Hieber's Pharmacy

Specializing in Custom & Sterile Compounding
3500 Fifth Avenue • Pittsburgh, PA 15213
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When your need is special...you need Hieber's
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February 24, 2015

Anne Johnson
Deputy District Director, Philadelphia District
Food and Drug Administration
US Customhouse, Room900
2nd and Chestnut Street
Philadelphia, Pennsylvania 19106

Re: Posting of FDA Form 483 Response
FEI: 1000121499
EI: 9/8/14-9/12/14, 9/18/14

Dear Ms. Johnson,

This letter is in regards to the FDA Form 483 Response submitted to your office by Hieber's Pharmacy on October 7, 2014 in response to FEI 1000121499 issued on September 18, 2014, to Hieber's Pharmacy ("Hieber's") located at 3500 Fifth Ave, Pittsburgh, Pennsylvania 15213; another copy of which has been enclosed for your convenience.

Hieber's Pharmacy requested in the Form 483 Response that the Form 483 Response not including Tabs 1 through 16, be included anytime FDA discloses to the public or otherwise provides a copy of the Form 483, including, but not limited to posting this Form 483 Response on FDA's Website. It has come to our attention that the Form 483 for the inspection has been posted on FDA's Website without posting our Form 483 Response.

Please accept this letter as authorization to post on the US FDA website Hieber's Pharmacy's response to the FDA Form 483 Notice of Observations, dated 10/7/2014, as previously requested when submitted to the US FDA Philadelphia District, un-redacted but without Tabs. We understand this response will be posted under the FDA Form 483 Notice of Observations for Hieber's Pharmacy, issued on 9/18/14 by Investigators Thomas E. Friehl and Cynthia L. Rakestraw.

Kind Regards,

Joseph G. Bettinger, R.Ph.
Owner and Compounding Specialist

JB/jm

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October 7, 2014

Anne Johnson
Deputy District Director, Philadelphia District
Food and Drug Administration
US Customhouse, Room900
2nd and Chestnut Street
Philadelphia, Pennsylvania 19106

Re: Hieber's Pharmacy:
Response to FDA Form 483, No. 10000121499

Dear Ms. Johnson:

This letter is in response to the FDA Form 483 issued on September 18, 2014, to Hieber's Pharmacy ("Hieber's") located at 3500 Fifth Ave, Pittsburgh, Pennsylvania 15213. At the conclusion of FDA's inspection, which occurred from September 8-14 and September 18, 2014, Hieber's Pharmacy received an FDA Form 483 listing five Observations.

We request that this Response, not including Tabs 1 through 16, be included anytime FDA discloses to the public or otherwise provides a copy of the Form 483, including, but not limited to posting this Response on FDA's Website. The Tabs listed in the Appendix are confidential and proprietary business information and should not be released.

Introduction

Hieber's Pharmacy, under current ownership, is a compounding pharmacy that serves patients in Pittsburgh and the surrounding areas. It has provided both non-sterile and sterile compounding preparations to its customers since 2001. Hieber's has an impeccable safety record. At the commencement of FDA's inspection, we were informed that we were incorrect in our interpretation that it was permissible to provide small amounts of compounded sterile preparations for emergency office stock use. Although it did so in the past, Hieber's Pharmacy no longer provides "emergency use" -- or any other sterile compounded preparations -- for office stock use, effective immediately. Hieber's Pharmacy is committed to only dispensing compounded sterile preparations to individually identified patients based on a valid prescription from a prescriber in accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA").

To the best of our knowledge and information, there have been no adverse effects or complaints associated with our dispensed sterile compounded preparations that would warrant

a "for cause" investigation by FDA. This was confirmed by the FDA investigators at the beginning of the inspection. As such, the Pennsylvania Board of Pharmacy is the primary authority to set regulations and enforcement for pharmacies operating within the Commonwealth of Pennsylvania. As a traditional compounding pharmacy, Hieber's Pharmacy follows the standards set forth in the United States Pharmacopeia ("USP") for compounding preparations, specifically USP <795> Pharmaceutical Compounding – Nonsterile Preparations and USP <797> Pharmaceutical Compounding – Sterile Preparations. Hieber's Pharmacy is also compliant with Pennsylvania Board of Pharmacy requirements. Hieber's Pharmacy is in good standing with the Pennsylvania Board of Pharmacy, and has no recorded safety or disciplinary actions.

