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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

NEW ENGLAND DISTRICT

MEMORANDUM

Date February 24, 2003

From [redacted] Consumer Safety Officer, NWE-DO / FDA
[redacted] Compliance Officer, NWE–DO / FDA

Subject February 5, 2003 Meeting with Massachusetts Board of Pharmacy / Division of Professional Licensure (239 Causeway Street, Boston, MA 02114).

To Central File

Firm: New England Compounding Center
697 Waverly Street
Framingham, MA
FEI: 3003 623 877

Background

This meeting was arranged at the request of [redacted], NWE–DO Compliance Officer, via email to Charles Young, Executive Director, on January 30, 2003. The meeting was held to review the inspectional history of the New England Compounding Center and develop a joint strategy for achieving safe compounding practices at the firm.

In attendance at the meeting were:

Representing the New England District—

Gail Costello, District Director
David Elder, Compliance Branch Director
[redacted], Compliance Officer
[redacted], Supervisory Consumer Safety Officer
[redacted], Consumer Safety Officer

Representing the Office of Compliance, CDER (via teleconference)—

[redacted], OC / DNDLC
Kathleen Anderson, OC / DNDLC
[redacted], ORO / DFSR

Representing the Commonwealth of Massachusetts—

Jean Pontikas, Director, Division of Professional Licensure
Charles Young, Executive Director, Board of Pharmacy
James Coffey, Associate Director, Board of Pharmacy
[redacted], Supervisory Investigator, Board of Pharmacy
[redacted], Investigator, Board of Pharmacy
Susan Manning, Legal Counsel, Board of Pharmacy

Note: This memorandum has been prepared in accordance with Staff Manual Guide FDA 2126.2

Summary of Meeting

Mr. Young and [redacted] facilitated introductions.

[redacted] began with an overview of the inspectional history of New England Compounding Center (NECC). This included a brief description of the recent regulatory history of Pharmacy Compounding.[1]

[redacted] then presented a table summarizing the results of FDA's current sample analyses.[2] [redacted] discussed current investigational findings.[3] It was stated that the FDA's next step would be to notify the firm of the violative sample results and inquire of his intentions regarding the violative product still in commerce. It was anticipated that the firm would initiate a voluntarily recall of the violative product.[4] If NECC does not take action regarding the violative lot, then depending on the quantities of the lot available FDA may initiate a seizure of the product. A Form FDA–483 (List of Inspectional Observations) will be issued to NECC with state representatives present at the FDA closeout meeting with NECC. [redacted] and Kathleen Anderson reminded everyone that in a similar situation with a South Carolina compounding pharmacy, FDA issued a press release when the firm failed to take recall action in a timely manner.

A discussion was held to decide if NECC should be considered a manufacturer or a compounder. It was decided that current findings supported a compounding role. The FDA discussed their ability to take action (through seizure) against the adulterated lot of Betamethasone that is still within expiry. The issues of NECC's poor compounding practices would not necessarily be ultimately resolved by such an action. It was decided that the state would be in a better position to gain compliance or take regulatory action against NECC as necessary. The state favored recall of the violative product

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1 See Attachment 1.
2 See Attachment 2.
3 See Form FDA–483 (Inspectional Observations), Attachment 3.
4 The firm has committed to recall this product.

within expiry. The state does not have the authority to subpoena records without cause or to embargo product, but agencies within their umbrella may be able to provide assistance in those matters. The state would ask Mr. Cadden, owner of NECC, to appear before the Board of Pharmacy to answer to the current complaints.

[redacted] stated that NECC is licensed as a pharmacy provider in the following states—South Carolina, Florida, Virginia, Missouri, Maine, Rhode Island, New Hampshire, Nebraska, Idaho, and Montana. NECC is pursuing licensure in Connectuct, Ohio, Vermont, and Kansas.

Susan Manning stated Massachusetts pharmacy law states that pharmacists must act in accordance with USP recommendations. She stated this alone would imply he could be held to those standards by the state. She requested of the FDA a list of the current inspectional observations and where NECC differs from acceptable practice per USP standards. It was decided that Ms. Anderson would work on documenting the deviations from USP standards for the state. Ms. Manning stated although the state's authority does not include the ability to fine pharmacists, the state is able to take actions against a pharmacy's license, including revocation and suspension.

The state's pharmacy compounding regulations that are under review are a blend of USP standards and regulations from three other states that already have such regulations in place (including Georgia and South Carolina).

The state requested the following information[5] from the FDA:

- Examples of previous Consent Agreements
- MedWatch reports regarding Adverse Events from products compounded by NECC.
- A list of NECC deviations from acceptable practice (referring to FDA's inspectional findings)
- Previous and current FDA 483 (List of Observations) issued to NECC, with available documentation to support the findings.
- Copies of FDA EIRs for NECC (April 2002 and current inspection when available)
- Analytical Worksheets for sample collection and analysis.
- Copy of regulatory action taken by the FDA against Professional Compounding Centers of America (PCCA).

