in-house depyrogenation of beakers and utensils used for producing sterile compounded animal drug products. For example, your firm used the depyrogenated glass beaker wrapped with foil to produce Detomidine HCl/Xylazine 2.5mg/100mg/ml injectable, Lot # 05052023@1 on 5/5/23; Your firm stated that in general, a beaker after depyrogenation could be held for 7 days; however this hold time has not been well established and validated. Also, your firm has established a 6-month hold time for vials placed in a pouch by operators used for producing sterile compounded drug products. For example, your firm produced Xylazine in water for injection @ 333mg/ml injectable, Lot# 04192023@2 on 4/19/2023 using a depyrogenated pouch dated 3/27/2023; however, you have not validated the 6-month hold time.

Observation 1F Response:

We acknowledge the observation but there are no requirements in USP <797> or California Board of Pharmacy Laws and Regulations to establish validated hold times for depyrogenated or autoclaved

supplies. Precision is a registered pharmacy in the state of California and it appears the FDA is holding us to CFR 210 and 211 standards which are not applicable to state-licensed pharmacies.

As discussed during the inspection, depyrogenated glassware is stored for a short period of time after depyrogenation, before use. Most beakers are used within 7 days of depyrogenation. Dates of depyrogenation are documented on the top of the foil wrapper beaker. The depyrogenated beaker observed on 9/22/23 had a depyrogenation date of 9/20/23.

Preventative Action 6: In general, foil-wrapped glassware is used within 7 days but in an effort of continuous improvement, glassware will be re-processed after 30 days. Precision will update SOP 1.060, General Aseptic Technique, to include a detailed procedure on dating foil-wrapped glassware with depyrogenation dates along with allowing the use of this glassware within 30 days of the depyrogenation date. If foil-wrapped glassware exceeds the 30 day timeline, SOP will outline instructions for re-processing. Sterile compounding staff and maintenance staff will be trained on this SOP by 12/31/23.

Precision would like to clarify that we do not use "depyrogenated pouches" as mentioned in Observation 1F regarding Xylazine 333mg/ml injection Lot# 04192023@2. Precision does sterilize some supplies in-house utilizing autoclave pouches. Additionally, inspectors were provided, at the time of inspection, with a statement from Dynarex, manufacturer of one of the autoclave bags, stating if the bag is left closed, the sterility shelf life is 6 months from the date of sterilization (Exhibit 1D). Medicom, another autoclave bag manufacturer used at Precision, provided a statement saying, "sterilization pouch maintains enclosed devices sterile up to one-year post-sterilization" (Exhibit 1E page 2). As a procedure, Precision uses the more conservative hold time provided by Dynarex for all autoclaved materials in a sealed autoclavable pouch of six months as stated in SOP 1.060, General Aseptic Technique (Exhibit 1F).

Observation 2:

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

Specifically,

Your firm has not performed sterility testing for any sterile compounded drug products to determine an extended beyond use date (BUD). For example, your firm assigned an extended BUD for 180 days for Ammonium Sulfate 0.75% Injection, Adenosine Monophosphate 200mg/ml injection, L-Arginine HCl 200mg/ml injection and Xylazine (base) 333mg/ml injection based on potency testing; however, sterility testing was only conducted at release of a batch, but not during stability study, so there is no assurance sterility could be maintained throughout the shelf life of each product. An example of product label for Xylazine in water for injection @ 333mg/ml injectable, Lot# 04192023@2 (compounding date: 4/19/2023) associated with Rx 00399595 shows "Discard After 10/16/23".

Observation 2 Response:

We acknowledge the observation but disagree with the conclusion that the stability studies were not complete or robust enough to assure sterility was maintained throughout the 180-day BUD. Stability studies are designed and documented in accordance with current USP <797> standards and California

Board of Pharmacy Laws and Regulations. As discussed at the inspection, Precision assigns BUDs according to SOP 9.050, Determination and Extension of Beyond-Use Dates (BUD) for Compounded Preparations. As described in this SOP, sterility testing is performed in accordance with USP <71> at timepoint zero. Container closure integrity tests have been performed on all sterile containers used for compounded sterile preparation (CSP) packaging. Container integrity is indicative of sterility being maintained up to the labeled BUD assuming a passing result from the initial sterility test.

