New England Compounding Center

Customized Pharmacy Services

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BY FACSIMILE/CONFIRMATION COPY BY MAIL

Ms. Daryl A. Dewoskin
Investigator
Food and Drug Administration
2224 Pawtucket Avenue, Suite 201
East Providence, Rhode Island 02914

Ms. Kristina M. Joyce, PharmD
Investigator
Food and Drug Administration
One Montvale Avenue
Stoneham, Massachusetts 02180

Re: Inspection of New England Compounding Center ("NECC")

Dear Ms. Dewoskin and Ms. Joyce:

This letter will constitute our initial written response to the FDA-483 delivered to NECC on February 10, 2003. As we showed you at our meeting, in order to resolve problems identified in the 483 and to ensure the integrity of our compounding of injectable drugs, we have taken a variety of corrective steps. For example, we have installed a new (b) (4) Class 10 glove-box environment, in which all critical steps in our sterile compounding will be performed, and have engaged the consulting services of (b) (4), an experienced and well-credentialed expert in the field of drug compounding. We have also enhanced several of our business practices, and drafted and implemented new written policies and procedures to strengthen our controls. These procedures are in the process of being further reviewed by Mr. (b) (4), who has inspected our facility. As part of this comprehensive corrective action program, we have worked to systematically improve our facility, and made many changes both before and after your inspection. We are committed to complying with applicable laws and regulations, to ensuring high-quality care for our patients, and to upgrading our compounding procedures.

While not mentioned in the FDA-483 Observations, we would also note that, in response to inquiries from the Commonwealth of Massachusetts Division of Professional Licensure, Department of Investigations, we have discontinued distributing order forms to physicians that have the names of any of our compounded drug products preprinted.

In addition to the general changes listed above, we have the following responses to the specific observations in the FDA-483. The numbering of our responses tracks the numbering in the FDA-483.

Observation 1. For the preparation of sterile drug products distributed by your firm (such as those intended for injection), there is no adequate documentation available to verify that they meet set standards (such as specifications and/or USP limits if applicable) at the time they are distributed or for the shelf life (expiration dating period) of these products. This includes the absence of documentation to verify the following:

Response: NECC has instituted Policies and Procedures (or Standard Operating Procedures, "SOPs") that ensure that drugs meet standards and the appropriateness of beyond-use dates of our products. We appreciate your recognition of the fact that the activities of NECC do not transform it from a compounding pharmacy into a drug manufacturer. Inasmuch as the degree of validation and verification required for compounding pharmacies is less stringent than those of the cGMPs (Current Good Manufacturing Practice regulations) applied to drug manufacturers, NECC is observing and applying relevant standards and guidelines of the United States Pharmacopeia and National Formulary, the Model Rules for Sterile Pharmaceuticals of the National Association of Boards of Pharmacy (the "Model Rules," see SOP 1.030), and any additional requirements of the Commonwealth of Massachusetts that govern the practice of pharmacy at NECC. We believe that the new SOPs, discussed in more detail below, address your concerns in light of those standards applicable to pharmacies.

Observation 1(A): Personnel performing preparation steps are not contaminating the finished products.

Response: Under the procedures now followed at NECC, the glove box environment is used for all sterile compounding, and any materials introduced into the glove box environment are carefully cleaned before entering the Class 10 environment. The glove-box environment is frequently cleaned, monitored and certified, as described below.

Specifically, SOPs now in effect at NECC permit only trained personnel in the aseptic compounding area (SOP 1.120(6.1)), require that compounding of injectables occur within the Class 10 [redacted] environment (SOP 7.140(6.3)), , , and require "contact plate testing of cleanroom personnel" at least [redacted] a [redacted] (SOP 4.010(6.1.4)). SOPs also spell out how aseptic technique should be conducted (SOP 5.080).

While not a requirement, NECC is developing and will shortly implement, with the assistance of Mr. [redacted], an aseptic process validation protocol similar to that recommended in USP monograph 1211 and similar to those set forth in FDA Compliance Policy Guides for aseptic processing. This protocol will demonstrate that the NECC process is controlled and aseptic, and results in sterile final compounded injectable medication.

Observation 1(B): Workspaces are cleaned and sanitized to prevent product contamination.

