

22 March 2017

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To: US FDA Seattle District Office (SEA-DO)  
ATTN: Miriam R. Burbach, District Director, SEA-DO  
Tracy Li, Consumer Safety Officer, SEA-DO  
Gerard P. De Leon, Consumer Safety Officer, SEA-DO  
22215 26th Ave. SE, Suite 210  
Bothell, WA 98021

Re: Posting of FDA Form 483 Response

Hello,

Please accept this letter as authorization to post on the US FDA Internet website RAM Pharma, Inc.'s response to the FDA Form 483 Notice of Observations, dated 22 March 2017, as submitted to SEA-DO, un-redacted but without attachments. We understand this response will be posted under the FDA Form 483 Notice of Observations for RAM Pharma, Inc., issued on 1 March 2017, by CSO's Li (SEA-DO) and De Leon (SEA-DO).

Thank you,



Robert A. Myers, PhD, RPh  
RAM Pharma, Inc.  
1125 Hollipark Drive  
Idaho Falls, ID 83401  
Tel: (208) 419-0613

FEI: 3012465222, RAM Pharma, Inc.

DOI: 07 February 2017 to 01 March 2017

22 March 2017

To: US FDA Seattle District Office (SEA-DO)  
ATTN: Miriam R. Burbach, District Director, SEA-DO  
22215 26th Ave. SE, Suite 210  
Bothell, WA 98021

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Response to Form FDA 483 issued on 1 March 2017 to RAM Pharma, Inc., 1125 Hollipark Drive, Idaho Falls, ID 83401.

FEI: 3012465222, RAM Pharma, Inc.  
DOI: 7 February 2017 to 1 March 2017\*

\*Inspection Dates: 2/7/2017, 2/8/2017, 2/9/2017, 2/10/2017, 2/13/2017, 2/15/2017, 3/1/2017.

#### OBSERVATION 1

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

A) An ATRIX VACOMEGASCT ESD 1 gallon vacuum was observed in use by the operator to vacuum the floor of the ISO 7 Cleanroom prior to the production of sterile drug Eylea 2mg/0.05mL injection, lot 201702081 on 2/8/17. Your SOP 05-001 Clean Suite Cleaning and Sanitizing Operation requires that you "\*\*\*\*Use UHEPA vacuum to clean floors" for daily cleaning.

Response: SOP 05-001 has been revised to replace the use of the HEPA vacuum with a clean room tacky roller. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

B) Media fills for the production operator were not performed prior to conducting sterile drug production of the first batch of sterile drug product on 7/26/16. From 7/26/16 to 2/8/17, 105 batches were produced without media fills being performed for the production operator according to the assigned schedule outlined in the following SOPs:

1) SOP 08-006 Personnel Monitoring - High-Risk Media Fill requires that "\*\*\*\*Each person authorized to compound high-risk level CSPs must perform this procedure semiannually."

Response: Compounding personnel will now follow this SOP and the high-risk media fill will be performed semi-annually. The first media fill test will be initiated by 1 May 2017.

2) SOP 08-007 Personnel Monitoring -Low-Risk Media Fill requires that "\*\*\*\*Persons authorized to compound must perform this procedure at least once annually."

Response: Compounding personnel will now follow this SOP and the low-risk media fill will be performed annually. The first media fill test will be initiated by 1 May 2017.

3) SOP 08-008 Personnel Monitoring -Medium-Risk Media Fill requires that  
"\*\*\*Persons authorized to compound must perform this procedure at least once annually."

Response: Compounding personnel will now follow this SOP and the medium risk media fill will be performed annually. The first media fill test will be initiated by 1 May 2017.

C) On 2/8/17 and 2/10/17 loose individual sterile gloves previously worn during sterile drug production were observed on a table stored next to open autoclaved bags of previously worn sterile gloves.

Response: All previously worn sterile gloves have been removed from the room. SOP 09-003 has been updated to reflect that sterile gloves and sterile disinfectants and wipes are to be used in the cleanroom. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

## OBSERVATION 2

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

A) Your environmental monitoring (EM) procedure SOP 08-004 Environmental Monitoring - Microbial is deficient in that it states to "\*\*\*\*Perform surface sampling in all ISO classified areas on a periodic basis." In addition, you are not performing EM according to the following methodologies and frequencies as you currently rely on EM to be performed by a third-party certifier every six months:

1) Viable air sampling is not performed in the Baker EG-4320, S/N 55304 ISO 5 horizontal laminar flow hood (LFH) when sterile drug products are produced.

