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3004549631



July 9, 2013

BY E-MAIL/FEDERAL EXPRESS

Reynaldo (Ricky) Rodriguez, Jr.
District Director, Dallas District
Food and Drug Administration
4040 North Central Expressway
Suite 300
Dallas, Texas 75204



Re: **FDA Disclosure of Warning Letter Response on FDA's Web Site**

Dear Mr. Rodriguez:

On behalf of Eagle Analytical Services, Inc., I authorize the United States Food and Drug Administration ("FDA") to publicly disclose the information in the attached two letters dated July 9, 2013, responding to the FDA's Form 483 observations for Eagle Analytical Services, Inc., issued June 17, 2013, excluding attachments thereto, on FDA's web site. I understand that the information may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. § 1905, 21 U.S.C. § 331, 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.

Authorization is given to FDA to disclose the above-referenced information, excluding attachments, which may include confidential commercial or financial or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of Eagle Analytical Services, Inc. and my full name, title, address, telephone number, and facsimile number is set forth herein for verification.

Sincerely,

A handwritten signature in blue ink, appearing to read "J. Willey".

James D. Willey
General Manager
jwilley@eagleanalytical.com



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July 9, 2013

BY E-MAIL/FEDERAL EXPRESS

Reynaldo (Ricky) Rodriguez, Jr.
District Director, Dallas District
Food and Drug Administration
4040 North Central Expressway
Suite 300
Dallas, Texas 75204

Re: Eagle Analytical Services, Inc., 9881 S. Wilcrest Dr., Houston, TX 77099 (FEIN #3004549631) Response to FDA Form 483 Issued June 17, 2013

Dear Mr. Rodriguez:

This letter is in response to the FDA Form 483 issued to Eagle Analytical Services, Inc. ("Eagle" or "Eagle Analytical"), located at 9881 S. Wilcrest Dr., Houston, Texas 77099. At the conclusion of the FDA inspection between June 5 and 17, 2013, Eagle Analytical received a FDA Form 483 (the "Form 483") listing eight observations.

We request that this document and the accompanying letter, excluding the attachments, be included with the Form 483 anytime the FDA discloses to the public or otherwise provides a copy of the Form 483. The attachments, however, including but not limited to Eagle Analytical's Standard Operating Procedures ("SOPs"), are proprietary and confidential and should not be released.

Introduction

Since 2004, Eagle Analytical has operated as a contract laboratory that performs analytical testing for compounding pharmacies. Eagle Analytical engages in testing and analysis for compounding pharmacies pursuant to and in compliance with applicable compounding guidelines.

Eagle understands that FDA possesses the authority to regulate drug manufacturers. As FDA well knows, however, Eagle does not engage in the practice of manufacturing drugs. Eagle also does not provide testing or analytical services to drug manufacturers. It provides no laboratory testing for API or finished product release testing. Eagle does not hold itself out as compliant with current good manufacturing practices ("cGMP"), nor does it make any cGMP claims concerning its products or



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testing services.¹ It also does not accept any customers other than compounding pharmacies and small specialty testing facilities, such as doctors' offices or clinics.

Eagle is registered with FDA as a "Contract Testing Laboratory." As FDA is aware based on statements and other findings in the EIR it prepared for Eagle Analytical just over a year ago (Tab A), Eagle has had not initiated "Contract Laboratory" activities as that term is applied under the Federal Food, Drug, and Cosmetic Act ("FDCA"). As FDA noted in the 2012 EIR, "No FDA regulation required currently for testing of Compounded Pharmaceuticals." And, consistent with its business and testing activities FDA observed during the 2011 inspection, Eagle continues to test only samples received from compounding pharmacies.² Congress has passed no law, and FDA has promulgated no regulation, that would permit FDA to now regulate the "testing of compounded pharmaceuticals" in a manner differently than it did in 2011 and 2012. Nor is Eagle is aware of any change in the law or regulations authorizing FDA to regulate Eagle as a drug manufacturer subject to cGMP or other requirements of the FDCA.

Eagle currently services over 1,200 compounding pharmacies and small specialty testing facilities. These entities rely on Eagle to provide sound analytical results for the safe dispensing of their preparations. The process of analyzing many different formulations one time over as opposed to one thing many times is the fundamental difference – and hallmark distinction – between providing analytical testing for compounded preparations and a drug that is manufactured.

Eagle analyzes compounded preparations: All analyses are performed by highly skilled, degreed chemists and microbiologists. We analyze over 400 different active ingredients and utilize more than 2,500 different methods to do so – more than any other testing facility servicing the compounding sector. Clients count on Eagle to perform the difficult and novel analyses that other facilities will not perform. Eagle is uniquely positioned as a company solely focused on compounding pharmacies. Eagle Analytical follows appropriate compounding guidelines in support of its good scientific practices.

Set forth below are Eagle Analytical's responses to FDA's Form 483 Observations. We are providing these responses to describe Eagle's commitment to testing quality. They do not constitute an acknowledgement that the cGMP apply to us.

Observation 1: *Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity.*

- **Observation 1(a):** *There is no validation performed on the Rapid Scan RDI instrument to determine its suitability for use as a sterility test for product that they test.*

¹ See Establishment Inspection Report ("EIR") for Eagle Analytical Services, Inc., (Mar. 12, 2012), attached hereto as Tab A.

² Note that neither of the pharmacies referenced in the Form 483 are registered with FDA as a manufacturer.



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- **Response to Observation 1(a):** Eagle has Installation Qualification, Operational Qualification, Performance Qualification (“IQ/PQ/OQ”) documentation from the manufacturer and operates equipment according to specifications set forth in that documentation. Annually, the manufacturer conducts a comprehensive performance qualification on the ScanRDI. In addition, a positive control process is performed during every analysis conducted using the ScanRDI. In accordance with the equipment manufacturer’s protocol, Eagle utilizes styrene beads during each analysis to validate that the ScanRDI is operating properly. We also test a known United States Pharmacopeia (“USP”) microorganism to validate that the unit will detect a microbe should one be present in a sample, and record this procedure for every test performed. FDA reviewed during its recent inspection the annual performance qualification report for the ScanRDI. That report is available upon request.
- **Additional Action by Eagle:** In addition to the foregoing, Eagle will conduct an additional internal validation of the ScanRDI equipment using USP<1223> (“Validation of Alternative Microbiological Methods”) as a guideline.
- **Timeline:** To be completed no later than July 31, 2013.
- **Observation 1(b):** *Your firm does not conduct growth promotion on the Trypticase Soy Broth (TSB) and Fluid Thioglycollate Medium (FTM) used in their membrane filtration and direct inoculation sterility tests for drug product as required in the USP<71> Sterility test.*
 - **Response to Observation 1(b):** Eagle is not a drug manufacturer; nor is it performing functions of a Contract Testing Laboratory as that term is used in the FDCA or regulations. Eagle performs certain testing for compounding pharmacies. Eagle does not “conduct growth promotion on the Trypticase Soy Broth (“TSB”) and Fluid Thioglycollate Medium (“FTM”) used in their membrane filtration and direct inoculation sterility tests for drug product as required in the USP<71> Sterility test” because Eagle only utilizes growth media from a manufactured source. The growth media Eagle purchases is from FDA-registered manufacturer bioMerieux, Inc., who provides a Certificate of Analysis (“COA”) to Eagle for its products. That COA shows the tests, including positive growth testing, that have been performed on that product by the manufacturer. See COA, Tab B.
 - **Additional Action by Eagle:** Eagle has created a log that maintains a record of media COA. Eagle conducted employee training regarding the maintenance of these COA records. Eagle will provide a copy of the log upon request.
 - **Timeline:** Completed June 17, 2013.