Response: The SOPs now in effect at NECC require that all workspaces be cleaned and sanitized to prevent product contamination, and logs of the cleaning to be recorded and maintained. Environmental monitoring and inspection and certification of the glove-box environment will ensure that workspaces are being adequately cleaned and maintained. The specific SOPs governing these procedures include 1.110(6.0), requiring the pharmacist-in-charge to ensure that the aseptic compounding area is kept clean at all times and that it is regularly cleaned in accordance with other SOPs; 7.110, which specifies [redacted] and [redacted] cleaning schedules for different areas; and 4.010, which requires that particulate matter levels in the cleanroom and the compounding hood be tested at least [redacted] a [redacted] (4.010(6.1.1) and

(6.1.2)), that compounding personnel perform environmental testing for microorganisms at least [redacted] a [redacted] (4.010(6.1.3)), and that all cleanroom surfaces be tested at least [redacted] (4.010(6.1.5)). Specific requirements for these tests are also set forth; SOP 4.030 – particulate testing in compounding hoods; SOP 4.040 – environmental testing of the cleanroom SOPs also address requirements for certification of the Class 10 glove-box environment. SOP 4.060 requires at least [redacted] testing for particulate matter in the antechamber, work chamber surface contamination testing at least [redacted] every [redacted], and [redacted] media testing and contact plate testing of personnel at least [redacted] a [redacted]. If environmental testing evidences pathogenic organisms in compounding areas, the area must be cleaned, and the test repeated until tests show the area to be free of pathogenic organisms (SOP 4.040(7.1)). Additionally, NECC will develop and implement protocols requiring periodic environmental monitoring for bioburden consistent with similar guidelines for compounding pharmacies contained in USP Monograph 1206, including the use of [redacted] settling plates, [redacted] surface contact plates, and "finger-dab" plates. These additional steps will further enhance control of the environment in which the aseptic process is included. With the assistance of Mr. [redacted], SOPs are being drafted at this time.

Observation 1(C): Equipment and supplies entering the product preparation area are decontaminated/cleaned to prevent product contamination.

Response: Materials entering the glove-box environment are thoroughly sanitized and cleaned in the Class 100 antechamber environment directly adjacent to the glove box environment. The materials are sprayed and cleansed with a solution of [redacted] (SOP 7.100(6.1)) and the [redacted] solution is allowed to evaporate before the items are introduced into the Class 10 environment. Specific SOPs governing these procedures include SOP 5.080 governing aseptic technique, and SOPs specifying in detail how equipment to be used in preparing injectable suspensions and solutions must be cleaned and utilized (SOPs 7.140, 7.150). The successful completion of aseptic process validation, including the monitoring of the environment for bioburden,

takes into account all aspects of the sterile compounding process including the effect of equipment and supplies. Additionally, NECC will periodically validate its cleaning products by swab testing of critical components and surfaces.

Observation 1(D): The environment in the area where the filling and closing operations are performed is adequate to prevent product contamination (this includes the lack of documentation pertaining to environmental monitoring in the immediate area while product is exposed to the environment, such as during filling and prior to container closure).

Response: The new glove box environment at NECC provides an environment that is adequate to prevent product contamination. As discussed above, SOPs require that the glove box environment be regularly cleaned, monitored, and certified. Relevant SOPs include: 1.030(6.1.1), incorporating the Model Rules requirement of a separate, entry-restricted sterile compounding area meeting certain specifications and the SOPs referenced in response to Observation 1(B). Additional measures to be implemented are discussed in responses to observations 1(B) and 1(C), above.

Observation 1(E): All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components (which includes vial stoppers and bulk product). Some examples are:

Response: The vials are sterilized off-site by a vendor. Vial stoppers are rinsed with sterile water to remove particulate matter and then autoclaved, under a detailed procedure set forth in SOP 7.140(6.3.2). A separate SOP will address validation of the procedure. In terms of the sterilization of preparation equipment and components at the facility, SOPs now require that the autoclave be cleaned, maintained, and tested. More specific responses follow.

Observation 1(E)(a): Lack of documentation to verify that all critical processing parameters and procedures being used are appropriate in ensuring that final products meet all standards (such as

sterility); this includes, sterilization time, temperature, size and nature of load, and chamber loading configuration.

Response: SOPs now in effect at NECC require validation of the efficiency of the autoclave (SOP 3.060). Details are provided below. Additionally, each bulk lot of a sterile end product must be tested for sterility and endotoxins by an independent laboratory (SOPs 5.040(4.1), 5.050(4.1)), and injectable or intrathecal formulations compounded for an individual patient are tested periodically for endotoxin and sterility as directed by the Pharmacy Director (SOPs 5.040(4.1), 5.050(4.1)). Bulk products must be quarantined until sterility and endotoxin test results are received (SOP 5.040(6.1) 5.050(6.1)).