Response: SOP 08-004 has been updated to include the use of open growth media plates in the ISO 5 LFH during sterile production. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

2) Surface sampling for microbiological monitoring is not performed in the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH when sterile drug products are produced.

Response: SOP 08-004 has been implemented to include surface sampling when sterile drug products are produced. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

3) Personnel monitoring is not conducted of production operators at least daily when sterile drug products are produced.

Response: SOP 08-004 has been implemented to include a fingertip touch plate test of the clean room operator daily when sterile drug products are produced. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

4) Non-viable air sampling is not performed in the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH and adjacent ISO-classified areas when sterile drug products are produced.

Response: SOP 08-004 has been updated to include a non-viable particulate air sampling of the ISO Class 5 LFH and adjacent ISO Class 7 room when sterile drug products are produced. This testing will be performed during the clean room suite certification. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

B) You are not following your SOP 09-002 Sterile Production Procedure which requires that "Hoods and aseptic environmental control devices must be certified for operational efficiency as often as recommended by the manufacturer or at least every six (6) months or if relocated." For example:

1) Certification of your Baker EG-4320, S/N 55304 ISO 5 horizontal LFH and adjacent ISO-classified areas expired on 12/31/16. However, from 1/2/17 to 1/27/17 you produced 19 lots of sterile drug product without performing recertification.

Response: Recertification of the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH and adjacent ISO-classified areas will take place at least every six months. The next certification will be scheduled prior to the certification expiration date.

2) Viable air and surface sampling of the ISO 8 Egress Room was not performed during certification of the sterile drug production suite on 6/17/16.

Response: SOP 05-004 has been implemented to direct the third-party certifier for viable sampling of the air and surfaces in the clean room suite including the ISO 8 Egress Room. A copy of this SOP is attached.

C) Positive air pressure differentials were not being monitored between the following: unclassified hallway and ISO 8 Pre-Gown Room; ISO 8 Pre-Gown Room and ISO 8 Gowning Room; ISO 8 Gowning Room and ISO 7 Cleanroom; ISO 8 Egress Room and ISO 7 Cleanroom; and ISO 8 Egress Room and unclassified hallway during the production of sterile drug products prior to 9/29/16. In addition, positive air pressure differentials are currently not being monitored between the ISO 7 Cleanroom and ISO 8 Egress Room and the ISO 8 Egress Room and unclassified hallway.

Response: The positive air pressure differentials for unclassified hallway and ISO 8 Pre-Gown



Room; ISO 8 Pre-Gown Room and ISO 8 Gowning Room; ISO 8 Gowning Room and ISO 7 Cleanroom are currently monitored each day that sterile drug products are produced. Positive air pressure differential gauges will be installed and monitored between the ISO 8 Egress Room and ISO 7 Cleanroom; and ISO 8 Egress Room and unclassified hallway each time the sterile drug products are produced. The new gauges will be installed by 1 May 2017.

D) The magnehelic gauges used to monitor the positive air pressure differentials of the sterile drug production suite have not been calibrated and are not on a routine preventative maintenance program. In addition, the doors between the rooms of the sterile drug production suite do not have a lockout mechanism to prevent multiple doors from being opened simultaneously.

Response: We will have the magnehelic gauges calibrated and placed into a routine maintenance program. The gauges will be calibrated after the new gauges have been installed. This will take place by 1 June 2017.

The sterile drug production SOP 09-002 has been updated to state that “no two doors will be open in a single room simultaneously.” This has been implemented as of 22 March 2017. A copy of this SOP is attached.