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- **Observation 1(c):** *There is no suitability testing performed on drug product samples prior to or concurrently during membrane filtration sterility testing as required in the United States Pharmacopeia Chapter <71> Sterility Tests.*
 - **Response to Observation 1(c):** Eagle conducts suitability testing via post-inoculation testing. Eagle randomly pulls samples that have completed the 14/18 day analysis of a membrane filtration or direct inoculation test *and* passed that test. It will then directly inject a known quantity of a USP microorganism (BioBall; *Staphylococcus aureus* or *Aspergillus brasillensus*) and reincubate the sample for five additional days. It will record any positive growth after that five day period. Eagle believes that this is a more cost effective way of validating that, if a detectable amount of organism had been present in a sample, it would have presented during the initial 14/18 day analysis. Eagle maintains a log of its results.
 - **Additional Action by Eagle:** What Eagle once referred to as USP<71> testing will now be called a “Membrane Filtration Sterility Test.” That test utilizes an internal testing method that does not include suitability testing for each pharmacy and for each preparation. In addition, Eagle will offer the full USP<71> compendia analysis upon a client’s request. Eagle will complete an SOP for the procedure described in its Response to Observation 1(c).
 - **Timeline:** To be completed no later than July 31, 2013.
- **Observation 1(d):** *Your firm does not indicate the number of samples received or required for sterility testing. USP<71> specifies the number of articles to be tested. While you provide reference to USP<71> for sample size, you do not ensure that your clients are submitting the required number of articles for testing.*
 - **Response to Observation 1(d):** Eagle believes that this is the responsibility of the entity submitting the samples to determine the number of samples received for sterility testing. Eagle follows USP<71> Table 2 (Minimum Quantity to be Used for each Medium). Eagle recommends verbally and on its website, and on its sample submission instructions it provides to clients, that they adhere to USP<71> Table 3 (Minimum Articles to be Tested in Relation to the Number of Articles in the Batch) when submitting samples, as the standard to which its clients should adhere. Eagle also provides documentation setting forth recommendations for compounded prescription products, with USP reprint rights, that contain both USP<71>, Tables 2 3. See Tabs C and D (Sample Submission Instructions; Recommendations).
 - **Additional Action by Eagle:** None
 - **Timeline:** N/A



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- **Observation 1(e):** *Your firm has not validated your “plate contaminations method” to determine whether it is suitable for its intended use by the customer as a sterility test method.*
 - **Response to Observation 1(e):** Eagle provided this testing service to a single client and was unaware of that client’s practice to purportedly characterize this plate contamination test as a “sterility test.” Eagle did not refer to this testing method as a “sterility test”; the client itself chose to use that terminology. Eagle’s Laboratory Information Management System (“LIMS”) documentation and laboratory reports confirm that this method was not a “sterility test” as described by the Observation, but instead a “Plate Contamination” test; thus Eagle did not determine that “it was suitable for its intended use by the customer as a sterility test method” because we did not intend it to be a “sterility test.” Notwithstanding the foregoing, Eagle no longer offers the Plate Contamination test in its portfolio of contract services. Eagle discontinued this service for the following reasons: (1) A single client was its sole user, and that client no longer uses Eagle’s services; and, (2) Eagle chose voluntarily to discontinue the service to avoid confusion concerning whether this test is in fact a “sterility” test.
 - ***Additional Action by Eagle:*** Eagle discontinued this test prior to the FDA inspection.
 - ***Timeline:*** Completed April 1, 2013.
- **Observation 1(f):** *Your firm does not conduct growth promotion on the Tryptic Soy Agar plates used in testing drug product samples for microbial contamination via TSA (Tryptic Soy Agar) Microbial Plating Method.*
 - **Response to Observation 1(f):** Eagle provided this testing service to a single client and was unaware of the client’s practice to purportedly characterize this plate contamination test as a “sterility test.” Eagle did not refer to this testing method as a “sterility test.” LIMS documentation and laboratory reports confirm that this method was referred to as a “Plate Contamination” test. Eagle no longer offers the Plate Contamination test in its portfolio of contract services.
 - ***Additional Action by Eagle:*** Eagle discontinued this service prior to the FDA inspection.
 - ***Timeline:*** April 1, 2013.
- **Observation 1(g):** *Finished product samples tested for microbial contamination using the Tryptic Soy Agar Microbial Plating Method were not tested for suitability to neutralize preservative interference and/or inhibition if present in finished product.*



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- **Response to Observation 1(g):** Eagle provided this testing service to a single client and was unaware of the client's practice to purportedly characterize this plate contamination test as a "sterility test." Eagle did not at any time refer to this testing method as a "sterility test." LIMS documentation and laboratory reports confirm that this method was referred to as a "Plate Contamination" test. Eagle no longer offers the Plate Contamination test in its portfolio of contract services.
- **Additional Action by Eagle:** Eagle discontinued this service prior to the FDA inspection.
- **Timeline:** April 1, 2013.
- **Observation 1(h):** *Certificates of Analyses of commercially purchased media used to test drug products for sterility tests (Trypticase Soy Broth and Fluid Thioglycollate) and Microbial plate contamination test using Tryptic Soy Agar are not maintained.*
 - **Response to Observation 1(h):** Eagle only utilizes growth media from a manufactured source. Eagle now electronically maintains the COA for that growth media. It also maintains a hard copy of COAs at the facility. Eagle will provide copies upon request.
 - **Additional Action by Eagle:** Eagle has created a binder to record and maintain media COAs. Eagle has trained responsible employees to record and maintain COAs for growth media for sterility testing. Each COA is dated upon receipt.
 - **Timeline:** Completed June 17, 2013.
- **Observation 1(i):** *Your firm does not calculate the Maximum Valid Dilution (MVD) for finished product samples that are tested for bacterial endotoxins as required in the United States Pharmacopeia <85> Bacterial Endotoxins Test. MVD is the maximum allowable dilution of a product at which the endotoxin limit can be determined.*
 - **Response to Observation 1(i):** Although not a drug manufacturer, and although Eagle does not perform testing on API (or for drug manufacturers), Eagle performs calculations to determine the bacterial endotoxin limit by requesting from clients the route of administration and maximum patient dosage for products that it tests. In the Eagle endotoxin testing protocol, a dilution ratio of 1:10,000 is specified as a maximum upper limit. In a "worst case scenario", if the route of administration is intravenous, then a dosage of less than 35mL/hr will allow a dilution ratio of not more than 10,000. Likewise, if the route of administration is intrathecal then a dosage of less than 1.4mL/hr will allow a dilution ratio of not more than 10,000. If the pharmacist-specified dosage is more than the above (35mL/hr for intravenous, or 1.4mL/hr for intrathecal) then a corresponding lower maximum dilution ratio is



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calculated, and Eagle performs independent calculations when communicated dosage limits from the client exceed the 35 mL/hr intravenous or 1.4 mL/hr intrathecal to verify that result. The request for information from the client is set forth on Eagle's client sample submission form (attached as Tab E). Eagle records the calculations in a log book by sample identification number.

- ***Additional Action by Eagle:*** Eagle will work with the provider of our LIMS to create fields that will require population and perform the calculations automatically. Those fields will include route of administration, dosage/hr, and standard patient weight of 70kg., which fields are necessary to make the required calculations.
- ***Timeline:*** Creation of fields in conjunction with provider of LIMS software to be completed December 20, 2013, so that use of the LIMS software will enable Eagle to perform calculations automatically.
- **Observation 1(j):** *Your firm does not calculate endotoxin limits for drug product samples and therefore, cannot determine if finished product samples have more than the allowable endotoxin limit as required in the USP<85> Bacterial Endotoxins Test.*
 - **Response to Observation 1(j):** As stated in response to Observation 1(i), Eagle performs calculations to determine the bacterial endotoxin limit by requesting from clients the route of administration and maximum patient dosage for products that it tests. The request for information is set forth on Eagle's sample submission form (attached as Tab E), and the calculations are recorded in a log book by sample identification number.
 - ***Additional Action by Eagle:*** Eagle will with the provider of our LIMS to create fields that will require population and perform the calculations automatically.
 - ***Timeline:*** Creation of fields in conjunction with provider of LIMS software to be completed December 20, 2013, so that use of the LIMS software will enable Eagle to perform calculations automatically. To be completed December 20, 2013.
- **Observation 1(k):** *Your firm does not test pH for drug product samples tested for bacterial endotoxin as required in USP Chapter<85> Bacterial Endotoxins Test.*
 - **Response to Observation 1(k):** Based on a verbal communication with the manufacturer of our endotoxin unit (Associates of Cape Cod ("ACC")), Eagle is informed and believes that, as long as there is spike recovery on the endotoxin, the testing of pH is unnecessary. Eagle uses the ACC Pyrotell-T Turbimetric test procedure. This test uses enzymes which are extremely sensitive to pH. If the pH is out of range, then the enzymes will not react to produce a spike recovery within range.