Observation (1)(E)(b): Records do not state the actual critical parameters used during processing

Response: As discussed elsewhere, SOPs in place at NECC describe how vessels and equipment that come into physical contact with drug solutions during the aseptic process are cleaned and handled, and how end products will be tested for sterility, endotoxins, and particulate matter. Formulation log sheets already include the lot number and expiration dates of active ingredients, which will enable NECC to trace which lots of compounded product used specific lots of active ingredients, in the event that becomes necessary. An SOP requires the calibration of weighing balances, and the printout of the balance for weights of all ingredients of compounded products will be attached to the Formulation Log Sheets. Formulation Log Sheets will be amended to reflect examinations of end product for closure integrity, color, clarity, and presence of visible foreign particulates. Formulation Log Sheets will also be revised to include expected yield and generated yield for each compounded product. Formulation Log Sheets will also be amended to include documentation of calibration of the [redacted] for each compounding procedure.

Observation (1)(E)(c): Lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function.

Response: The SOPs now in effect at NECC require that the autoclave be cleaned, maintained and tested. Specifically, SOP 3.060 requires that, at least (b) (4), an autoclave challenge kit be used to test the efficiency of the autoclave, and the results recorded and maintained (SOP 3.080(6.0)). The SOPs also require that the autoclave load be minimized to "expose more surface area on the items being sterilized" (SOP 3.080(7.0)).

Observation 1(E)(d): The autoclave process used on bulk drug products does not have an effect on stability or product specifications.

Response: As noted in correspondence to Susan Liner of FDA on February 21, 2003, NECC has determined that, with regard to one product, the autoclave process apparently did have an effect on stability or product specifications. NECC has instituted an SOP that will ensure that the potency of finished product is not affected by the autoclaving process. SOP 5.090(2.1) specifically requires that moist heat (of an autoclave) shall not be used to sterilize a product unless "referenced material" demonstrates "the stability of the product when exposed to the sterilization parameters."

Observation 1(F): The transfer of bulk drug product and equipment from the autoclave (after it went through an autoclave process) from one room to another room in which further preparation steps are performed in a laminar air flow workbench, is not introducing contamination into the finished product.

Response: The autoclave has been moved to the same room where the glove box environment is located. This will permit all autoclaved materials to be immediately introduced into the Class 100 antechamber environment adjacent to the Class 10 glove box environment. The packaging for all materials introduced into the antechamber environment adjacent to the Class 10 environment will be carefully cleaned and sanitized as discussed above. Because the transfer of equipment and materials is part of the aseptic process, the risk of contamination will be assessed in the aseptic process validation discussed in responses to observations 1(B) and 1(C), above.

Observation 1(G): All components, including drug substances, vials, and rubber stoppers, meet set standards making them suitable for their intended use. This includes that components and process water are not contaminating finished products.

Response: Most drug substances, including all solutions, are passed through a (b) (4) micron filter (SOP 7.190). Use of a (b) (4) micron filter to sterilize solutions is a well-recognized method of sterilization. For example, this method is discussed in the Pharmacopeia of the United States 26th Revision, Chapter 1211 at 2436-37. Drug substances that are not filtered are autoclaved, and an SOP describes the details of the autoclave procedure (SOP 5.090). Vials are sterilized by an independent facility that ships the materials to NECC in autoclave bags that protect the integrity of the components until they are opened in the glove-box environment. Stoppers are autoclaved as discussed above. Other drug components, such as "process water," are supplied by FDA-registered drug manufacturers, and are required to meet USP standards of sterilization.

Observation 1(H): Equipment used to measure the amount of ingredients/components are calibrated and maintained to perform their intended function.

Response: SOPs now in effect at NECC require the calibration and maintenance of all measuring equipment. No less than (b) (4), an internal calibration of all balances is performed (SOP 3.060(6.1), and the balances are also inspected and certified by the Town of Framingham, Dept. of Weights and Measures (SOP 3.060(6.3).

Observation 1(I): Testing procedures and sampling procedures being performed for all drug products are representative of the lots/batches being tested.

Response: Ensuring product uniformity is a requirement of CGMPs, not applicable to compounding pharmacies. The very nature of compounding, requiring smaller batches of drugs to be prepared, does not present the same sort of issues as to product uniformity as drug manufacturing, nor does it render it feasible to sample, for example,

the beginning, middle, and end of a drug's production, as is the case with drug manufacturing.

Observation 1(J): That for each preparation of sterile product or batch of sterile products there has been appropriate laboratory determination of conformity with purity, strength, sterility, and non-pyrogenicity, in accordance with established written specifications and polices.