E) Your SOP 05-002 Monitoring Daily Measurements Operations and SOP 08-004 Environmental Monitoring – Microbial is deficient in that there are no established alert or action limits for the following:

1) Pressure differential limits of the sterile drug production suite;

Response: SOP 05-002 has been updated to include alert limits for room pressure differentials. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

2) Viable and non-viable air sample results in the sterile drug production suite;

Response: SOP 08-004 has been updated to include alert limits for viable and non-viable air samples. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

3) Temperature and humidity of the ISO 7 Cleanroom;

Response: SOP 05-002 has been updated to include alert limits for the temperature and humidity levels of the ISO Class 7 cleanroom. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

4) Temperatures of the refrigerators and freezers used to store in-process and finished drug products; and

Response: SOP 05-002 has been updated to include alert limits for the temperature levels of the refrigerators and freezers. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

5) Temperatures of the incubators used in the "7 Product Release" room.

Response: SOP 05-002 has been updated to include alert limits for the temperature levels of the incubators. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

OBSERVATION 3

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions. Specifically, during the production of Eylea 2mg/0.05mL injection, lot 201702081 conducted on 2/8/17:

A) A piece of apparent exposed particle board measuring approximately three-quarter inches thick, 44 inches wide, and at least six inches deep was observed through the front edge guard vent of the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH in the ISO 7 Cleanroom. The apparent particle board was observed seated on two metal u-channels and adhered to the underside of the metal workbench of the ISO 5 horizontal LFH.

Response: The apparent particle board is contained in the inner workings of the horizontal LFH and therefore should not be considered an exposed surface. All airflow across the apparent board is directed away from the product work area into the LFH. This area of the LFH is analogous to the pre-filter area. All air passing these portions of the LFH are subsequently passed thru the HEPA filter prior to passing into the work surface.

B) Two pieces of apparent plastic were observed missing from a frame installed between the ceiling and metal HEPA filter grate of the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH which exposed a groove that appears to not be smooth or easily cleanable.

Response: Nothing is missing from the frame installed between the ceiling and metal HEPA filter grate. The apparent observation is erroneous and due to how the manufacturer painted the surface. A photograph has been taken with the protective grill removed for clarity. A photo of this area is attached.

OBSERVATION 4

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions. Specifically,

A) Your firm uses non-sterile, low-shedding wipes sprayed with sterile 70% isopropyl alcohol (IPA) to clean and wipe down the metal HEPA filter grate and metal workbench of the ISO 5 horizontal LFH prior to sterile drug production. This practice was observed on 2/8/17.

Response: SOP 09-003 has been updated to include the use of sterile wipers. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

B) You are not following your SOP 05-003 Aseptic Technique and Related Practices Assessment of Compounding Personnel which states in part "\*\*\*\*Disinfects components/vials with an appropriate agent prior to placing into ISO Class 5 work area." For example, drug containers, components, closures and equipment used in the production of Eylea 2mg/0.05mL injection, lot 201702081 on 2/8/17 were placed into the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH without first disinfecting the outer surface.

Response: SOP 09-002 has been updated to include a statement that all materials are now disinfected prior to placing into the ISO 5 horizontal LFH. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

C) The Accel TB wipes used for wiping down the metal bench and interior of the pass-through in the TSO 8 Gowning Room and Accel TB Ready to Use Liquid used in the ISO 7 Cleanroom is not sterile and it is not a sporicidal agent.

Response: The Accel TB products have been replaced with a sterile peroxide disinfecting agent. A sporicidal agent has been added to the cleaning regimen. SOP 05-001 has been updated to include specific disinfecting agents and a use/rotation schedule. A copy of this SOP is attached.

D) Non-sterile 70% isopropyl rubbing alcohol is dispensed from an "EasySat Bucketless Floor Mop" and it is used to clean the floor of the sterile drug production suite on a weekly basis. In addition, a sporicidal agent has not been used to clean the floors of the sterile drug production suite.

Response: SOP 05-001 has been updated to include the use sterile disinfecting agents (ie. 70% isopropyl alcohol) and a use/rotation schedule. A sporicidal agent has also been added to the cleaning regimen. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

## OBSERVATION 5

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

A) The Tuttnauer Brinkmann 2340E, S/N 2106804 autoclave has not been validated to confirm effective sterilization through the designated sterilization time and temperature cycle of seven minutes at 273° F (134°C) for the syringe capper/de-capper device used in sterile drug production. Biological indicators are also not used during this sterilization process.