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- **Additional Action by Eagle:** Eagle is adding a statement to its current SOP, (No. 54, "Endotoxin Results Interpretation") reflecting the above, and will make the SOP available upon request.
- **Timeline:** To be completed not later than July 15, 2013.
- **Observation 1(l):** *Your firm has failed to validate the Test Method for any potency assays conducted by your firm. You have not determined the evaluation of accuracy, sensitivity, specificity, and reproducibility of the test methods used in the analyses of drug products submitted by clients to your firm. Your firm routinely conducts analyses by HPLC per USP method of drug products to include: Vitamin D3, Thiamine HCL, Thioctic Acid, Methylcobalamine.*
 - **Response to Observation 1(l):** Eagle conducts, and will continue to conduct, the level of analysis described in this Observation when requested by a particular client. Eagle has conducted eight monograph analyses since July 1, 2013. Eagle considers the validation activities described in this Observation to be testing required of a drug manufacturer, and not a pharmacy compounder (and Eagle is neither of the two). Performing this validation is neither required nor practicable. Pharmacy compounders often compound dozens if not hundreds of specialized, patient-customized medications in a day or week. Any variation in the compounded preparation may invalidate the test method. Eagle performs testing services for compounding pharmacies and not for drug manufacturers or of manufactured products. If a failure occurs, Eagle does re-run the sample to verify results.
 - **Additional Action by Eagle:** None
 - **Timeline:** N/A
- **Observation 1(m):** *Your firm does not perform System Suitability for any HPLC analyses conducted on samples.*
 - **Response to Observation 1(m):** USP<621> states that System Suitability must be performed each time an analysis is conducted on samples. System Suitability for HPLC analyses conducted on samples would be appropriate for activities conducted by drug manufacturers; however, it is outside the scope of the practice of pharmacy compounding, for the reasons stated in response to Observation 1(l), above and in the accompanying letter.
 - **Additional Action by Eagle:** None
 - **Timeline:** N/A

Observation 2: *Deviations from written specifications are not justified.*



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- **Observation 2(a):** *31 out of 33 drug product samples were released as were tested for sterility on the SCAN RDI instrument on March 21, 2013. A typical run consists of Quality Control C3 beads, drug product samples, one positive control and one negative control. The positive control used for the run was Staphylococcus aureus. It was run but it was not detected by the machine. Drug product samples that were run on March 21, 2013 via Rapid Scan RDI were passed and released even though the positive control was not recovered or out of specification. No documentation of this deviation was recorded except the printout of results for that day. The SOP for Rapid Scan RDI Quality Control #45B, dated 02/22/11 requires an OOS investigation for a failed control. There was no documentation of an investigation and the results were released with the positive control with no growth. There was no positive control sample included 02/15/2013, and 03/22/2013. Additionally, the positive controls for 03/20/2013, and 06/19/2012 also had positive control with no microbial recovery/no growth.*
 - **Response to Observation 2(a):** Eagle will update and revise its current SOP to reflect a procedure where it will run positive control samples first, conduct an investigation concerning a failed control, and provide a written report when a documented deviation occurs. The revised SOP will be provided upon request. Eagle will train all responsible employees on the revised SOP.
 - **Timeline:** Revised SOP and employee training to be completed by July 31, 2013.

Observation 3: *Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.*

- **Observation 3(a):** *The sterility Tracking Logs and the Contamination Test Tracking Logs that your firm uses to record the placement of samples on sterility/plating testing Incubators #1 and #2 are not maintained. All sterility and TSA Microbial Plating (formerly) samples are incubated by the firm in these two incubators by temperature. The incubator logs are the raw data for each sample placed in the incubator, interim observations (3, 7, and 14 days for sterility) and final test results. The records could only be located for approximately 4 months (January to April 2013) of samples analyzed by the firm. According to your Microbiologist Assistant Manager, the records were not maintained prior to this time period.*
 - **Response to Observation 3(a):** Eagle disagrees with this Observation. Eagle maintains the referenced logs and other documents in an electronic database (Laserfische). Although Eagle maintains such records, they were difficult to retrieve through the database during the FDA inspection. Eagle also maintains records for longer than a four-month period; Eagle has retained the logs referenced in the Observation dating back to 2005. Eagle will provide records upon request.



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- **Additional Action by Eagle:** Eagle is working with its information technology and administrative staff so that electronic information is more readily available, organized and retrievable. Eagle will create folders in Laserfische by test, and subfolders by month/year, in order to render results more easily accessible results. Eagle will re-train its employees so that they can readily access electronic information and will make the referenced information and records available to FDA upon request.
- **Timeline:** Ongoing, anticipated completion by September 30, 2013.
- **Observation 3(b):** *The Reference Standards used in Potency Assay of Vitamin D sample ID 264253, 268952, and 271216 was not documented in the sample analysis records.*
 - **Response to Observation 3(b):** A former employee failed to input this data in the standards log book as required pursuant to SOP No. 14 (“Management of Analytical Standards”). However, the relevant data was located on a potency worksheet.
 - **Additional Action by Eagle:** Eagle is conducting retraining of staff to ensure the employees fully and accurately complete sample analysis records. Such records will continue to be maintained in a log. The log will be made available upon request.
 - **Timeline:** To be completed no later than July 15, 2013.

Observation 4: *Laboratory records do not include initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.*

- **Observation 4(a):** *The Sterility Tracking Logs and Contamination Test Tracking Logs (TSA Microbial Plating Records) that were only available from approximately January 2013 through March 2013, do not have any signature for review. According to management, these records were not maintained until the start of January 2013.*
 - **Response to Observation 4(a):** Eagle no longer offers the Plate Contamination test in its portfolio of contract services. With respect to the referenced records, including the Sterility Tracking Logs and Contamination Test Tracking Logs, Eagle maintains these documents in an electronic database (Laserfische). However, employees had some difficulty retrieving the requested documents during the inspection. As stated in response to Observation 3, Eagle is working with its information technology and administrative staff so that electronic information is more readily available, organized and retrievable. Records are maintained for a period greater than four months; Eagle has maintained this log in its digital database since 2005. To the extent that “management” stated that records were not maintained until the “start of January 2013,” that statement is incorrect. With respect to the missing signatures on the logs,



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Eagle's employees have been re-trained to ensure that two signatures are set forth thereon.

- **Additional Action by Eagle:** Eagle is in the process of creating a quality control unit to address, among other matters, maintaining, reviewing, and signing of records and log books under the appropriate circumstances.
- **Timeline:** To be completed no later than October 1, 2013.
- **Observation 4(b):** *The annual requalification records of HPLCs #1069, 1071, and #1073 were not signed by management to indicate review and approval of the requalification.*
 - **Response to Observation 4(b):** Although Eagle believes that this is a cGMP requirement, Eagle will ensure that requalification records will be reviewed and signed by management.
 - **Additional Action by Eagle:** Eagle will revise its SOP (No. 28; "Startup and Maintenance Procedures of HPLC Systems") so that it will include procedures to ensure that annual requalification records of HPLCs #1069, 1071, and 1073, and future HPLCs, are signed by management documenting review and approval of requalification. Eagle will provide training on the revised SOP, and ensure that applicable employees are trained on the procedures set forth therein. Eagle will provide the revised SOP upon request.
 - **Timeline:** To be completed no later than July 31, 2013.

Observation 5: *There is no quality unit. Your firm failed to establish an effective Quality Control Unit (QCU) that has responsibility and authority for approving rejecting all procedures, methods, and specifications related to the identity, strength, quality, and purity of drug product submitted to your firm for analysis, and for reviewing laboratory records to assure that no error had occurred or, if errors had occurred, that they have been fully investigated. Additionally, your firm has not developed any procedures describing these responsibilities.*

- **Response to Observation 5:** Eagle is not a manufacturer and does not provide testing services to manufacturers; thus cGMP, including establishment of an effective "Quality Control Unit" as that term is defined or otherwise used in FDA regulations or guidance documents is inapplicable to Eagle. Notwithstanding, Eagle is in the process of establishing a quality control unit that, among other things, will have responsibility and authority for approving and/or rejecting all procedures, methods, and specifications related to the identity, strength, quality, and purity of drug products that are submitted to Eagle for analysis. Eagle's quality control unit will also have responsibility for conducting a review of laboratory records as part of that quality control process, which review would include, but not be limited to, a review and



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investigation of any laboratory errors. Eagle will also develop procedures describing these quality control responsibilities.