Set forth below are Hieber's Pharmacy's Responses to FDA's Form 483 Observations. The Responses address Hieber's Pharmacy commitment to safe and high quality compounding of both sterile and non-sterile preparations based on the standards set forth in USP <795> and <797>, and state law.

Observation 1: *Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.*

Observation 1(1): *The firm has not validated the terminal sterilization process for autoclave for injectable drug products.*

Response to Observation 1(1): Hieber's Pharmacy does not manufacture drug products, and thus is not required to comply with FDA's current good manufacturing practices ("cGMP"), which require validation of the sterilization process; specifically, the terminal sterilization process for each type of compounded sterile preparation ("CSP"), as would be required for injectable drug products.

Hieber's Pharmacy complies with USP <797>, which states that, for CSPs, "*the effectiveness of steam sterilization shall be verified using appropriate [biological indicators] of Bacillus stearothermophilus and other confirmation methods such as temperature sensing devices.*"

a) In accordance with USP <797>, a biological indicator ("BI") containing *Geobacillus stearothermophilus*[1] is placed within each autoclaved batch load to validate the sterilization process of the CSP batch. Upon completion of the autoclave cycle, the BI is activated and incubated at 60°C for twenty-four hours (as directed by the manufacturer) and documented on Hieber's Pharmacy Autoclave Log. (Tab 1). A Certificate of Analysis ("CofA") is provided by the manufacturer for each lot number of the BI. (Tab 2). Additionally, a positive and negative control for each BI lot number is processed by Hieber's Pharmacy and documented on Hieber's Pharmacy Biological Indicator Log (Autoclave). (Tab 3).

b) A printout is provided by the Tuttnauer autoclave for each autoclaved CSP batch cycle, which documents the temperature-over-time values present within the autoclave sterilization chamber during the cycle. The printout is attached to each autoclaved CSP batch preparation formula log to document compliance with minimum times and temperatures required for sterilization. (Tab 4).

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[1] Geobacillus is the more modern nomenclature of Bacillus.

Observation 1(2): *The firm has not validated the sterilization and depyrogenation processes for components such as vials and stoppers used in products.*

Response to Observation 1(2): Hieber's Pharmacy does not manufacture drug products, and thus is not required to comply with cGMP, which require the manufacturer to validate the sterilization and depyrogenation processes for components such as vials and stoppers used in CSPs.

Hieber's Pharmacy complies with standards set forth in USP <797>, which states that, for autoclaved CSPs, "*the effectiveness of steam sterilization shall be verified using appropriate BIs of Bacillus stearothermophilus and other confirmation methods such as temperature sensing devices*".

a) In accordance with USP <797>, a BI containing *Geobacillus stearothermophilus* [2] is placed within each autoclaved batch load to validate the sterilization process of the CSP batch. Upon completion of the autoclave cycle, the BI is activated and incubated at 60°C for twenty-four hours (as directed by the manufacturer) and documented on Hieber's Pharmacy Autoclave Log. (Tab 1). A CofA is provided by the manufacturer for each lot number of the BI. (Tab 2). Additionally, a positive and negative control for each BI lot number is processed by Hieber's Pharmacy and documented on Hieber's Pharmacy Biological Indicator Log (Autoclave). (Tab 3).

b) A printout is provided by the Tuttnauer autoclave for each autoclaved CSP batch cycle which documents the temperature-over-time values present within the autoclave sterilization chamber during the cycle. The printout is attached to each autoclaved CSP batch preparation formula log to document compliance with minimum times and temperatures required for sterilization. (Tab 4).

c) USP <797> includes an exception, which states, *"sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units."* All vial sterilization cycles are done in batches of 25 or less, thus Hieber's is not required to perform sterility tests for autoclaved vial CSPs.

Hieber's Pharmacy also complies with USP <797> standards for depyrogenating glassware used with CSPs. USP<797> states, "d*ry heat depyrogenation shall be used to render glassware or containers such as vials free from pyrogens as well as microbes. A typical cycle would be 30 minutes at 250°(C)".* USP <797> further states that, *"the effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (EVC). The bacterial endotoxin test should be performed to verify that the cycle is capable of achieving a 3-log reduction in endotoxin."*

a) The process for depyrogenating glassware is verified annually using an endotoxin depyrogenation kit, which simulates the maximum load volume for the convection oven. The EVC in the depyrogenation validation kit used by Hieber's Pharmacy is capable of showing a greater than 3-log reduction of *E.Coli* endotoxin during the validation cycle for depyrogenating glassware, as required by USP <797>. (Tabs 5A and 5B).