Response: Biological indicators are now being used to validate the Tuttnauer Brinkmann



2340E, S/N 2106804 autoclave. The sterilization of the capper/de-capper device will be validated per technical protocol TP2017-009. This technical protocol will be initiated by 1 May 2017. A copy of this technical protocol is attached.

B) The production process of using a non-sterile hemostat for handling a sterile dropper bottle in the ISO 5 horizontal LFH without adequate sterilization of the hemostat has not been validated to ensure sterility of the finished sterile ophthalmic products: Vigamox lot 201609202; Phenylephrine Hydrochloride Ophthalmic Solution lot 201609272; Neomycin/Polymyxin B Sulfates/Dexamethasone Ophthalmic Suspension lot 201610051; and Tobramycin/Dexamethasone Ophthalmic Suspension lot 201610052.

Response: Hemostats used for handling sterile dropper bottles in the ISO 5 horizontal LFH now for all future batches of this type will be sterilized. The sterilization of the hemostats will be validated per technical protocol TP2017-010. This technical protocol will be implemented by 1 May 2017. A copy of this technical protocol is attached.

C) There is no documentation to support that the in-situ air pattern analysis (smoke study), performed on June 17, 2016, was performed under dynamic conditions and that it was reviewed by firm personnel for adequacy.

Response: All future smoke studies will be videotaped and reviewed for adequacy. SOP 08-009 has been created to ensure that smoke studies under dynamic conditions are recorded and reviewed. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

#### OBSERVATION 6

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements. Specifically,

A) Sterility testing was not performed on each finished or representative finished batches for 20 of 23 drug products produced since 7/26/16 that are purported to be sterile. For example, sterility testing was not performed on the following sterile drug products:

- 1) Vigamox, beyond use date (BUD) of 1 month ambient, lot 201609202.
- 2) Phenylephrine Hydrochloride Ophthalmic Solution; unknown BUD, lot 201609272.
- 3) Neomycin/Polymyxin B Sulfates/Dexamethasone Ophthalmic Suspension BUD of 30 days ambient, lot 201610051.
- 4) Tobramycin/Dexamethasone Ophthalmic Suspension BUD of 30 days ambient, lot 201610052.

Response: All products purported to be sterile are now being tested for sterility per SOP 10-005. This has been implemented as of 22 March 2017.



B) Endotoxin testing was not performed on each finished or representative finished batches for the 23 drug products produced since 7/26/16 that are purported to be pyrogen-free. For example, endotoxin testing was not performed on the following sterile drug products: Oxytocin 30U/500mL NS bag BUD of 6 weeks ambient, lots 201611082, 201611112, 201611291, 201612151, 201701041, 201701111, and 201701241.

Response: All drug products purported to be pyrogen-free are being sent out for endotoxin testing per SOP 10-006. This has been implemented as of 22 March 2017. A copy of this SOP is attached.

C) Your SOP 10-005 Finished Product Sterility Testing is deficient in that there is no established scientific rationale for the release of the following sterile filtered drug products after a passing Day 4 sterility test result:

1) Lidocaine 1%/Phenylephrine 1.5% injection; BUD of 66 days ambient for lots 201609231, 201610061, 201610201, 201611301 and 201702021.

2) Lidocaine 7.5mg/mL/Epinephrine 0.25mg/mL injection; BUD of 45 days frozen for lots 201611181 and 201701061.

Response: Final release of product will be dependent upon the 14 day sterility test results. The four-day sterility check will be used as an initial check, but the product release will be dependent on the 14 days result. This has been implemented as of 22 March 2017.

#### OBSERVATION 7

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,

A) Potency testing is not performed for each batch of finished sterile and non-sterile drug products produced prior to release. For example:

1) The following sterile drug products:

a) Lidocaine 1 %/Phenylephrine 1.5% injection; BUD of 66 days ambient for lots 201609231, 201610061, 201610201, 201611301 and 201702021.

b) Lidocaine 7.5mg/mL/Epinephrine 0.25mg/mL injection; BUD of 45 days frozen for lots 201611181 and 201701061.

Response: Potency of all future batches of these products will be verified via gravimetric and mathematical determinations. This has been implemented as of 22 March 2017.