- **Additional Action by Eagle:** Eagle is establishing a quality control unit.
- **Timeline:** To be completed no later than October 1, 2013.

Observation 6: *Written records are not made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications.*

- **Observation 6(a):** *Your firm has no SOP on how to handle Out of Specifications (OOS) results of a Sterility, Endotoxin, Tryptic Soy Agar Microbial Plate Contamination and Potency failures.*
 - **Response to Observation 6(a):** Eagle is not a manufacturer and does not provide testing services to manufacturers; thus cGMP, including maintaining SOPs on “how to handle Out of Specifications (OOS) results of a Sterility, Endotoxin, Tryptic Soy Agar Microbial Plate Contamination and Potency failures” as required by cGMP, FDA regulations, or other guidance documents is inapplicable to Eagle. Notwithstanding, Eagle is in the process of establishing a quality control unit that, among other things, will have responsibility and authority for approving and/or rejecting all procedures, methods, and specifications related to the identity, strength, quality and purity of drug products that are submitted to Eagle for analysis. Eagle’s quality control unit will also have responsibility for conducting a review of laboratory records as part of that quality control process, which review would include, but not be limited to, how to handle OOS results.
 - **Additional Action by Eagle:** Eagle will create a quality control unit.
 - **Timeline:** To be completed no later than October 1, 2013.

Observation 6(b): *Your firm has not conducted OOS investigations for your firm’s analyses for any possibility of laboratory error, control samples issues, etc. For example:*

- 1) *Sample # 280479 (Ascorbic Acid) was analyzed by your firm on 03/21/2013 using Rapid ScanRDI for sterility determination. The data for this day indicates the positive control failed in that no microbial contamination was detected. There was no investigation for this failure. The same sample #280479 was reported as a sterility failure with 1 “Event” reported. Additionally, Rapid Scan RDI data for 03/20/2013 and 06/19/2012 reported no growth for the positive control. There was no investigation.*
- 2) *Potency OOS reported by your firm include: Sample #271216 –Vitamin D3 assay results were reported as 13.8% potency, Sample # 264253 – Vitamin D3 assay results were reported*



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as 212% potency, Sample #263680 – Thiocetic Acid Assay results were reported as 39.2%. There was no investigation for these OOS.

- **Response to Observation 6(b):** Please see response to Observation 6(a) above. Eagle is not a drug manufacturer and does not provide testing services to manufacturers; thus cGMP, including “OOS investigations for your firm’s analyses for any possibility of laboratory error, control sample issues, etc.,” and the other examples identified above, as required by cGMP, FDA regulations, or other guidance documents are inapplicable to Eagle. Notwithstanding, Eagle is in the process of establishing a quality control unit that, among other things, will have responsibility and authority for approving and/or rejecting all procedures, methods, and specifications related to the identity, strength, quality, and purity of drug products that are submitted to Eagle for analysis. Eagle’s quality control unit will also have responsibility for conducting a review of laboratory records as part of that quality control process, which review would include, but not be limited to, how to handle OOS results under certain conditions.
- **Additional Action by Eagle:** Eagle will create a quality control unit.
- **Timeline:** To be completed no later than October 1, 2013.

Observation 7: *Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Your firm has no control or security of your electronic records. The database used by your firm (Lab Light) to receive sample requests, assign sample numbers, and reports sample results can be accessed and change [sic] by any firm employee. The sample numbers generated by Lab light can be deleted as was demonstrated during this inspection. Additionally, the electronic software (Empower) used to manage your analytical lab equipment such as HPLC’s and UHPLCs does not have any security measures in place. For example: Any technician can access any analysis being run on the six liquid chromatography stations. Additionally, the ability to manually integrate the peaks is accessible to any technician before the particular assay is set to complete.*

- **Response to Observation 7:** Eagle is not required to maintain a “Part 11” database or meet other requirements in 21 C.F.R. Part 211. Eagle is not a drug manufacturer, and does not provide Contract Testing Laboratory or other testing services to drug manufacturers.
- **Additional Action by Eagle:** None
- **Timeline:** N/A

Observation 8: *GMP training is not conducted on a continuing basis to insure that employees are remaining familiar with cGMP requirements applicable to them. Your firm does not adequately train*

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laboratory personnel. For example: staff performing bacterial endotoxin test indicate they were not trained in the principles and methodologies of the test and could not determine appropriate endotoxin limits for products under test.

- **Response to Observation 8:** Eagle is not a drug manufacturer. Eagle does not perform Contract Testing Laboratory or other testing services to drug manufacturers. cGMP training or other requirements applicable to Contract Testing Laboratories that perform testing services for drug manufacturers are not applicable to Eagle. Eagle utilizes appropriate compounding guidelines and good scientific practices for the testing of products compounded by pharmacies. All Eagle staff conducting such testing and analyses are highly skilled and degreed chemists or microbiologists. Contrary to FDA's Observation, staff performing bacterial endotoxin tests are trained in the principles and methodologies of bacterial endotoxin testing and would be able to "determine appropriate endotoxin limits for products under test."
- **Additional Action by Eagle:** None
- **Timeline:** N/A

As FDA acknowledged during its 2011 inspection, Eagle Analytical is not a drug manufacturer subject to cGMP. *See* EIR (Mar. 12, 2012). Eagle has not changed its business practice since that 2011 FDA inspection. Although Eagle tests compounded pharmaceuticals, it is also not a Contract Testing Laboratory subject to cGMP or other FDA regulations or guidance. To eliminate any further confusion, and although FDA is aware that Eagle has never held itself out as a Contract Testing Laboratory, Eagle fully intends to de-register itself as a Contract Testing Laboratory as soon as practicable. Eagle provides no laboratory testing for API or finished product release testing. Eagle does not hold itself out as compliant with cGMP, nor does it make any cGMP claims concerning its products or testing services. Eagle Analytical's responses above, and its well-established reputation, show that it has established, and continues to maintain, appropriate procedures to ensure the safety of testing performed at its facility.

Sincerely,



J.D. Willey



ANALYTICAL SERVICES

A P C C A C O M P A N Y

Enclosures

Cc: Andrea A Branch, Investigator, FDA

Patty P. Kaewussdangkul, Investigator, FDA

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July 9, 2013

Reynaldo (Ricky) Rodriguez, Jr.
District Director, Dallas District
Food and Drug Administration
4040 North Central Expressway
Suite 300
Dallas, Texas 75204

Dear Mr. Rodriguez:

I. INTRODUCTION

This letter is in response to the Food and Drug Administration's ("FDA's") recent inspection and Form 483 observations issued to Eagle Analytical Services ("Eagle" or "Eagle Analytical") on June 17, 2013. Eagle has addressed FDA's specific inspection observations in the attached document, which also describes improvements it is making in its laboratory operations.

During the course of the FDA inspection, Eagle repeatedly asked why it was being inspected against FDA's current Current Good Manufacturing Practice ("cGMP") regulations. That question was never answered. However, it is apparent that Eagle is being held to cGMP and this is because it performs testing for compounding pharmacies.

As a threshold matter, Eagle is not subject to cGMP. Eagle Analytical's mission is to assist and support compounding pharmacies. Ninety-seven percent of Eagle's clients are compounding pharmacies; three percent of its business derives from patients, physicians, hospitals, and clinics. Eagle does not do business with entities that manufacture finished drug products; nor does it conduct research for entities wishing to submit products for new drug approval to the FDA. Eagle is not aware of a single client that is registered with FDA as a drug manufacturer, and none were cited during the inspection.

Although never stated, apparently the premise for the inspection was that Eagle's clients are subject to cGMP. Yet those regulations do not apply to compounding pharmacies unless they are acting as manufacturers. The regulations are even more clearly inapplicable to Eagle Analytical, which is neither a drug manufacturer nor a compounding pharmacy: it provides testing and other services to compounding pharmacies.