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[2] Geobacillus is the more modern nomenclature of Bacillus.

b) USP <797> does not require validation for pyrogen reduction in components used in compounding CSPs which are not capable of withstanding the heat required to depyrogenate using a dry heat cycle, such as vial stoppers.

c) Vial stoppers are only used in CSPs that are terminally sterilized with either steam heat (autoclaved) or dry heat (convection oven). Sterility of components for CSPs that are terminally sterilized is not required under USP <797>.

d) None of the endotoxin testing to date for finished CSPs at Hieber's Pharmacy has shown endotoxin values outside of allowable limits.

Additional Action by Hieber's Pharmacy: Hieber's Pharmacy SOP 2.280, Oven (Convection) will be updated to clarify the process of depyrogenating glassware and vials used in the compounding of CSPs. Employees involved with sterile compounding will be trained on the procedures, which training will be documented, and provided to FDA upon request.

Expected Date of Completion: November 1, 2014

Additional Action by Hieber's Pharmacy: Commencing November 1, 2014 each batch log for depyrogenated glassware or vials will include written documentation of the start time and temperature, and the end time and temperature, of the depyrogenation cycle to document that the correct time and temperature for depyrogenation has been reached for each cycle. Employees involved with sterile compounding will be retrained on the new procedure, which training will be documented, and provided to FDA upon request.

Expected Completion Date: November 1, 2014

Additional Action by Hieber's Pharmacy: Vials that are sterilized by Hieber's Pharmacy for subsequent use in CSPs will only be used for high risk CSPs. Staff involved with sterile compounding will be trained on the new procedures; master formula logs for low and medium risk CSPs will be revised to specify that only manufactured sterile vials (which include a CofA certifying sterility and endotoxin levels below allowable limits) are suitable for use in compounding or packaging low and medium risk CSPs. Employees involved with sterile compounding will be retrained on the new procedure, which training will be documented and provided to FDA upon request.

Expected Completion Date: November 1, 2014

Additional Action by Hieber's Pharmacy: Although to date Hieber's Pharmacy has not observed any CSP endotoxin testing results outside of allowable limits, and USP <797> does not address endotoxin limits for CSP components other than glassware and vials, Hieber's Pharmacy will create a log to document processing vial stoppers (with the intent of reducing possible endotoxins), which are not capable of withstanding the heat required to depyrogenate through the dry heat process. Employees involved with sterile compounding will be retrained on the new procedure, which training will be documented and provided to FDA upon request.

Expected Completion Date: November 1, 2014

Observation 1(3): *The filter sterilization for producing batches of injectable product has not been validated. The firm has no documentation to qualify the filters used with regard to bacterial retention, extractables and hardware compatibility. The firm has no documentation to challenge the bacterial retention of the filters with challenge organisms or bioburden quantity for formulations such as Cyanocobalamin. (with preservative) 2000 mcg/ml Inj lot # 08192014@16 and Doxycycline 20mcg/ml inj lot # 06272014@22.*

Response to Observation 1(3): Hieber's Pharmacy does not manufacture drug products, and thus is not required to comply with cGMP, which would require a manufacturer to validate filter sterilization for each preparation.

Hieber's Pharmacy instead complies with USP <797> standards for filter sterilization of CSPs. USP <797> states, "*the compounding supervisor shall ensure, directly or from appropriate documentation, that the filters are chemically and physically stable at the pressure and temperature conditions to be used, that they have enough capacity to filter the required volumes, and that they will achieve sterility and maintain prefiltration pharmaceutical quality, including strength of ingredients of the specific CSP*".

a) The type of filter required for sterilization is listed in the master formula log for each CSP sterilized by filtration. The filter chosen for sterilization is evaluated using appropriate literature (including, but not limited to, manufacturer information on filter properties and limitations compared to a preparations chemical qualities) to determine which type of filter is appropriate for use with that individual preparation. Additionally, a summary of filter properties and volume limitations is posted in the sterile compounding area. (See Tab 6A).