2) The following non-sterile drug products:

a) Lidocaine/Epinephrine/Tetracaine (LET) topical gel BUD of "150 days refrigerated; 21 days room temperature" for lots 201612222 and 201701171.

b) Lidocaine/Prilocaine/Tetracaine/Phenylephrine (TAP) topical gel BUD of 90 days ambient for lot 201612221.

Response: Potency of all future batches of these products will be verified via gravimetric and mathematical determinations. This has been implemented as of 22 March 2017.

B) Finished preservative content testing is not performed for each batch of non-sterile drug products produced prior to release. For example:

1) LET Gel containing methyl paraben and propyl paraben as a preservative for lots 201612222 and 201701171.

2) TAP Gel containing methyl paraben and propyl paraben as a preservative for lot 201612221.

Response: The preservative system for all future batches of these products will be removed or a technical protocol will be implemented to show preservative efficacy of these products. This technical protocol will be initiated by 1 May 2017.

#### OBSERVATION 8

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

A) Your SOP 12-004 Determination of Beyond Use Dating is deficient in that it does not describe tests that evaluate the sterility and potency for the BUD claimed. For example, stability testing has not been performed for the following sterile drugs:

1) Lidocaine 1%/Phenylephrine 1.5% injection formulated from non-sterile components; BUD of 66 days ambient for lots 201609231, 201610061, 201610201, 201611301 and 201702021.

Response: The stability of lidocaine and phenylephrine has been studied in the literature. J Clin Hosp Pharm. 1986 Dec;11(6):449-52.

"Chemical stabilities of lignocaine hydrochloride and phenylephrine hydrochloride in aqueous solution."

Das Gupta V, Stewart KR.

**Abstract:**

The chemical stabilities of lignocaine hydrochloride (lidocaine hydrochloride) and phenylephrine hydrochloride in a combination aqueous solution have been determined using stability-indicating high-performance liquid chromatographic methods. The drugs did not interact and were stable for at least 66 days at room temperature. The pH value changed from 6.0 to 5.8 after 66 days but was still within the optimum pH range for the stabilities of lignocaine and phenylephrine.

This study shows that the product is chemically stable. Technical protocol TP2017-006 will look at the sterility of this product over the BUD. This technical protocol will be implemented by 1 May 2017. A copy of the technical protocol and updated SOP 12-004 are attached.

**2) Sterile drugs repackaged in the LFH:**

- a) Phenylephrine Hydrochloride Ophthalmic Solution 2.5%; BUD is unknown for lot 201609272.
- b) Tobramycin/Dexamethasone Ophthalmic Suspension; BUD of 30 days ambient for lot 201610052.
- c) Vigamox; BUD of 30 days ambient for lot 201609202.
- d) Neomycin/Polymyxin B Sulfates/Dexamethasone Ophthalmic Suspension; BUD of 30 days ambient for lot 201610051.

**Response:** These products are no longer being produced.

3) Oxytocin 30U/500mL NS intravenous solution; BUD of 6 weeks ambient, lots 201611082, 201611112, 201611291, 201612151, 201701041, 201701111, and 201701241.

**Response:** The stability of oxytocin has been studied in the literature.

Int J Pharm Compd. 2006 Mar-Apr;10(2):156-8.

Extended stability of oxytocin in common infusion solutions.

Trissel LA1, Zhang Y, Douglas K, Kastango E.

Author information

**Abstract**

The objective of this study was to evaluate the physical and chemical stability of oxytocin 0.08 U/mL admixed in 5% dextrose injection, 0.9% sodium chloride injection, and lactated Ringer's injection bags. Triplicate test samples of oxytocin 0.08 U/mL in each infusion solution were prepared by adding the required amount of oxytocin injection to bags of the three infusion solutions. The samples were stored protected from light and evaluated at appropriate intervals for up to 90 days at room temperature (near 23 deg C). Physical stability was assessed by using an evaluation procedure that included both