FDA has long asserted and exercised authority against facilities that are licensed as pharmacies, but acting as manufacturers. The observations here, though, go further: they apply drug manufacturer requirements to a laboratory conducting testing for state-licensed pharmacies without asserting that the pharmacies are anything other than pharmacies. FDA's exercise of regulatory authority here is impermissible.

It is not clear why FDA believes Eagle is now subject to cGMP. In December 2011, Eagle was inspected by FDA. Although the investigator had some comments, no 483 was issued. The Establishment Inspection Report ("EIR") issued in 2012 explains why:

A review of operations and samples received for testing for approximately the last year revealed the firm has apparently received samples from only Compounding Pharmacies. No FDA regulation required currently for testing of Compounded Pharmaceuticals. No FDA 483 was issued.

The statement in the EIR that "[n]o FDA regulation required currently for testing of Compounded Pharmaceuticals" remains accurate. There has been no change in the law since the EIR.

It is not clear why this time a 483 was issued. It is clear, though, that FDA is explicitly holding Eagle to cGMP, and this is linked to the belief that the pharmacies themselves were subject to cGMP. For the reasons set out in this letter, the Form 483 issued to Eagle rests on a doubly invalid premise: pharmacies acting as pharmacies are not subject to cGMP, and even if a pharmacy (unbeknownst to Eagle Analytical) had been found to be a manufacturer, Eagle Analytical – a compounding pharmacy testing laboratory – still was not required to meet cGMP.

The inspection focused on documents relating to pharmacies, [REDACTED] (b) (4)
[REDACTED] (b) (4) These two pharmacies were inspected as part of a recent wave of federal pharmacy inspections. As FDA announced on April 11, 2013, its "2013 Pharmacy Inspection Assignment" involved the identification and "priority" inspection of 29 pharmacies that purportedly meet two of three "risk-based criteria." These inspection

criteria, which are not defined in any statute, regulation, or other guidance and represent a departure from established FDA practices, consist of (1) serious adverse event reports, (2) historical inspection data, and (3) reports of quality problems.¹ FDA's announced criteria did not include that the pharmacy was a manufacturer. The inspections focused on the pharmacies' "sterile drug production practices." Of the 29 pharmacies it inspected, FDA issued Form 483 inspection observations to 28, and subsequently posted the Form 483s on its website.²

On April 16, 2013, Commissioner Hamburg testified before Congress about this unprecedented flurry of supposedly risk-based pharmacy inspections.³ During that hearing, Dr. Hamburg asserted repeatedly that FDA's enforcement authority over compounding pharmacies is "unclear," "ambiguous," "and the law is not well suited to effectively regulate this evolving industry." Hamburg Testimony at 6. Notwithstanding this testimony, FDA's recent inspection observations seek to hold these pharmacies to standards legally applicable only to FDA-regulated drug manufacturers – not compounding pharmacies. Thus, while FDA has told Congress its authority is uncertain and the Agency needs more legislative authority, the Agency simultaneously is invoking its current authority against pharmacies, and then leveraging this unsettled authority to regulate Eagle. It is inexplicable that FDA would use "unclear" and "ambiguous" to describe its authority against Eagle's pharmacy clients, and then assert that Eagle itself violated cGMP by providing laboratory services for those facilities.

Thus, the Form 483 issued to Eagle Analytical rests on a novel position: that pharmacies which are licensed and regulated by the state must meet the same standards applicable to FDA-regulated pharmaceutical manufacturers without an FDA finding that

¹ FDA, Summary, 2013 FDA Pharmacy Inspection Assignment (Apr. 11, 2013) *available at* <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm>.

² FDA issues thousands of 483s each year without immediately posting them on its website. FDA has not provided a rationale for choosing to post these pharmacy inspection 483s. These 483s do not themselves explain why FDA considered the pharmacies to be manufacturers. As of the date of this letter, FDA has actually posted on its website in excess of 50 FDA Form 483s for compounding pharmacies. *See* FDA, Pharmacy Compounding: FDA Actions, *available at* <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm>.

³ *A Continuing Investigation into the Fungal Meningitis Outbreak and Whether it Could Have Been Prevented: Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. On Energy and Commerce, 113th Cong.* (testimony of Margaret A. Hamburg, M.D., Commissioner, FDA) (Apr. 16, 2013) ("Hamburg Testimony").

they are actually acting as manufacturers, and laboratories that perform testing for these pharmacies therefore must also meet cGMP, despite neither having customers that are registered drug manufacturers nor representing the facility as meeting cGMP.

Indeed, FDA acknowledged that it did not rely on state laws and United States Pharmacopeia (“USP”) guidance when inspecting these pharmacies, but instead “the Agency inspected these firms according to federal standards regarding aseptic practices.”⁴ The Agency fails to state from what statute or lawful regulation it obtained these “federal standards,” what those “federal standards” were, how it could apply “federal standards” to compounding pharmacies without finding them to be manufacturers, or how cGMP could then be invoked against a testing laboratory that does not represent itself as providing testing services to the pharmaceutical industry. FDA’s unprecedented position is inconsistent with the long-standing, state-licensed, state-regulated profession of pharmacy.

A. Pharmacy Compounding is a Well-Recognized and Critically Important Profession in the United States.

At the core of the 483 observation is that compounding – and laboratory services for compounders – is impermissible. As has been widely recognized, compounding pharmacies cannot meet cGMP written for drug manufacturers, rendering all compounded drugs adulterated under FDA’s regulations.⁵

That premise cannot be reconciled with history or law. Compounding is an accepted, long-standing practice under federal and state law, and has been a core component of the practice of pharmacy in the United States since the 17th century. See *Remington’s Practice of Pharmacy* 13 (12th ed. 1961). The USP, itself an official compendium of drug information deemed “authoritative” by the Federal Food, Drug, and Cosmetic Act (“FDCA”), 21 U.S.C. § 351(a)(1) and (b), has included instructions for compounding since 1820. Okeke, et al., *History and Background Information on USP’s Activities in Compounding Pharmacy Practices*, 27 *Pharmacoepial Forum* 3169 (Sept.-Oct. 2001). In 1938, when Congress enacted the FDCA, pharmacy compounding was widely practiced; it was often the only way to supply medical practitioners with medications

⁴ FDA, Summary, 2013 FDA Pharmacy Inspection Assignment (Apr. 11, 2013) available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm>.

⁵ FDA’s criteria for selecting pharmacies to inspect are so vague and elastic as to not meaningfully limit which pharmacies are inspected. Moreover, given that the inspectional criteria are not grounded in any statute or regulation, FDA is effectively asserting untrammelled authority to apply cGMP to pharmacies.

needed to treat patients. Even back then, pharmacists compounded more than 250 million prescriptions annually. *Proceedings of the Local Branches*, 14 J. Am. Pharm. Ass'n 232, 233 (1935). In 1938, the pharmacy laws of every state also defined the practice of pharmacy to include compounding. *Joint Session of the American Pharmaceutical Association, the American Association of Colleges of Pharmacy and the National Association of Boards of Pharmacy*, 17 J. Am. Pharm. Ass'n 1000, 1010-13 (1938). Compounding was an essential element of the practice of medicine in 1962 when Congress gave FDA the power to establish cGMP, and has remained essential ever since.

In order to meet patient needs and the demands of an increased market for compounded medications, the practice of pharmacy has evolved to the point where pharmacies ship compounded products interstate, compound for office use, extemporaneously compound for emergency use in the event of drug shortages, or at times compound in anticipation of receiving prescriptions for products. It is well-established that pharmacies compound life-saving and critical drugs under all of the above circumstances for patients, and the unavailability of these drugs would have severely adverse health consequences. The compounded drugs include those that are in short supply or back-ordered and thus are not commercially available from drug manufacturers. In recent years this has included scores of drugs, such as electrolytes, atropine, epinephrine, sodium bicarbonate, and dextrose. Such drugs are staples of emergency rooms, clinics, and ambulances, and are frequently contained on life-saving "crash carts" in hospitals throughout the country. The continued availability of compounded drug products is an integral part of patient care provided by hospitals and physicians throughout the United States.