Preventative Action 7: While Precision believes we are currently in compliance with regulatory BUD requirements, we are in the process of conducting additional testing on sterile formulations for BUD extension for Category 3 CSPs effective 11/1/23 according to newly revised USP <797> requirements.

Observation 3:

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

Specifically,

According to SOP 9.010, The Quality Assurance Program, Version Number 12.0, potency test will be conducted for at least 25% of compounded formulations made annually for sterile drug products and at least 10% for non-sterile drug products; however there is no assurance your finished drug products conform to product specifications from batch to batch without conducting appropriate testing. For example, your firm did not conduct potency testing for most batches of finished drug products prior to release, examples listed as follows: Rx 403123 Diclazuril/Levamisole in oil @ 30mg/80mg/ml suspension Batch #08072023@43, Rx 393017 Doxycycline in oil (FC) @ C 100mg/ml suspension Batch #04182023@3, Rx I90040102 Enrofloxacin > C 200mg/ml paste Batch #05222023@27, Rx 398192 Estradiol Cypionate in Sesame Oil @ 2mg/ml injectable Batch #C04112023@3, Rx 394902 Fluoxetine @ 200mg/scoop powder Batch#08032023@45, Rx 396041 Gentamicin Sulfate/Ketoconazole/Dexamethasone Topical Ointment @ 0.3%/2%/0.1% Ointment Batch #07072023@37, Rx 399799 Histrelin (As Histrelin Acetate) @ 0.5mg/ml injectable Batch #07112023@5, Rx I90039017 Enrofloxacin 200mg/ml suspension Batch #07272023@27.

Observation 3 Response:

We acknowledge the observation that the specific lot numbers listed were not potency tested prior to release. According to California Board of Pharmacy Laws and Ragulations, the quality assurance plan shall include a schedule for routine testing and analysis of specified compounded drug preparations to ensure integrity, potency, quality, and labeled strength, on at least an annual basis. Precision follows a potency testing program as specified in SOP 9.010, The Quality Assurance Program, which outlines the percentage of formulas made on an annual basis that need to be sent for potency testing. Year to date, we have sent 8 sterile potency samples and need to send a total of 11 samples before 12/31/23. For non-sterile samples, we have sent a total of 92 and to comply with our SOP, need to send a total of 100 Before 12/31/23. Based on the number of samples sent year-to-date, we are on schedule to send the required samples as outlined in SOP 9.010.

Observation 4

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

Specifically,

During the walk-through of the facility on 8/23/2023, contamination was observed in your sterile and non-sterile production areas for the following:

A) Unknown yellow stains were observed on HEPA filters inside the ISO 5 LAFH used for producing sterile non-hazardous animal drug products in the Sterile non-hazardous suite.

B) The frame of the HEPA filter inside the LAFH peeled off in the Sterile Non-Hazardous Drug Suite.

Observation 4A/B Response:

We acknowledge the observation, but for clarity, LAFH 1 was observed to have the observations listed in Observation 4A/B while LAFH 2, in the same ISO 7 buffer room, was inspected with no issues. In an abundance of caution, LAFH 1 was not used after discussing the possible issues during inspection until a full assessment could be made. A qualified third-party certifier, utilizing CETA guidance, conducted a HEPA leak test on LAFH 1 with the discolored HEPA filter on 9/12/23. The HEPA filter passed the leak test showing the filter was not compromised despite the discoloration. The HEPA filter in LAFH 1 was then replaced on 9/13/2023. The paint chips observed were repaired also on 9/11/2023 prior to replacing the HEPA filter (Exhibit 4A). All batches compounded in LAFH 1 within their beyond use date have passed sterility testing. There have been no environmental monitoring action levels or customer complaints of adverse reactions for any compounded sterile preparations processed using the equipment identified in Observation 4A/B within their beyond use date.