turbidimetric measurement and visual inspection. Chemical stability was assessed by using a stability-indicating high-performance liquid chromatographic analytical technique and was based on the determination of drug concentrations initially and at appropriate intervals over the study period. The oxytocin admixtures in 5% dextrose and 0.9% sodium chloride were clear and colorless when viewed in normal fluorescent room light and when viewed with a Tyndall beam initially and throughout 90 days. Measured turbidity was low initially and exhibited little change throughout the study. High-performance liquid chromatographic analysis revealed that little or no decomposition occurred in the samples. Oxytocin in the infusion solutions remained stable at room temperature for 90 days. The lactated Ringer's injection samples remained clear and colorless for up to 28 days. However, after that time a small amount of white fluffy microprecipitate developed in two of the three samples by the 35-day observation point. High-performance liquid chromatographic analysis revealed that oxytocin remained stable in lactated Ringer's injection for 28 days at room temperature; substantial losses of oxytocin occurred in all three samples after that time, with about 10% loss at 35 days and up to 21% loss at 60 days. Oxytocin 0.08 U/mL in 5% dextrose injection or 0.9% sodium chloride injection is physically and chemically stable for at least 90 days at room temperature. However, oxytocin in lactated Ringer's injection should be restricted to a use period no greater than 28 days at room temperature to avoid microprecipitate formation and drug loss.

This study shows that the product is chemically stable in 0.9% sodium chloride longer than our proposed 42 days BUD. A technical protocol TP2017-007 will look at the sterility of this product over the BUD. This technical protocol will be implemented by 1 May 2017. A copy of the technical protocol and updated SOP 12-004 are attached.

B) The BUD of sterile drug products exceeded the expiry date of a raw material component used in production. For example:

1) Raw material component Vancomycin 500mg vial lot 511058E03; expiry 3/1/17 was formulated into Vancomycin 100mcg/0.1mL injection, lot 201702022; given BUD of 4/20/17.

Response: This is actually for Vancomycin 1000mcg/0.1mL injection. The bill of materials section of the batch record will be updated to include a "verified by" column. This will aid in catching this type of discrepancy. A draft sample of an updated Eylea batch record is attached as a reference. The batch records for all products will be updated to this new format. This has been implemented as of 22 March 2017.

2) Raw material component Phenylephrine HCl Powder lot 1403040074; expiry 10/12/16 was formulated into Lidocaine 1%/Phenylephrine 1.5% injection, lot 201609231; given BUD of 11/28/16.

Response: The bill of materials section of the batch record will be updated to include a

“verified by” column. This will aid in catching this type of discrepancy. A draft sample of an updated Eylea batch record is attached as a reference. The batch records for all products will be updated to this new format. This has been implemented as of 22 March 2017.

C) The literature source you used to support the BUD of 66 days ambient for sterile drug Lidocaine 1%/Phenylephrine 1.5% injection solution is taken from a study that investigated the chemical stability of Lignocaine hydrochloride and Phenylephrine hydrochloride aqueous solution containing preservatives; the sterile drug Lidocaine 1%/Phenylephrine 1.5% intended as an intraocular injection that you produce is preservative-free. In addition, you do not have stability data to ensure sterility for the BUD claimed and that the product is endotoxin- free.

Response: A technical protocol TP2017-006 will look at the sterility of this product over the BUD. This technical protocol will be implemented by 1 May 2017. A copy of the technical protocol is attached.

#### OBSERVATION 9

Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform. Specifically,

A) The following attire worn by the operator on 2/8/17 during the production of Eylea 2mg/0.05mL injection, lot 201702081 in the Baker EG-4320, S/N 55304 ISO 5 horizontal LFH was inadequate as follows:

1) Non-sterile boot covers, non-sterile coveralls, non-sterile hair cover, non-sterile surgical mask, and protective eyewear that had not been previously disinfected prior, that were observed worn during sterile drug production.

2) The hood of the non-sterile coverall and non-sterile surgical mask worn did not provide adequate coverage of the forehead, cheeks, and chin of the operator during sterile drug production.

Response: SOP 09-003 has been updated to include the use of sterile gowning materials. The updated sterile hood provides adequate coverage of the forehead, cheeks, and chin of the operator during sterile drug production. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

B) An ATRIX VACOMEGASCT ESD 1 gallon vacuum and its power cord, attachments and hose were observed in direct contact with a non-sterile coverall worn by the operator in the ISO 7 Cleanroom during vacuuming of the floor. The vacuum was returned to the ISO 8 Egress Room and the operator was observed returning to the ISO 7 Cleanroom



without changing or performing adequate sanitization of his non-sterile coverall or sterile gloves prior to production of Eylea 2mg/0.05mL injection, lot 201702081 in the ISO 5 horizontal LFH.