As FDA is well aware, drug shortages are a major, recurring problem. FDA has worked with manufacturers to alleviate these shortages and has developed other solutions, e.g., allowing the importation of unapproved drugs, and yet shortages still persist. For example, an article in the *Philadelphia Inquirer* on June 30, 2013 stated, "Currently more than 300 medicines crucial to treating cancer, infections, cardiac arrest, premature infants, pain, and more, are in short supply."⁶

Compounding pharmacies enable health care facilities to meet these needs in cases where doctors or hospitals are unable to compound the drugs themselves. In many cases, hospital pharmacies possess neither the expertise nor the facilities to compound certain

⁶ Marie McCullough, "Medication Shortages: Truly a Public Health Crisis," *Philadelphia Inquirer*, June 30, 2013, http://articles.philly.com/2013-07-01/news/40288181_1_shortages-15-deaths-patients.

drugs. If a hospital pharmacy cannot fill a physician's order for which the manufactured version is unavailable, hospitals often "outsource" the order to a compounding pharmacy that can meet this critical medical need. A recent report, issued by the Department of Health and Human Services' Office of Inspector General ("OIG Report"), found that a significant number of acute care hospitals used compounded sterile preparations or purchased them from outside sources during 2012. The report highlights the importance of compounding pharmacies in the care of patients and meeting hospitals' medical needs.⁷

Compounding pharmacies play a critical role in ameliorating inadequate supply of manufactured drugs. The OIG Report notes, for example, that ensuring an adequate supply of compounded sterile products was "very important" to hospitals when determining whether to obtain outsourced sterile compounded products. OIG Report at 1. Many hospitals surveyed (62%) specifically cited shortages in the supply of commercial products as "very important." Compounding pharmacies, whether filling one prescription or providing otherwise commercially unavailable outsourced medications to hospitals, help to fill the gaps created by the lack of manufactured drugs. Without compounding pharmacies filling these gaps, hospitals, physicians, and patients may not be able to obtain life-saving, critical medications that are in short supply.⁸ Compounding also plays another crucial role: allowing physicians to tailor therapy to the individualized needs of patients. This role was recognized by the Supreme Court in *Thompson v. Western States Medical Center, et al.*, 535 U.S. 357 (2002).

FDA has long had criteria for determining when an activity by a pharmacy is manufacturing, not compounding. We are not questioning, for example, that a pharmacy that routinely compounds and distributes inordinate quantities of commercially available drugs could be subject to regulation as a manufacturer. In the past, FDA did issue warning letters to pharmacies based on conduct that FDA considered indicative of being a manufacturer. However, FDA has stated it did not base the inspectional assignments for the pharmacies that preceded Eagle's Form 483 by applying these established criteria. Rather, FDA has invoked the cGMP requirements against Eagle without determining that any pharmacy client was a manufacturer under established criteria, let alone without showing that Eagle knew a client was a manufacturer.

⁷ HHS OIG, Report to Margaret A. Hamburg, Commissioner, FDA, *High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them*, OEI-01-13-00150 (Apr. 16, 2013) ("OIG Report").

⁸ FDA's website lists about 130 drug products, including several injectable and critical, life saving drugs. FDA, Current Drug Shortages Index, available at <http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050792.htm>. This understates the drug shortage problem.

B. FDA Cannot Hold A Laboratory Providing Tests for Pharmacies to the cGMP Regulations.

In the wave of coordinated inspections of state-licensed compounding pharmacies, FDA has taken action by attempting to hold them to the same standards as drug manufacturers subject to cGMP. FDA cannot do so, though, because there is no statutory basis for applying cGMP to these pharmacies. Indeed, FDA has itself prominently and publicly stated it has no clear legal authority permitting the Agency to apply cGMP to compounding pharmacies. FDA's repeated assertions of regulatory ambiguity cannot be reconciled with its holding compounding pharmacies – or a testing laboratory – to cGMP requirements.

For example, on November 14, 2012, FDA Commissioner Margaret Hamburg testified before Congress concerning FDA's response to the New England Compounding Center ("NECC") matter. She argued that FDA's ability to take action against NECC and other compounders "has been hampered by gaps and ambiguities in the law, which has led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions." *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight and Investigations of the H. Comm. On Energy and Commerce 112th Cong. (Nov. 14, 2012) (testimony of Margaret A. Hamburg, M.D., Commissioner, FDA) ("Hamburg Testimony, 2012")*. Whether this view of FDA's authority is correct is immaterial. FDA cannot tell Congress it needs more power because of "ambiguities in the law" and then issue a Form 483 based on that same law. As discussed below, inspectional findings should rest on clear violations and not on a legally ambiguous foundation.

Dr. Hamburg also addressed the regulatory framework that Congress had established to regulate compounding: The Food and Drug Administration Modernization Act of 1997 ("FDAMA"). According to Dr. Hamburg, FDAMA's provisions were the subject of subsequent court challenges, which produced "conflicting case law and amplified the perceived gaps and ambiguity associated with FDA's authority over compounding pharmacies." Hamburg Testimony, 2012, at 10-11. Specifically, after a challenge to the advertising provisions of FDAMA, the Court of Appeals for the Ninth Circuit found those provisions unseverable from the statute's other provisions and struck down Section 503A in its entirety. *See Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001). In 2002, the Supreme Court upheld the Ninth Circuit's finding that Section 503A was an unconstitutional restriction on commercial speech. *Thompson v. Western States Medical Center, et al.*, 535 U.S. 357 (2002). As a result, FDA stated that "presently section 503A in its entirety is *invalid*." FDA, Compliance Policy Guide for FDA Staff and Industry,

§ 460.200 (Pharmacy Compounding) (2002) (*emphasis added*). Subsequently, pharmacies filed another lawsuit in Texas in 2005 challenging FDA's authority to regulate compounded drugs under FDAMA. The United States Court of Appeals for the Fifth Circuit refused to be bound by the Ninth Circuit's decision in *Western States*, and held in 2008 that the commercial speech provisions of 503A, while unconstitutional, were severable from the statute's other provisions, leaving the rest of 503A in effect. *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008). Thus, in the Fifth Circuit, contrary to the Ninth Circuit, compounded drugs are exempt from the cGMP requirements so long as those pharmacies comply with 503A. Eagle Analytical is located in the Fifth Circuit (in Houston, Texas), as are the pharmacies referenced in the Form 483 issued to Eagle. Thus, section 503A's cGMP exemption applies to the referenced pharmacies, making FDA's Form 483 observations even more attenuated and lacking in any legal foundation.

FDA has also stated, "Other circumstances further blur the line," including a "patchwork" of state laws and regulations.⁹ Arguing for clearer enforcement authority, FDA has asked what exactly *is* the appropriate regulatory path for pharmacy compounding. For example, FDA questioned, "Should hospitals and other healthcare entities be considered doing traditional compounding, even when they make batches of drug in advance of receiving prescriptions or orders?" And, "If a pharmacy crosses over from a traditional compounder to a non-traditional compounder, how should the handoff from the state to FDA occur, and vice versa?" Or, "How can non-traditional compounders be distinguished from manufacturers?" *Id.*

Subsequently, in an FDA blog article dated March 22, 2013, Commissioner Hamburg stated that there currently are *no discernible federal standards* to regulate pharmacy compounding. Specifically, she stated, regulatory "authorities are limited and not the right fit for FDA to provide appropriate and efficient oversight of this growing industry." Margaret A. Hamburg, M.D., Commissioner, FDA, *FDA Must Have New Authorities to Regulate Pharmacy Compounding* (Mar. 22, 2013), available at <http://blogs.fda.gov/fdavoices/index.php/2013/03/fda-must-have-new-authorities-to-regulate-pharmacy-compounding>. It is difficult to understand how FDA can tell Congress that there are numerous unresolved issues and its authority is "not the right fit," and then issue Eagle a 483, when 483 findings should be issued only for violations of clearly-stated legal requirements.

⁹ See FDA Presentation, *The Legislative Framework: Sterile Pharmacy Compounding Summit* (Feb. 6, 2013) ("FDA Presentation").

FDA investigators issued 483s to numerous pharmacies based on purported cGMP violations, or as the Agency put it, based on inspections conducted “according to federal standards regarding aseptic practices.”¹⁰ Yet, an FDA Form 483 observation is supposed to be based on a perceived violation of law. FDA investigators are instructed that “deviations from policy or guidance documents” are not supposed to be cited as “deviations.”¹¹ FDA has publicly and repeatedly stated that its authority is ambiguous and uncertain. The Agency’s assessment of its own authority is clearly correct when inspectional findings are based on unspecified “federal standards regarding aseptic practices.” And the assertion of this authority is doubly ambiguous and uncertain when extended to Eagle Analytical. FDA’s statements – including its testimony to Congress – undermine the fundamental premise underpinning the Form 483 observations issued to Eagle: that the compounding activities by the pharmacies violated cGMP.