Precision understands the importance of regular inspection of HEPA filters as outlined in SOP 4.200, Use and Maintenance of the Air Sciences Powder Containment/Fume Hoods/BSC Class I & II/LAFW, weekly visual inspections are required. If any abnormalities are observed, it must be reported to the Facility Supervisor and sterile compounding pharmacist on duty. Abnormalities shall be addressed/corrected before compounding resumes. Additionally, non-passing units shall not be used for compounding until repaired and recertified by a contracted third party.

Corrective Action 3: To reinforce the importance of this process, sterile staff was re-trained on SOP 4.200 for weekly visual inspections of LAFH HEPA filters and appropriate reporting to the Facility Supervisor and sterile compounding pharmacist on duty. Re-training was performed on 10/10/23 (Exhibit 4B).

Corrective Action 4: In addition to staff re-training, the Facility Supervisor has started performing monthly audits as of 10/10/23 to ensure visual inspections are conducted at the frequency outlined in the SOP and to ensure proper reporting is occurring.

Corrective Action 5: Precision has updated SOP 1.030, Deviations- OOS and Corrective and Preventative Action (CAPA) Management, to expand the definition of procedural deviations to include equipment abnormalities utilized in aseptic processing or equipment abnormalities that have the potential of cross-

contamination risk. All procedural deviations require a documented investigation (Exhibit 4C). Precision also updated SOPs 1.040, Use and Control of LUMACs, and 4.010, Compounding Equipment, to include reporting instructions of equipment abnormalities to the Facility Supervisor and pharmacist supervisor with specific responsibilities for each (Exhibits 4D and 4E). SOP 1.040, Use and Control of LUMACs, also has an increased frequency of equipment review from annually to monthly. SOPs are effective as of 10/13/23. Staff training will be completed by 11/15/23.

Observation 4C/D:

C) Many white stains were observed on scales and walls of three powder hoods (#9, #10, #11) used for producing sterile non-hazardous drug products.

D) Unknown stains were observed on a scale inside the powder hood used for compounding of sterile hazardous drug products in the Sterile Hazardous Drug Suite.

Observation 4C/D Response:

We acknowledge the observation. Precision acknowledges the importance of regular equipment checks for discoloration and abnormalities. We would like to clarify, observations noted in 4C and 4D are in the ISO 8 preparation area, not in the ISO 5 buffer area, of the clean room where non-sterile ingredient mixing, and manipulations occur before batches are brought into the ISO 7 buffer area for aseptic processing. All batches compounded using this equipment, within their beyond use date, have passed sterility testing. There have been no environmental monitoring action levels in the hazardous clean room ISO 8 area for any compounded sterile preparations processed using this equipment within their beyond use date. Additionally, no customer complaints of adverse reactions for any compounded sterile preparations processed using the equipment identified in Observation 4C/D within their beyond use date have been reported.

Corrective Action 6: Walls of powder hoods (9,10,11) have since been replaced on 9/29/23, 10/9/2023 and 10/10/2023, respectively, and documented in the corresponding LUMACs (Exhibit 4F).

Corrective Action 7: All scales with white discoloration have been replaced or put out of service if the discoloration could not be removed as of 10/10/2023 (Exhibit 4G). A scale and hood used for weighing dimethylacetamide will be dedicated to this process and have a disposable protective covering to prevent permanent discoloration for future batches.

Corrective Action 5 (from Observation 4A/B Response): Precision has updated SOP 1.030, Deviations-OOS and Corrective and Preventative Action (CAPA) Management, to expand the definition of procedural deviations to include equipment abnormalities utilized in aseptic processing or equipment abnormalities that have the potential of cross-contamination risk. All procedural deviations require a documented investigation (Exhibit 4C). Precision also updated SOPs 1.040, Use and Control of LUMACs, and 4.010, Compounding Equipment, to include reporting instructions of equipment abnormalities to the Facility Supervisor and pharmacist supervisor with specific responsibilities for each (Exhibits 4D and 4E). SOP 1.040, Use and Control of LUMACs, also has an increased frequency of equipment review from annually to monthly. SOPs are effective as of 10/13/23. Staff training will be completed by 11/15/23.