USP <797> also states that *"filter units used to sterilize CSPs shall also be subjected to manufacturer's recommended integrity test, such as the bubble point test."*

a) Only one filter is used to sterilize each batch of CSPs, and the integrity of that filter is tested using the bubble point test. If bubbles fail to appear prior to the PSI listed for each type of filter (as indicated by the manufacturer), then the filter has maintained its integrity throughout the sterilization process for that CSP batch. The paper filter backing and the results of the bubble point test are attached to the batch CSP formula log and the results of the bubble point test are documented on each printed CSP formula log. (See SOP 2.130; Bubble Point Filter Integrity Tester (Tab 6B)). Formula logs are available upon request.

USP <797> further states, *"filters shall be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of Brevundimonas (Pseudomonas) diminuta on square centimeter of membrane surface under conditions similar to those in which the CSPs will be sterilized".*

a) The filters that Hieber's Pharmacy uses for filter sterilization are tested by the manufacturer and comply with the USP <797> requirements. The manufacturer performs bacterial retention studies using *Brevundimonas diminuta* through a test which statistically

correlates to the *Brevundimonas diminuta* ASTM bacterial challenge test. With regard to bioburden quantity, test samples show no more than 50 microorganisms per unit prior to sterilization (Tab 7A and 7B).

Additional Action by Hieber's Pharmacy: Each master formula log for CSPs sterilized by filtration states the type of filter required to effectively sterilize the preparation, and that filtration must take place within the ISO 5 environment. However, Hieber's Pharmacy has recently edited SOP 4.30; Sterile Preparations, to clarify the basis for choosing the sterilization filters used for a CSP. All employees involved with sterile compounding will be trained on the new procedure, and that training documentation and revised SOP will be available upon request.

Expected Completion Date: November 1, 2014

Observation 2: *Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established. Specifically, there are no antimicrobial effectiveness testing data for injectable drug products containing preservatives.*

Response to Observation 2: Hieber's Pharmacy does not manufacture drug products, and thus is not required to comply with cGMP, pursuant to which it would be necessary to validate microbial effectiveness testing for each preparation, as in manufactured drug products.

Hieber's Pharmacy complies with USP <797>, which does not require testing CSPs for antimicrobial effectiveness testing. The only reference to antimicrobial effectiveness testing in USP <797> relates to manufactured multiple dose vials. USP <797> states, "*The beyond use date (BUD) for an opened or entered (e.g., needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days (see Antimicrobial Effectiveness Testing <51>), unless otherwise specified by the manufacturer.*" Although antimicrobial effectiveness testing is mentioned as a reference, there is no specific mandate to perform antimicrobial effectiveness testing for CSPs in USP <797>.

Observation 3: *Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements. Specifically, sterility and endotoxin testing are not performed for all lots of injectable drug product. Lot #07072014@18 was released without sterility and endotoxin testing.*

Response to Observation 3: Hieber's Pharmacy does not manufacture drug products, and thus is not required to comply with cGMP, which requires endotoxin and sterility testing for each lot of manufactured drug product.

Hieber's Pharmacy complies with the sterility and endotoxin testing standards set forth in USP <797>. The lot number specified in this Observation met all of the requirements under USP <797>; therefore, it would not have been tested for sterility or endotoxins prior to release.

Furthermore, under USP <797>, not every batch of CSPs must be tested for sterility. Sterility testing is required for, *"all high risk level CSPs that are prepared in groups of more than 25 identical individual single dose packages (e.g. ampuls, bags, syringes, vials) or in multiple*

dose vials for multiple patients or that are exposed longer than 12 hours at 2°(C) to 8°(C) and longer than 6 hours at warmer than 8°C before they are sterilized shall meet the sterility test (see Sterility Tests <71>) before they are dispensed or administered."

a) CSPs that meet the requirements listed above are tested for sterility either by an outside laboratory or by Hieber's Pharmacy according to USP <71>. (See SOP 4.30; Sterile Preparations, Tab 8). Sterility tests performed by Hieber's Pharmacy are documented on Hieber's Pharmacy In-house Sterility Testing Log. (See Tab 9). The CSP specified in this Observation was a batch consisting of twenty-five or less packages, so sterility testing would not have been required according to USP <797>.

b) Additionally, any risk level CSP (low, medium, high) that is assigned a beyond use date ("BUD") longer than a USP <797> recommended BUD based on chemical stability, is tested for sterility, unless the preparation is autoclaved (see "c", directly below).