C. Even If FDA Had the Statutory Authority to Regulate Pharmacies as Drug Manufacturers, FDA’s Attempt to Force Pharmacies and Laboratories to Comply with “Manufacturing Regulations” Violates the Administrative Procedure Act.

It is within this regulatory environment – full of what FDA refers to as “gaps,” “ambiguities,” and a “faulty legal framework” – that FDA seeks to enforce cGMP against compounding pharmacies, and then, derivatively, against Eagle Analytical. Unless a pharmacy is acting as a drug manufacturer, it is not subject to cGMP, regardless of whether there have been adverse events, quality problems, or the results of past FDA inspections. Nor is sterile compounding itself a basis for applying cGMP. In issuing this spate of 483s, FDA expanded the scope of compounding to which it is applying cGMP while

¹⁰ FDA, Summary, 2013 FDA Pharmacy Inspection Assignment (Apr. 11, 2013), *available at* <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm347722.htm>.

¹¹ FDA’s Investigations Operations Manual (“IOM”) section on “Reportable Observations” states that an investigator “should cite factual observations of significant deviations from the FD&C Act [21 U.S.C. § 301], PHS Act, 21 CFR, and other acts where FDA has enforcement authority” FDA, IOM, Ch. 5.2.3.2 (Reportable Observations). Observations “are listed on a FDA Form 483 when, in an investigator’s judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA’s requirements.” FDA, Inspections, Compliance, Enforcement, and Criminal Investigations, *Inspection Observations*, *available at* <http://www.fda.gov/ICECI/EnforcementActions/ucm250720.htm>. The IOM specifically advises investigators, “Do not cite deviations from policy or guidance documents on your FDA 483.” FDA, IOM, Ch. 5.2.3.1.4 (Observations).

simultaneously claiming it is bereft of adequate statutory authority to regulate pharmacies and needs new statutory powers. Rather than waiting for Congress to act, the Agency has unilaterally – and improperly broadened – the conduct to which it applies cGMP.

The courts have long recognized that agency policies creating new rights or duties require federal agencies to comply with provisions of the Administrative Procedure Act, including notice and comment rulemaking. *See Community Nutrition Institute v. Young*, 818 F.2d 943, 946 (D.C. Cir. 1987); *American Hospital Ass'n v. Bowen*, 834 F.2d 1037 (D.C. Cir. 1987); *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 95 (D.C. Cir. 1997); *see also Prevor v. FDA*, 895 F. Supp. 2d 90 (D.D.C. 2012). Fundamentally, although FDA is attempting to assert that the compounding pharmacies are subject to cGMP, FDA cites no federal legal requirement that the pharmacies have violated. If FDA's position is that pharmacies which compound sterile drugs for hospitals or doctors must meet cGMP, then the Agency is relying on a new policy.

Applying that new policy to Eagle Analytical goes yet a step further. FDA's current position – that Eagle should be held to cGMP – is wholly contradictory to the position it took concerning Eagle only a year ago. FDA inspected Eagle in December 2011 to “determine the firm's compliance as a Contract Laboratory as a result of the firm's [FDA] registration as a Contract Laboratory.” The EIR noted that the firm's SOPs were not meant to be cGMP compliant, and that “the firm does not make any cGMP claims at this time, nor accept any customers other than compounding pharmacies, and small specialty testing.” EIR at 3. FDA also stated:

A review of operations and samples received for testing for approximately the last year revealed the firm has apparently received samples only from Compounding Pharmacies. *No FDA regulation required currently for testing of Compounded Pharmaceuticals.*

EIR at 1 (emphasis added). Eagle has not changed a single legally relevant aspect of its business, its practices, or client base since FDA's EIR declared just last year that Eagle's current business practices were *not* subject to FDA regulation. Nor has FDA changed its regulations.

The government's new position runs afoul of basic principles of administrative law. An agency can create a new substantive prohibition only through notice and comment rulemaking. *See Jean v. Nelson*, 711 F.2d 1455, 1476 (11th Cir. 1983); *Paralyzed Veterans v. D.C. Arena L.P.*, 117 F.3d 579, 588 (D.C. Cir. 1997); *National Family Planning &*

Reprod. Health Ass'n v. Sullivan, 979 F.2d 227, 238-39 (D.C. Cir. 1992) (agency must proceed by rulemaking when it relies on a statutory interpretation that “produce[s] other significant effects on private interests”). This requirement reflects the concern that regulatory obligations must be set forth with sufficient definition that ordinary people can understand what conduct is prohibited, and in a manner that avoids arbitrary and discriminatory enforcement. *United States v. Wayerski*, 624 F.3d 1342, 1347 (11th Cir. 2010); *Georgia Pac. Corp. v. Occupational Safety & Health Review Comm’n*, 25 F.3d 999, 1005 (11th Cir. 1994); *Prevor*, 895 F. Supp. 2d 90 (D.D.C. 2012) (FDA’s change in interpretation of its own policies for little or no apparent reason is entitled to little deference). Likewise, “The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious.” *Bracco Diagnostics, Inc.*, 963 F. Supp. 20, 28 (D.D.C. 1997). FDA inspected Eagle in 2011. Nothing has changed in the intervening months – not the law, not the regulations, and not Eagle’s business practices. It is difficult to imagine agency conduct that is more “arbitrary and discriminatory” than an inspection in 2011 that concludes a facility is not subject to FDA regulation and an inspection 18 months later resulting in a 483, without any intervening change in law or conduct.

D. Even If FDA Had the Requisite Regulatory Authority, Federal cGMP Regulations Are Not Only Inapplicable but Also Fundamentally Inconsistent with the Practice of Pharmacy.

Even if FDA had the legal authority to impose cGMP on compounding pharmacies, and then extending that authority to a laboratory that provides testing services to compounding pharmacies, FDA fails to recognize that neither these pharmacies nor laboratories could comply with the provisions of cGMP.

Current good manufacturing practice regulations establish comprehensive requirements for all aspects of pharmaceutical manufacturing. 21 C.F.R. Parts 210 and 211. cGMP provisions are principally designed for large-scale production of well-defined, finished dosage forms that have an extended shelf life pursuant to FDA-approved New Drug Applications, Abbreviated New Drug Applications, or regulatory drug monographs. Indeed, the regulations specify that they apply to the “manufacture, processing, packing, or holding of a drug,” and define “manufacture” to include – not compounding but – “packaging and labeling operations, testing, and quality control of drug products.” 21 C.F.R. §§ 210.1(a), 210.3(b)(12). They require manufacturers to submit or maintain extensive documentation, validate the process and product, and conduct extensive testing of the product. These requirements are appropriate for facilities making a few products consistently and repeatedly. These requirements are unworkable both for pharmacies that

extemporaneously compound to fill the immediate needs of hospitals and patients, and for the laboratories testing those products. The cGMP requirements are incompatible with compounding to address shortages of medications, which require hospitals to obtain supplies of compounded medications for their patients on an urgent or emergency basis, or when a new product is prescribed to meet the unique needs of a patient.

For example, the requirements for validating drug manufacturing processes require a massive amount of time and effort, with multiple validation batches of the drug being produced, sampled and tested, a process that must be repeated for every specific drug formulation. Specifically, 21 C.F.R. § 211.100(a) requires drug manufacturers to maintain “written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.” FDA interprets this regulation to require that manufacturing processes for drugs – even over-the-counter drugs – be properly “validated.” *See, e.g.*, FDA Warning Letter to Kanebo Cosmetics, Inc. (Apr. 1, 2013) ¶ 4.