Summary

Mr. Elder concluded the meeting by summarizing the discussions and emphasizing the potential for serious public health consequences if NECC's compounding practices, in particular those relating to sterile products, are not improved. The point was made that, so long as a pharmacy's operations fall within the scope of the practice of pharmacy (as

[5] This information was forwarded to the Board of Pharmacy (to the attention of Ms. Manning) via Federal Express on February 11, 2003.

outlined in FDA's Compliance Policy Guide 460.200), FDA will generally continue to defer to state authorities for regulatory oversight. In such cases FDA will seek to engage cooperative efforts aimed at achieving regulatory compliance and ensuring the safety and quality of compounded products.

[redacted]

Consumer Safety Officer
New England District, FDA

[redacted]

Compliance Officer
New England District, FDA

Attachments (3)

bcc:

[redacted]

Central File
Reading File
Legal Reading File

[redacted](HFD–310)
Anderson (HFD–310)

U:[redacted] Inspections / NECC / Meeting with State / Memorandum of Meeting.doc

ATTACHMENT 1

INSPECTIONAL HISTORY OF NEW ENGLAND COMPOUNDING CENTER (NECC)

Presentation to Board of Registration in Pharmacy, Division of Health Professions Licensure, Department of Public Health, Commonwealth of Massachusetts

February 5, 2003

April 2002

- New England District receives inspection assignment from CDER / Office of Compliance / DPDSC. Two MedWatch reports implicated product compounded at NECC in adverse events (dizziness, shortness of breath, diaphoresis, drop in blood pressure to 55/44).
- Product in question is Betamethasone Repository 6 mg/ml (Betamethasone Acetate 3mg/ml / Betamethasone Sodium Phosphate 3 mg/ml USP), available commercially as Celestone Soluspan.

April 2002

- This is the same formulation that was involved in 13 hospitalizations (including 5 cases of meningitis, 3 of which were fatal) and was compounded at Doc's Pharmacy in Walnut Creek, CA.
  - As a result of this incident the Atty General of California brought a formal accusation (on behalf of the Exec. Officer of the Board of Pharmacy) before a judge.

April 2002

- FDA team, along with Leslie Doyle of BRP conducted an inspection of NECC.
- FDA issues list of observations (Form 483).
- BRP pursues independent follow-up

July 2002 (and ongoing)

- Second inspection assignment is received from CDER as a result of 2 additional MedWatch reports associated with ***another*** product from NECC, in this case Methylprednisolone Acetate Suspension (Injectable, Preservative Free), 80 mg/ml.

- Both patients were hospitalized (pain, headache) and recovered. Units from suspect lot were collected from a (b) (6), (b) (7)(C) hospital.

July 2002 (and ongoing)

- Assistance of BRP requested as before.
- Section 503A of FDCA has since been invalidated by U.S. Supreme Court
- Inspection is initiated in August. Multiple samples are collected.

July 2002 (and ongoing)

- ***Urgent Care, Spartanburg, SC.***
  - On September 16, 2002 there is a recall of Methylprednisolone Acetate Injection compounded by this pharmacy as a result of fungal meningitis (4 patients contract this infection, 1 dies).
  - Nationwide alert issued by FDA on November 15, 2002 for all injectable products produced by Urgent Care.
  - Cease and desist order is issued by SC Board of Pharmacy.

July 2002 (and ongoing)

- ***Urgent Care, Spartanburg, SC.***
  - MMWR (CDC, December 13, 2002) publishes assessement of this incident (*Exophiala* Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy — United States, July–November 2002).

January 2003

- Samples with significant findings
  - 193610 *Burkholderia cepacia* and *Sphingomonas paucimobilis* (Methylprednisolone Acetate Injection)
  - 169127 Subpotency (Betamethasone Repository) Expired on Jan 29, 2003
  - 169129 Subpotency (Betamethasone Repository) **Expires on June 8,2003.** ***This product is adulterated under Sec. 501(b) of FDCA.***
  - 169128 Superpotency (Methylprednisolone Acetate Injection) Expired on Jan 10, 2003

Existing Concerns

- Analytical evidence demonstrates inability of NECC to reliably compound suspensions with dose uniformity.

- Sterilization techniques and aseptic practices continue to raise questions, despite no positive (nonsterile) results from latest samples. Absence of evidence is not evidence of absence.

ATTACHMENT 2

SUMMARY OF SAMPLE COLLECTION/ANALYSIS FOR NECC
FEBRUARY 5, 2003

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
169126	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	20	1/25/03	Assay= Within Range
169127	Betamethasone Repository (PF) 6mg/ml x 5ml (BSP+BA)	11302002@1	10	1/29/03	Assay= Subpotent BSP 77.4 (O); 74.6 (C/A) BA 71.6 (O); 71.0 (C/A)
169128	Methylprednisolone AC (PF) 40 mg/ml x 1 ml	11262002@5	50	1/10/03	Sterility= Negative Endotoxin- "not performed" Assay= Superpotent 131.4 (O) & 133.1% (C/A)
169129	**Betamethasone Repository 6mg/ml x 2 ml**	**12102002@11**	**50**	**6/8/03**	**Sterility= Negative** **Endotoxin= Negative** **Assay- subpotent** **BSP 67.0 (O); 62.0 (C/A)** **BA 59.8 (O); 58.7 (C/A)**
169130	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	50	1/25/03	Sterility= Negative Endotoxin= Negative
169131	Triamcinolone Acetonide 40 mg/ml x 5 ml	112020002@8	34	2/18/03	Sterility= Negative Endotoxin "not performed"
169132	Prochlorperazine Edisylate 5 mg/ml x 10 ml	11112002@11	18	2/9/03	Sterility= Negative Endotoxin "not performed"
169133	Saline PF 10% injectable x 15 ml	12122002@14	5	3/12/03	Sterility= Negative Endotoxin= "not performed"
208553	Betamethasone Repository (PF) 6mg/ml x 2ml	11302002@1	50	1/29/03	Sterility= Negative Endotoxin= "not performed"
	Sterile Vials				
	Vial stoppers				