Observation 4E:

E) Unknown powders/residues were observed on a scale inside Powder Hood 22 used for producing non-sterile products while the hood was not in use on that day.

Observation 4E Response:

We acknowledge the observation but disagree with your conclusions. We believe the residue observed to be left behind from a cleaning agent. Precision's SOP 3.050, Cleaning and Maintenance of the Non-Sterile Compounding Areas currently states equipment must be cleaned and disinfected on a daily basis, as needed.

Preventative Action 8: Precision is in the process of updating SOP 3.050, Cleaning and Maintenance of the Non-Sterile Compounding Area to cleaning frequencies outlined in newly revised USP <795>, effective 11/1/2023. The new update outlines minimum cleaning and sanitizing frequencies which must be done at minimum, at the beginning and end of each shift when compounding occurs, after spills and when surface contamination is known or suspected. Cleaning and sanitizing must also occur on work surfaces between compounding non-sterile preparations with different components. Once the SOP is updated, non-sterile compounding and maintenance staff will be trained and assessed on proper procedures. We will be compliant with new cleaning frequencies by 10/31/2023. Once training of staff occurs, regular weekly focused audits performed by the Non-Sterile Compounding Supervisor and team leads will occur for the first three months after implementation and will be incorporated into our routine auditing process thereafter.

Observation 4F:

F) Opened drink cans and drink cups with visible liquid and spoons were discarded in trash bins in the non-sterile production area.

Observation 4F Response:

We acknowledge the observation. We would like to clarify the observation of spoons found in trash bins in the non-sterile compounding area. These are single use spoons used for weighing out powders and other compounding manipulations, not eating. Food and drinks are not allowed in the non-sterile compounding area while actively compounding according to SOP 9.160, Attachment 2, Non-Sterile Compounding Process Validation (Exhibit 4H).

Corrective Action 8: In an effort of continuous quality improvement and compliance with pharmacy SOPs, Precision set up a drink storage area in the pharmacy entry way outside of the non-sterile compounding area where staff can keep drinks nearby. Signs have been posted to notify staff that drinks will not be allowed past a certain point in the entry. Re-training of staff was performed on 9/29/23 (Exhibit 4I), to ensure staff are aware of drink storage area and defined boundaries. Precision will also update SOP 3.040, Non-Sterile Compounding Area Requirements, before 11/1/2023 to include language for food and drink to remain outside of the non-sterile compounding area.

Preventative Action 9: Regular weekly focused audits performed by the Facility Supervisor will occur for the first three months after re-training and will be incorporated into our routine auditing process thereafter.

Observation 4G:

G) A filter used to filter supply air inside the wall of the ISO 7 Negative Pressure Clean Room next to the ISO 5 BSC looked dirty with apparently visible debris in the Sterile Hazardous Drug Suite.

Observation 4G Response:

All filters were examined in this area including the ones in the ceiling and on top of the BSC. No visible debris was observed. There is no filter in the "wall" of the ISO 7 Negative Pressure Clean Room in the Sterile Hazardous Clean Room. Air supply only comes from the ceiling in this room. Please refer to Hazardous Clean Room Diagram (Exhibit 4J).

Observation 5

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

Specifically,

Your firm does not conduct microbiological testing of finished non-sterile drug products for both patient-specific prescriptions and office use. Your firm produces compounded non-sterile drug products for the following dosage forms: scoop powders, oral liquids, oral pastes, topical creams, topical ointments, transdermal gels, oral capsules, otic preparations.