FDA states that process validation of “manufacturing processes is a requirement of the Current Good Manufacturing Practice (cGMP) regulations for finished pharmaceuticals (21 C.F.R. §§ 211.100 and 211.110).” FDA, Compliance Policy Guide for FDA Staff and Industry, Sec. 490.100, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval (2004). An FDA Guidance further states that a “manufacturer must successfully complete PPQ [Process Performance Qualification] before commencing commercial distribution of the drug product,” and requires multiple samples to be tested from multiple batches. FDA, Guidance for Industry and FDA Staff, Process Validation: General Principles and Practices (2011), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>, at 4, 12. “Concurrent release” – that is, release of batches while the PPQ process is ongoing, is permitted rarely, and only under certain circumstances, and the PPQ process must continue even after the product has been distributed. *Id.* at 16. These and other cGMP requirements cannot coexist with extemporaneous compounding, a point FDA has previously acknowledged.

Furthermore, cGMP provisions are not “scalable”: they cannot be modified, customized, or adopted to individual dosing, which is critical to pharmacy compounding. When a hospital orders a sterile drug to meet the needs of a few patients, a pharmacy cannot test multiple batches in a validation study before dispensing the drug. Nor can the hospital wait for a laboratory to develop and fully validate its test methods. FDA has

recognized that extemporaneous compounding to meet the needs of individual patients is at the heart of traditional compounding. Yet that is precisely the kind of compounding that can never comply with cGMP.

In contrast, the standards for quality in pharmacy compounding reside with state statutes and regulations and with the USP, Chapters <795> (Non-Sterile Preparations) and <797> (Sterile Preparations). Congress declared the USP an official compendium under the FDCA, 21 U.S.C. § 321(j). Chapter <797> was introduced in 2004 and finalized in 2008; its intent is “to prevent patient harm and fatality from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients” in compounded sterile preparations. A number of states have incorporated these USP sections in their state pharmacy regulations. After the introduction of USP <797>, hospitals greatly increased outsourcing of sterile preparations to compounding pharmacies due in part to limited compounding capabilities, perceived costs, and other burdens associated with compliance with rigorous USP requirements. Unlike cGMP, USP <797> was developed for compounding pharmacies.

E. Sterility and Preservative Testing Required of Drug Manufacturers Demonstrates the Incompatibility of cGMP with Pharmacy Compounding.

A brief review of sterility and preservative testing required of manufacturers also reveals why compliance with manufacturing cGMP is incompatible with the practice of pharmacy. Several recent Form 483s that FDA issued to compounding pharmacies observed that the pharmacies maintained no written testing program designed to assess the stability characteristics of drug products.

According to FDA’s cGMP, manufactured drug products must be placed in a stability program to determine shelf life and to test the viability of any preservative used in the product. 21 C.F.R. § 211.166. This is done through the use of an extensive stability study that places an “adequate number of batches of each drug product” in different environmental conditions (including elevated temperature, controlled humidity, and room-temperature, refrigerated, or frozen conditions) over a long period of time (i.e., for accelerated stability studies, 90 or more days; and for long-term stability studies, generally for one year more than the shelf life of the drug. 21 C.F.R. § 211.170(b)(1); 21 C.F.R. § 211-166(b)). The active pharmaceutical ingredients in these drug products undergo a forced degradation process by which any degraded products are identified.

Additionally, finished drug products that include preservatives must undergo other tests (preservative effectiveness challenges) that take three months to one year to complete. If the drug formulation changes, the sterility and preservative test results are no longer applicable, and new tests should be done. And drug manufacturers are required to retain samples of every lot of drugs they produce. 21 C.F.R § 211.170.

These cGMP requirements are designed for the repeated manufacturing of single, specific products, where manufacturers can meet the time requirements. Enforcing these types of requirements on compounding pharmacies, where individualized preparations are made and dispensed on a daily or emergency basis, would negatively affect patient care by severely limiting or precluding access to needed medications. For example, maintaining sufficient retained samples of every lot of drug products, when some pharmacies compound dozens of products in small batches every day, would render compounding nonviable. Even more problematic is a requirement for long-term stability testing. A pharmacy that receives an order from a hospital for a drug that is now suddenly unavailable cannot meet the hospital's acute needs and comply with cGMP stability requirements. Adhering to cGMP's stability testing requirements would mean that patients would go without the prescribed drug.

F. Cleaning Validation Studies Required Under cGMP Are Unworkable for Compounding Pharmacies.

Pharmacies likewise would not be able to comply with cGMP validation studies for cleaning equipment. Federal cGMP regulations state that equipment shall be maintained in a clean and orderly manner. *See* 21 C.F.R. § 211.67 (Equipment Cleaning and Maintenance). FDA further states via guidance documents,¹² that manufacturers must have written SOPs addressing cleaning processes for each drug manufactured. These SOPs must include: (1) written general procedures on how cleaning processes will be validated, general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required; (2) specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods; (3) validation studies conducted in accordance with the protocols and to document the results of studies; (4) a final validation report which is approved by management and which states whether or not the cleaning process is valid; the study data should support a

¹² *See, e.g.,* FDA Inspection Guide, "Validation of Cleaning Processes" (7/93) available at <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm>.

conclusion that residues have been reduced to an “acceptable level;” and (5) appropriate methods to swab/sample equipment as well as the analytical processes used to analyze the samples to validate that “clean is clean.” This rigorous validation process makes sense for a single product made repeatedly on a manufacturing line. It is unworkable for pharmacies that are asked to provide individualized medications in a timely or exigent manner. These validations, which, under cGMP, must be performed for every drug formulation, can take days to complete. A compounding pharmacy cannot comply with these elements of cGMP and extemporaneously compound drug products to meet the needs of patients that day.

FDA has acknowledged the importance of compounding to meet the unique needs of individual patients. *See* Hamburg Testimony at 6. The cGMP is antithetical to fulfilling this objective. A pharmacy that receives an order for a single sterile drug product cannot fill that order and meet cGMP. Indeed, FDA’s invocation of cGMP here has a perverse effect: the more individualized the compounding, the more obvious it becomes that attaining cGMP compliance is impossible.

The same limitations apply to testing laboratories providing services to compounding pharmacies. Eagle Analytical conducts thousands of tests each year, some for unique formulations. The cGMP requirements rest upon a model of repeatedly testing a relatively small number of products. That model does not fit a facility dedicated to testing a large variety of products, many of which are newly formulated to meet emerging needs, and illustrate why the cGMP was never intended to apply to laboratories providing testing services to compounding pharmacies.

FDA has recognized that the cGMP regulation does not fit compounding pharmacies. FDA has admitted to Congress that FDA does not have authority to require pharmacies to follow cGMP simply because they compound. When Rep. Dingell asked Janet Woodcock, “Does FDA have the authority to require all compounding pharmacies to follow good manufacturing practices? Yes or no?,” she replied, “No.”¹³ At a minimum, a testing laboratory cannot be obligated to meet cGMP unless its customers are obligated to follow cGMP.

Yet, even if one of Eagle Analytical’s more than 1,200 customers had been subject to cGMP, that would not be sufficient to impose cGMP requirements upon Eagle. The company did not represent itself as a cGMP-compliant facility or a facility that provided

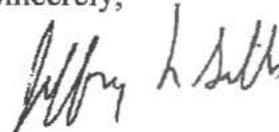
¹³ Examining Drug Compounding: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce, 113th Cong. 1 (2013) (testimony of Janet Woodcock, M.D., Director, CDER) (preliminary transcript).

testing services to manufacturers subject to cGMP. A laboratory does not need to comply with cGMP simply because some state-registered pharmacy was subsequently deemed a drug manufacturer.¹⁴ In its 2012 EIR, FDA concluded that Eagle was not subject to cGMP. That conclusion was correct then, and remains correct.

II. CONCLUSION

Invoking cGMP requirements against laboratories providing services to pharmacies has no basis in the law or regulations. Moreover, FDA is now saying that a testing laboratory must meet cGMP regulations without having any way of knowing which customers must be tested under cGMP conditions, and without disclosing the criteria by which FDA decides to invoke cGMP against either the client or the laboratory itself. That kind of conduct epitomizes arbitrary and capricious agency action. The 483 findings applying cGMP requirements to Eagle Analytical are not based on law and are in conflict with the Administrative Procedure Act.

Sincerely,



Jeffrey N. Gibbs

JNG/KLP/rh

cc: Dr. Jane A. Axelrad
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¹⁴ As noted above, FDA never did say during the inspection that any of Eagle's customers actually were manufacturers.