c) USP <797> includes an exception, which states, *"sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units."* CSPs at Hieber's Pharmacy are prepared in small quantities as needed, or as small quantities of stock in anticipation of receiving a valid prescription from a prescriber for a patient (yet not regularly or in inordinate amounts). Furthermore, Hieber's Pharmacy does not manufacture large batch volumes of CSPs; it in fact manufactures no drug products. Typically, autoclaved CSPs are prepared in batches of twenty-five or less, but any autoclaved CSP batches that contain more than 25 containers are tested for sterility. The CSP specified in this Observation was a batch consisting of twenty-five or less packages, which was sterilized by autoclaving. (See Response to Observation 1(1) for USP <797>, addressing compliance for validating sterility for autoclaved CSPs).

Additional Actions by Hieber's Pharmacy: SOP 4.30, Sterile Preparations, has been revised; the total number of units (vials, syringes, etc.), and the volume per unit of the CSP batch, will be documented on each CSP preparation log to demonstrate that the requirements of USP <797> and USP <71> have been fulfilled. Employees involved in sterile compounding will be trained on the new procedure, and training documentation and the revised SOP will be available upon request.

Expected Completion Date: November 1, 2014

d) USP <797> states, *"when high-risk level CSPs are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSPs when there is any evidence of microbial growth in the test specimens."* The CSP specified in this Observation was exempt from sterility testing because it was autoclaved. Hieber's Pharmacy follows this requirement for CSPs when sterility testing is required. Incubator contents are checked daily and documented on Hieber's Pharmacy Sterile Compounding Area Cleaning Log. (Tab 10). SOP 4.30, Sterile Preparations (Tab 8) outlines the conditions under which CSPs may be released prior to obtaining sterility results under USP <797>. Recalls are carried out as per SOP 5.50, Recalls. (Tab 11).

Hieber's Pharmacy complies with USP <797>. USP <797> does not require endotoxin testing for every batch of CSPs. USP <797> states, "*all high risk level CSPs, except those for*

inhalation and ophthalmic administration, that are prepared in groups of more than 25 identical individual single dose packages (e.g., ampuls, bags, syringes, vials) or in multiple-dose vials (MDVs) for administration to multiple patients or that are exposed longer than 12 hours at 2°(C) to 8°(C) and longer than 6 hours at warmer than 8°(C) before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins."

a) The CSP cited by FDA in this Observation was a preservative-free preparation intended for single use only, and prepared in a batch of less than twenty-five. Under USP <797>, this preparation would have been excluded from endotoxin testing. Endotoxin testing is performed when necessary and according to USP <797> standards as outlined in SOP 4.30; Sterile Preparations. (Tab 8).

b) No endotoxin testing results to date have been outside allowable limits for endotoxins.

Observation 4: *An adequate number of batches of each drug product are not tested to determine an appropriate expiration date. Specifically, there is no data to support the beyond use dates assigned to compounded formulations.*

Response to Observation 4: Hieber's Pharmacy does not manufacture drug products, thus it is not required to comply with cGMP, for which it would be necessary to test each type of preparation to determine an appropriate expiration date, as would be required for manufactured drug products.

Hieber's Pharmacy follows USP <797> and USP <795> recommendations for assigning Beyond Use Dates ("BUD") to CSPs. BUDs are assigned to sterile preparations either according to USP <797> recommendations, or the BUD may be extended if there is evidence that the preparation will maintain chemical stability. Direct testing of each preparation to determine an expiration date is not required under USP <797> or USP <795>.

USP <797> states that BUDs may be *"assigned on the basis of direct testing OR extrapolation from reliable sources," and* that, *"BUDs for compounded preparations are usually assigned on the basis of professional experience, which should include careful interpretation of appropriate information sources for the same or similar formulation."*

USP <795> states that, "*when assigning a BUD, compounders shall consult and apply drug-specific and general stability documentation and literature when available.*" This section of USP <795> further states, *"the compounder shall refer to... the literature for applicable information on stability, compatibility, and degradation of ingredients, shall consider stability factors in <1191>, and shall use his or her compounding education and experience."* While it is recommended that assigning BUDs may be a result of direct testing for each formula preparation, USP does not specifically require the same.

a) Hieber's Pharmacy assigns BUDs for CSPs per USP <797> and USP <795> recommendations, as outlined in SOP 4.40; Beyond Use Dates. (See Tab 12).

b) Hieber's Pharmacy determined the 120-day BUD for chemical stability for the formula preparation cited in this Observation through information presented in a study, which used a stability indicating assay. (See Tab 13A). The Extra Pharmacopeia (28th Edition, Martendale) was also used, which describes the chemical properties and methods of sterilization for histamine, including autoclaving as a method of sterilization (See Tab 13B).

c) Hieber's Pharmacy does not assign BUDs to CSPs beyond six months, regardless of chemical stability, as per USP <795> (SOP 4.40; Beyond Use Dates (Tab 12)).