For example, microbiological testing was not conducted for batches produced during the period of 5/23/2023 to 8/23/2023 prior to release for the following: Rx I90039017 Enrofloxacin 200mg/ml susp Lot# 07272023@27, Rx I90040224 Methimazole 5mg/0.1ml in Lipoderm Transdermal Gel Lot# 05302023@48, Rx I90040440 Enrofloxacin 150mg/ml in oil susp Lot# 07172023@8, Rx 90039584 Praziquantel/Pyrantel/Fenbendazole 45.4mg/45.4mg/50mg/ml in oil susp Lot# 08152023@28, Rx 399434 Acetazolamide 250mg/ml in oil susp Lot#06142023@8, Rx 400961 Azithromycin 200mg/ml in oil susp Lot# 06092023@20, Rx I90038191 Enrofloxacin 200mg/ml paste Lot# 06052023@6.

Observation 5 Response:

We acknowledge your observation but disagree as microbiological testing is not required of a state licensed pharmacy according to USP <795> and California Board of Pharmacy Laws and Regulations for non-sterile compounds. The current and newly revised USP <795> only require visual inspection of the final compounded non-sterile preparation prior to release. This release check is clearly documented on the compounding record by a pharmacist for all non-sterile batches, currently.

Observation 6

Component testing is deficient in that each component is not tested for conformity with all appropriate written specifications for purity, strength and quality.

Specifically,

Your firm does not perform identity testing for any bulk drug substances used for producing compounded animal drugs.

Your firm purchased sterile water for injection (WFI) for compounding of sterile animal drug products; however, certificates of analysis are not validated to ensure conformity.
For example, sterile water for injection, USP, Lot# Y416559 was used to compound Cimetidine in water for inj @150mg/ml injectable, Lot# 07052023@4 on 7/5/2023. Release of WFI is based on review of Certificate of Analysis without appropriate tests being conducted for validation.

Observation 6 Response:

We acknowledge your observation but disagree as sterile water for injection, USP (SWFI) is an FDA approved manufactured product produced in an FDA-registered facility, not a bulk drug substance. USP and California Board of Pharmacy Laws and Regulations do not require sample testing of an FDA approved finished good or bulk drug substance used in compounding. Precision relies on the Certificate of Analysis (COA) provided by the supplier. Precision approves vendors according to the requirements outlined in SOP 6.010, Product Procurement, Receipt, Inspection and Chemical Supplier Qualification (Exhibit 6A), therefore relying on the supplier to provide quality ingredients with appropriate testing as stated in the COA. Upon receipt, all chemicals are quarantined from regular inventory in shipping and receiving until a pharmacist inspects the chemical container and matches the Certificate of Analysis to the chemical. The pharmacist will then initial and date the Certificate of Analysis. Once this process is complete, the chemical may be released from the quarantine area. If the pharmacist determines the chemical needs to undergo further analytical testing, it will remain in quarantine until testing is complete.

California Board of Pharmacy Laws and Regulations states (c) Active ingredients shall be obtained from a supplier registered with the Food and Drug Administration (FDA). All other chemicals, bulk drug substances, and drug products used to compound drug preparations shall be obtained, whenever possible, from FDA-registered suppliers.

Accordingly, sterile water for injection is not an active ingredient. It is an FDA manufactured product produced in an FDA-registered facility and as such would be an acceptable component for use in compounded preparations according to USP standards and California Board of Pharmacy Laws and Regulations.

Observation 7

Written records are not made of investigations into unexplained discrepancies.
Specifically,
Your firm did not conduct inspections of nonconformances for compounding animal drug products, examples listed as follows:

A) *Many white stains were observed on surfaces of scales and walls of three powder hoods (#9, #10, #11) used for producing sterile non-hazardous drug products that could not be cleaned or removed. Your firm attributed the root cause to spill of a chemical- dimethylacetamide during production; however, there is no documented evidence showing your firm has conducted an investigation and risk analysis on its potential impact on product quality during compounding of sterile drug products.*

Observation 7A Response:

We acknowledge the observation that the discoloration observed was most likely caused by splashes from a single ingredient, dimethylacetamide, on equipment. Precision acknowledges the importance of regular equipment checks for discoloration and abnormalities. We would like to clarify, observations noted are in the ISO 8 preparation area, not in the ISO 5 buffer area, of the clean room where non-sterile ingredient mixing, and manipulations occur before batches are brought into the ISO 7 buffer area for aseptic processing. All batches compounded using this equipment, within their beyond use date, have passed sterility testing. There have been no environmental monitoring action levels in the hazardous clean room ISO 8 area for any compounded sterile preparations processed using this equipment within their beyond use date. Additionally, no customer complaints of adverse reactions for any compounded sterile preparations processed using the equipment identified in Observation 4C/D within their beyond use date have been reported.

Corrective Action 6 (From Observation 4C/D Response): Walls of powder hoods (9,10,11) have since been replaced on 9/29/23, 10/9/2023 and 10/10/2023, respectively, and documented in the corresponding LUMACs (Exhibit 4F).

Corrective Action 7 (From Observation 4C/D Response): All scales with white discoloration have been replaced or put out of service if the discoloration could not be removed as of 10/10/2023 (Exhibit 4G). A scale and hood used for weighing dimethylacetamide will be dedicated to this process and have a disposable protective covering to prevent permanent discoloration for future batches.

Corrective Action 5 (From Observation 4A/B Response): Precision has updated SOP 1.030, Deviations-OOS and Corrective and Preventative Action (CAPA) Management, to expand the definition of procedural deviations to include equipment abnormalities utilized in aseptic processing or equipment abnormalities that have the potential of cross-contamination risk. All procedural deviations require a documented investigation (Exhibit 4C). Precision also updated SOPs 1.040, Use and Control of LUMACs, and 4.010, Compounding Equipment, to include reporting instructions of equipment abnormalities to the Facility Supervisor and pharmacist supervisor with specific responsibilities for each (Exhibits 4D and 4E). SOP 1.040, Use and Control of LUMACs, also has an increased frequency of equipment review from annually to monthly. SOPs are effective as of 10/13/23. Staff training will be completed by 11/15/23.

Preventative Action 10: To prevent splashes and spills of dimethylacetamide in the future, compounding batch instructions have been updated to pour the ingredient into a separate beaker from the supplier's container before adding the liquid to the weighing beaker on the scale. This will ensure more pouring control, preventing spills on the scale, as it is easier to pour from a beaker rather than the supplier's container. Instructions have also been updated to add dimethylacetamide incrementally to the mixing vessel, preventing splashes on the inside of the powder hood, instead of all at once.

Observation 7B

B) *Unknown yellow stains were observed on HEPA filter inside the ISO 5 LAFH used for producing sterile non-hazardous animal drug products in the Sterile Non-Hazardous Drug Suite; however, there is no documented evidence showing your firm has investigated the root cause and its potential impact on product quality.*

Observation 7B Response:

We acknowledge the observation. In an abundance of caution, LAFH 1 was not used after discussing the possible issues during inspection until a full assessment could be made. A qualified third party certifier, utilizing CETA guidance, conducted a HEPA leak test on LAFH 1 with the discolored HEPA filter on 9/12/23. The HEPA filter passed the leak test showing the filter was not compromised despite the discoloration. The HEPA filter in LAFH 1 was then replaced on 9/13/2023. The paint chips observed were also repaired on 9/11/2023 prior to replacing the HEPA filter (Exhibit 4A). All batches compounded in LAFH 1 within their beyond use date have passed sterility testing. There have been no environmental monitoring action levels or customer complaints of adverse reactions for any compounded sterile preparations processed using the equipment identified in Observation 7B within their beyond use date.

Precision understands the importance of regular inspection of HEPA filters as outlined in SOP 4.200, Use and Maintenance of the Air Sciences Powder Containment/Fume Hoods/BSC Class I & II/LAFW, weekly visual inspections are required. If any abnormalities are observed, it must be reported to the Facility Supervisor and sterile compounding pharmacist on duty. Abnormalities shall be addressed/corrected before compounding resumes. Additionally, non-passing units shall not be used for compounding until repaired and recertified by a contracted third party.