1. PF= Preservative Free (for some products, NECC makes product both with and without preservative)
2. Betamethasone Repository= Betamethasone Sodium Phosphate & Betamethasone Acetate.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
193610 (9/13/02)	Methylpredisolone AC (PF) 80MG/ML INJ		16		1/14= *Sphingomonas paucimonas* 4/14= *Burkholderia cepacia*

SUMMARY OF FDA INSPECTIONAL OBSERVATIONS FOR NECC
FEBRUARY 5, 2003

ASSAY ISSUES

1) No documentation to verify sterile drug products meet set standards, such as:
    a. No specifications (ie. USP or other) are set for finished products
    b. No evidence products meet assigned shelf life.

2) Preparation: No documentation of the following:
    a. Equipment used to measure components are calibrated and maintained to perform their intended function
    b. Preparation steps are being performed in a correct manner since batch record preparation instruction sare lacking significant preparation steps, including mixing and transfilling procedures.
    c. All components (drug substances, water, vials, rubber stoppers) meet set standards making them suitable for their intended use and don't contaminate the finished product.
    d. Testing and sampling procedures performed for finished drug products are representative of the lots/batches being tested.

3) Testing/Sampling: No documentation of the following
    a. No testing is done to confirm product meets specifications. (the only finished product testing for selected lots is sterility and endotoxin).
    b. Testing and sampling procedures performed for finished drug products are representative of the lots/batches being tested.

STERILITY ISSUES

1) Lack of assurance/documentation:
    a. Equipment, supplies and workspaces are sufficiently cleaned to prevent contamination of finished product.
    b. No Environmental Monitoring of Clean Room.
    c. All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components.
    d. Transfer of bulk drug product and equipment from the autoclave (from one room thru ante-room to "clean room") for further processing doesn't contaminate product.
    e. Transfilling procedures are being performed in a correct manner since batch record preparation instructions lack transfilling instructions.

ATTACHMENT 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue, 4th Floor Stoneham, MA 02180 [redacted]	10/24, 12/12&18/02, 1/14-15/03, 2/10/03
	FEI NUMBER 3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

To: Barry J. Cadden, Director of Pharmacy

FIRM NAME	STREET ADDRESS
New England Compounding Center	697 Waverly Street
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Framingham, MA 01702	Pharmacy

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

The below observations pertain to drug products that personnel prepare at your firm for which you claim are sterile (for example, injections) and are prepared in anticipation of a prescription.

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 they meet set standards (such as specifications and/or USP limits if applicable) or the shelf life (expiration dating period) of these products. This includes the absence of documentation to verify the following:
   A. Personnel performing preparation steps are not contaminating the finished products.
   B. Workspaces are cleaned and sanitized to prevent product contamination.
   C. Equipment and supplies entering the product preparation area are decontaminated/cleaned to prevent product contamination.
   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).
   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:
      a. Lack of documentation to verify that all critical processing parameters being used are appropriate in ensuring that final products meet all standards (such as sterility). Critical processing parameters include sterilization time, temperature, size and nature of load, and chamber loading configuration.
      b. Records do not state the actual critical parameters used during processing.
      c. Lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function.
      d. The autoclave process used on bulk drug products does not have an effect on stability or product specifications.

   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. All components, including drug substances, vials, and rubber stoppers, meet set standards making them suitable for their intended use.
   G. Components and process water are not contaminating finished products.
   H. Equipment used to measure the amount of ingredients/components are calibrated and maintained to perform their intended function.
   I. Testing procedures and sampling procedures being performed for all drug products are representative of the lots/ batches being tested.
   J. That for each preparation of a sterile product or batch of sterile products there has been appropriate laboratory

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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One Montvale Avenue, 4th Floor Stoneham, MA 02180 [redacted]	10/24, 12/12&18/02, 1/14-15/03, 2/10/03
	FEI NUMBER 3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Barry J. Cadden, Director of Pharmacy

FIRM NAME	STREET ADDRESS
New England Compounding Center	697 Waverly Street
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Framingham, MA 01702	Pharmacy

determination of conformity with purity, accuracy, sterility, and non-pyrogenicity, in accordance with established written specifications and policies.

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

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

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.

In addition, for all of the items above there were no written procedures available pertaining to the performance of these duties and processes.

2. There are no written procedures pertaining to the handling of complaints, nor does your firm maintain a complaint file.

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.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED

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