Response: The vacuum has been replaced with a tacky roller to eliminate this issue. SOP 05-001 has been updated to reflect this change. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

C) On 2/7/17 two non-sterile gowns previously worn during sterile drug production were observed hanging in the ISO 8 Gowning Room. Per the firm President, the non-sterile gowns are reused after sterile drug production and changed every three to five batches produced.

Response: This practice has been discontinued. SOP 09-003 has been updated to state the gowns can be reused only during one shift. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

#### OBSERVATION 10

There is no quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products. Specifically,

A) There is no procedure for the release of finished drug products.

Response: SOP 10-001 has been implemented for the release of finished drug products. This has been implemented as of 22 March 2017. A copy of the SOP is attached.

1) Your current practice for the release of sterile filtered drugs are subject to an in-house Day 4 sterility test; however, there are no records to show quality control unit review of such records and no documentation of the date you distributed these sterile filtered drugs:

a) Lidocaine 1%/Phenylephrine 1.5% injection lots 201609231, 201610061, 201610201, 201611301 and 201702021.

b) Lidocaine 7.5mg/mL/Epinephrine 0.25mg/mL injection lots 201611181 and 201701061.

Response: A quality review of the sterility test results has been added to the Executed Batch Records. SOP 14-001 has been updated to document product distribution. This has been implemented as of 22 March 2017. A copy of the updated SOP is attached.

2) You do not have a production batch record for Lidocaine 4%/Epinephrine 0.05%/Tetracaine 0.5% (LET) Topical Gel, lot 201612031 that was produced on 12/3/16. RAM Pharma, Inc. Invoice no. 1055 dated 12/5/16 documented the sale and distribution of 10/3mL LET Gel syringes from this lot.



Response: This batch record is still missing. We will continue to look for it.

B) There is no procedure for the review of production batch and control records.

Response: SOP 01-005 has been implemented for the review of production batch and control records. This has been implemented as of 22 March 2017. A copy of the SOP is attached.

1) The person designated "Quality Assurance" in your organizational chart who had "approved" all executed production batch records since 7/26/16 are reviewing records for "completeness" before or after the distribution of drugs. The batch record reviews are deficient. For example:

a) Your production batch record does not contain accurate representation of products produced. For example: Batch record for Lidocaine 1%/Phenylephrine 1.5% injection lot 201609231 shows 30 syringes produced. RAM Pharma Inc. Invoice 1020 shows 34 Lidocaine 1%/Phenylephrine 1.5% syringes under lot 201609231 were distributed.

Response: This is an isolated incident. Current practice is accurately documenting number of units produced upon batch completion. Implementation of SOP 14-001 will ensure this does not happen in the future. This has been implemented as of 22 March 2017. An copy of the updated SOP is attached.

b) There are no records of the actual drug product labels used in any drug product batches produced since 7/26/16.

Response: Sample labels are now being attached to each executed batch record. This has been implemented as of 22 March 2017.

c) You do not have an appropriate drug product container label for any of your drug products. Your production batch records documented the use of a unit, product label as the container label. For example, 21 product labels were used to package Lidocaine 7.5mg/mL/Epinephrine 0.25mg/mL injection, lot 201701061, 20 of which were used on each 2mL finished product vials and "1 for box".

Response: A unit label will continue to be placed on the outer container with a secondary label containing all required labeling information including product ingredients and Med Watch reporting. This has been implemented as of 22 March 2017. Samples of these labels are attached.

d) Production and control records did not have the observed value of the bubble point test performed on the sterilizing filter used in the production of a sterile drug product. Records show a bubble point test was performed with the results recorded as "PASS" for each lot, for example: Lidocaine 1%/Phenylephrine 1.5% injection lots 201609231, 201610061, 201610201, 201611301, and 201702021; and Lidocaine 7.5mg/mL/Epinephrine 0.25mg/mL injection lot 201701061.

Response: The actual value for the test is now being recorded on each applicable executed batch record. This has been implemented as of 22 March 2017. A sample batch record is attached.