Corrective Action 3 (From observation 4A/B response): To reinforce the importance of this process, sterile staff was re-trained on SOP 4.200 for weekly visual inspections of LAFH HEPA filters and appropriate reporting to the Facility Supervisor and sterile compounding pharmacist on duty. Re-training was performed on 10/10/23 (Exhibit 4B).

Corrective Action 4 (from observation 4A/B response): In addition to staff re-training, the Facility Supervisor has started performing monthly audits as of 10/10/23 to ensure visual inspections are conducted at the frequency outlined in the SOP and ensuring proper reporting is occurring.

Corrective Action 5 (From Observation 4A/B Response): Precision has updated SOP 1.030, Deviations-OOS and Corrective and Preventative Action (CAPA) Management, to expand the definition of procedural deviations to include equipment abnormalities utilized in aseptic processing or equipment abnormalities that have the potential of cross-contamination risk. All procedural deviations require a documented investigation (Exhibit 4C). Precision also updated SOPs 1.040, Use and Control of LUMACs, and 4.010, Compounding Equipment, to include reporting instructions of equipment abnormalities to the Facility Supervisor and pharmacist supervisor with specific responsibilities for each (Exhibits 4D and 4E). SOP 1.040, Use and Control of LUMACs, also has an increased frequency of equipment review from annually to monthly. SOPs are effective as of 10/13/23. Staff training will be completed by 11/15/23.

Observation 8:

The quality control unit lacks the responsibility and authority to approve and reject all components. Specifically,

Your firm used ungraded ingredients to produce non-sterile compounded drug products for animal use with examples listed for the following:

Chromium Picolinate, Lot# 190122/A used to produce Chromium Picolinate @ 10mg/scoop powder, Lot# 190122/A on 6/6/23

Stevia (Stevioside 90%) Powder, Lot# 20221007 used to produce Ponazuril in oil >C 150mg/ml suspension

The ingredients are ungraded according to the Certificate of Analysis and label from each supplier.

Observation 8 Response:

We acknowledge your observation but Precision does have quality control personnel with the authority to approve and reject all components. According to SOP 6.010, Product Procurement, Receipt, Inspection and Chemical Supplier Qualification, if a chemical is found in non-conformance, it shall be brought to the attention of the pharmacist on duty immediately. The procedure states the pharmacist shall ask the supplier to conduct an internal investigation. Based on the supplier's findings, it will be at the discretion of the Pharmacist-in-Charge to keep the supplier in active status. According to the SOP, if non-conformance is confirmed, the ingredients shall be quarantined, and the supplier must provide instructions to return or destroy the material.

Additionally, with the upcoming newly revised USP <795> and <797> chapter implementation, there will be a designated responsible person for non-sterile compounding requirements and another for sterile compounding requirements. These supervisors will be directly responsible for the ingredients received by the pharmacy for specific sterile and non-sterile compounding needs and will have the authority to approve and reject all components.

According to USP <795>, when components of compendial quality are not obtainable, components of high quality such as those that are chemically pure, analytical reagent grade, or American Chemical Society–certified may be used. We obtained these materials that were of the highest grade.

Stevia does not have a USP or NF monograph and is an excipient used as a sweetening agent in non-sterile oral preparations. Based on the COAs provided by the supplier and at the time of inspection, many tests were performed, and this ingredient has been deemed high quality by a reputable supplier. After the inspection concluded, NutriScience (supplier of Stevia), sent a statement confirming Stevia is food grade (Exhibit 8A). Although there is no requirement to use food grade ingredients according to USP standards, Precision felt it important to confirm the ingredient is high quality and is deemed food grade.

Chromium Picolinate is a dietary supplement used for non-sterile oral compounded preparations. This product meets the USP dietary supplement monograph testing requirements. The supplier provided the original manufacturer's COA which states the ingredient is USP food grade (Exhibit 8B).