Observation 5: *Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release. Specifically, it was reported that only one batch annually representing each of the three (3) sterilization methods (Sterile Filtration, Autoclave and Dry Heat) is tested for potency. Lot # 041504@9 failed testing for potency. No additional batches of (the preparation) have been analyzed for potency to date.*

Response to Observation 5: Hieber's Pharmacy does not manufacture drug products, thus it is not required to comply with cGMP, which would require laboratory determination of satisfactory conformance to the identity and strength of each active ingredient for a CSP prior to release, as would be required for manufactured drug products.

Hieber's Pharmacy follows USP <795> guidelines for selecting components for CSPs. USP <795> states, "*Compounders shall first attempt to use components manufactured in an FDA registered facility. When components cannot be obtained from an FDA-registered facility, compounders shall use their professional judgment in selecting an acceptable and reliable source and shall establish purity and safety by reasonable means, which should include a Certificate of Analysis, manufacturer reputation, and reliability of source.*"

a) Hieber's Pharmacy uses active pharmaceutical ingredients ("APIs"), which include a CofA for each lot number. If no expiration date is assigned to the lot number, a 1-year expiration is assigned as per USP <797>. (SOP 3.10; Inventory Control (Tab 14)).

b) Hieber's Pharmacy reviews CofAs of APIs upon receipt at the Pharmacy for chemical purity assays and other factors (including, but not limited to, water content, microbial and endotoxins limits), which may affect the potency of the finished CSP. (SOP 3.10, Inventory Control (Tab 14)). Hieber's Pharmacy does not use bulk drug ingredients for which there is no CofA.

Hieber's Pharmacy follows USP <797> guidelines for finished preparation checks to be performed prior to releasing CSPs. USP <797> does not require that each batch of CSP be subjected to potency testing to determine satisfactory conformance to the identity and strength of each active ingredient prior to release.

USP <797> outlines several compounding accuracy checks that are followed for CSPs during preparation and immediately prior to release, which provide sufficient evidence that a CSP meets its declared potency. SOP 4.50, Finished Preparation Check (Tab 15), summarizes the compounding accuracy checks performed at Hieber's Pharmacy prior to the release of each CSP. The following are a list of checks designed to ascertain that the expected potency of a finished CSP is within the limits of labeled strength. Hieber's Pharmacy performs additional checks for potential contamination, sterility, and endotoxins, which are not listed here.

a) CSPs are not released until components, sources, and quantities have been confirmed.

b) CSPs are not released until calculations have been confirmed.

c) CSPs are not released until the CofA purity assay is confirmed for the active ingredients. CofAs are checked upon receipt in the facility.

d) CSPs are not released until expected pH is confirmed.

e) When possible, devices that indicate volumes used in compounding CSPs are verified. Syringes are kept with the preparation to confirm volumes used for CSP batches.

USP <795> requires potency testing for compounding technicians, but does not specify a schedule for testing. Neither USP <795> nor <797> require that CSPs be routinely tested for potency. Hieber's Pharmacy employs a potency testing schedule as a means of evaluating compounding technicians, not as part of a potency testing program for CSPs.

FDA is incorrect when it states that no additional batches of the preparation cited in the Observation have been analyzed for potency to date. The technician who compounded the sub-potent preparation submitted subsequent samples for the same strength of preparation. One batch of the preparation was compounded, and from that batch one sample was autoclaved and one sample was sterilized by filtration. Both samples were tested by an outside laboratory, and were within specification for the active ingredient. (Tab 16A and 16B).

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Hieber's Pharmacy and its employees take seriously their obligations to comply with laws concerning the compounding of sterile and non-sterile preparations. Safety of patients and the provision of high-quality preparations are of paramount concern to our Pharmacy. We look forward to continuing to compound high-quality and safe preparations, and working with FDA to ensure this goal.

Please let us know if you have further questions concerning this Response.

Best regards,