C) You did not follow SOP 10-003 Inspecting and Releasing Incoming Raw Materials for the release of raw materials. For example:

1) Packages of sterile syringes that have not been released that were stored on a shelf labeled "TO BE RELEASED" were used in production. These 8mm, 31G gauge sterile BD insulin syringes under lot 6144783 were used in the production of Eylea 2mg/0.05mL injection lots 201701271, 201701133, and 201701132.

Response: All released materials now have a "Released" sticker on their outer packaging.

2) The container holding Prilocaine hydrochloride USP lot 1610030044 did not have a released sticker per section 1.1 of SOP 10-003 which address placement of a released sticker if the material has been "cleared by inspection". Prilocaine hydrochloride USP lot 1610030044 was used in the production of TAP Gel lot 201612221.

Response: All released materials now have a "Released" sticker on their outer packaging.

#### OBSERVATION 11

Routine calibration of electronic equipment is not performed according to a written program designed to assure proper performance. Specifically,

A) The digital balance used in the weighing of raw material components for production, namely Torbal AGZN100 balance, 100g capacity; A&D EJ-123 balance, 120g capacity; and Ohaus Scout Pro balance, 400g capacity have not been calibrated. The calibration weights that are available for use are also not calibrated.

Response: SOP 11-011 has been implemented to address the calibration of all balances and calibration weights. All balances will be scheduled for calibration by a third party by 1 May 2017. A copy of the SOP is attached.

B) The digital thermometers used to monitor temperatures of the refrigerator in the "2 Incoming Release" room; and the refrigerator and freezer in the "8 Shipping" room have not been calibrated.

Response: SOP 11-012 has been implemented to address the calibration of all digital thermometers. All digital thermometers will be scheduled for calibration by a third party by 1 May 2017. A copy of the SOP is attached.

#### OBSERVATION 12

The labels of your outsourcing facility's drug products do not include information required by sections 503B(a)(10)(A) and (B). Specifically,

The following information is not found on some of your drug product labels:

A) Product labels consisting of the statement "Compounded Drug" are deficient in that it does not include the statements "This is a compounded drug", quantity or volume, and inactive ingredients. Examples of drug products that do not contain this information are:

- 1) Cefazidime 2250mcg/0.1mL
- 2) Dexamethasone Sodium Phosphate 400mcg/0.05mL
- 3) Phenylephrine Hydrochloride 2.5mg/mL solution
- 4) Vancomycin Hydrochloride 1000mcg/0.1 mL

Response: Labels have been updated to include all required information in sections 503B(a)(10)(A) and (B). Samples of updated labels are attached. A copy of SOP 12-002 is attached.

B) A list of active and inactive ingredients, identified by established name and the quantity or proportion of each ingredient. Examples of drug products that do not contain this information are:

- 1) Drug product Lidocaine 4%/Epinephrine 0.05%/Tetracaine 0.5% topical gel is identified on the product label as "LET Gel 4%/0.05%/0.5% TOPICAL GEL".
- 2) Drug product Lidocaine 10%/Prilocaine 10%/Tetracaine 4%/Phenylephrine 2% dental gel is identified on the product label as "TAP Gel 10%/10%/4%/2% DENTAL GEL".

Response: A list of the active and inactive ingredients along with their concentration amount are now included on each label. Samples of updated labels are attached.

C) The containers of your products do not include the following information required by section 503B(a)(10)(B) in order to facilitate adverse event reporting: [www.fda.gov/medwatch](http://www.fda.gov/medwatch) and 1-800-FDA-1088.

Response: The Med Watch reporting information is now included on all products. Samples of updated labels are attached.

#### OBSERVATION 13

The drug product report your outsourcing facility submitted to the FDA as required by section 503B(b)(2)(A) is not accurate. Specifically,



You underreported 6 units of Vancomycin 1000mcg/0.1 mL syringe and 6 units of Ceftazidime 2250mcg/0.1mL syringe in the drug product report your outsourcing facility submitted to the FDA on 12/28/16 for drugs produced during the previous six months through 11/30/16.

Response: SOP 14-001 has been implemented to ensure accurate recording and reporting of all units produced. A copy of the SOP is attached.