Response: NECC has added new SOPs and revised prior SOPs to address these issues. SOPs at NECC require that, if bulk compounding is performed using nonsterile chemicals, end product testing, must be documented prior to the release of the product from quarantine" including testing for pyrogens and particulate matter. (SOP 1.050(6.1)). Visual inspection is required of all sterile preparations to ensure that there is no "inappropriate particulate matter or signs of deterioration" (SOPs 1.070(6.1.1), 5.030(6.2), 7.120(6.1.4)). SOPs also require that "appropriate samples are collected and microbial tests are completed" to ensure that products are sterile. SOP 1.070 (6.1.3). Additionally, each bulk lot of a sterile end product must be tested for sterility, endotoxins, and fungal growth by an independent laboratory (SOPs 5.040(4.1), 5.050(4.1), 5.070(4.1)). SOPs also require potency testing of parenteral products according to a schedule determined by the Pharmacy Director to be appropriate (SOP 5.06.(4.1). Potency testing of every compounded prescription is neither practical nor meaningful in the pharmacy setting. NECC, with the assistance of Mr. [redacted], is developing and will implement a protocol that validates the potency of like compounds when they are subjected to the same compounding processes.

Observation 1(K): Preparation steps are being performed in a correct manner since batch record preparation instructions are lacking significant preparation steps, which includes mixing procedures.

Response: Preparation instructions for compounding products are now being revised, and SOPs require that a "Logged Formula Worksheet" be completed for each compounded product. SOP 6.020. The instructions on each logged formula worksheet include a variety of

topics, including mixing procedures, measuring requirements, and product quality checks.

Observation 1(L): Final containers are capable of maintaining product integrity (i.e., identity, strength, quality, and purity) throughout the shelf life of the product.

Response: The requirement of a stability program, and validation of containers and closures to ensure that product integrity will be maintained, is a requirement of CGMPs not applicable to compounding pharmacies. However, NECC has shortened some products' beyond-use dates, and has instituted an SOP addressing setting of beyond-use dates, as set forth below.

Observation 1(M): All drug products prepared and packaged at your site meet specifications and USP limits (if applicable) for the expiration dating period assigned. According to documentation and your statements, all drug products are assigned an expiration date of 60 days if they do not contain a preservative, three months if they are not filtered, and 6 months if they are filtered. No data was available for any of your products prepared at your firm to support these expiration date periods.

Response: Stability programs are required under the cGMPs applicable to drug manufacturers, and are not required for compounding pharmacies. Nonetheless, NECC has implemented an SOP relating to determination of "beyond use" dates. The "beyond use" dates are now determined according to Chapter 795 of the United States Pharmacopeia (SOP). SOPs 1.060(6.0) and 6.030(6.0) provide that, if written justification is not available supporting different expiration dates, the "product must be adopted according to USP Guidelines." SOPs also specify documentation that can justify longer beyond-use dates. (SOP 6.030(6.3)).

Observation 2: There are not written procedures pertaining to the handling of complaints, nor does your firm maintain a complaint file.

Response: NECC has implemented an SOP requiring that "any untoward effects exhibited by a patient that may be due to the product" reported to NECC are investigated (SOP 1.070 (6.1.2)). Where there is any sign of contamination of a tested sample of a lot, an immediate investigation of the lot will be conducted, and appropriate remedial action taken (SOP 5.040(7.1)). Where a complaint is received about any problem relating to a drug dispensed by NECC, an incident report must be created, an investigation conducted and documented, and remedial action taken, where appropriate (SOP 6.060(6.0).

Observation 3: There was no documentation available for the handling and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported. For example, after a medical facility reported adverse events associated with lot 05312002@16, your firm conducted a recall of injectable steroid products and implemented shorter expiration dates and use of pre-sterilized vials. You stated you have no documentation available pertaining to an investigation being performed for this and other related lots which shows that adequate follow-up action was taken.

Response: NECC has investigated the reported incident, and determined that the two patients who experienced problems were injected intrathecally with the drug, which is not an approved method of dosing patients with this drug. Moreover, NECC has taken further steps to ensure that injectable drug products it distributes are not contaminated, and are sterile. Future complaints will be thoroughly investigated, as discussed in response to Observation 2, and the investigation will be documented. Where there is any sign of contamination of a tested sample of a lot, an investigation of the lot will be conducted, and appropriate remedial action taken. (SOP 5.040(7.1)). These steps also will be documented.

We hope that this information is satisfactory. We look forward to working with the agency to resolve any remaining issues. As indicated in several places in this letter, NECC is engaged in further steps designed to control its compounding processes. We will update you on our progress, as appropriate.

In the meantime, if you have further questions or would like further information, please do not hesitate to contact me.

Sincerely,

New England Compounding Center, Inc.
Barry Cadden, R.Ph., Manager

cc: Leslie Doyle, R.Ph.
(b) (4) [redacted]