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 I 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 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:

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 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.

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.

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.

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 determination of conformity with purity, strength, 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

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[redacted]		2/10/03 2/10/03

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

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
	[redacted]		2/10/03 2/10/03

New England Compounding Center EF
Framingham MA 01702
EI: 10/24/02-2/10/03 KMJ/DAD
Attachment# II Page 2

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

Footnotes
72 – 73, 82

Food and Drug Administration Establishment Inspection Report

Date Assigned: 12/17/2002 **Inspection Start Date:** 10/24/2002 **Inspection End Date:** 02/10/2003

Firm Name & Address: New England Compounding Center , 697 Waverly Street Framingham, MA 01720 US

Firm Mailing Address:

FEI: 3003623877 **JD/TA:** 13 **County:** MIDDLESEX **Est Size:** 0 - 24,999

Phone: [redacted] **District:** NWE-DO **Profiled:** No

Conveyance Type: **% Interstate:** **Inspectional Responsibility:**

Endorsement

SUMMARY: This inspection covered the firm's compounding processes for sterile injectable steroid products which included the following: methylprednisolone acetate and betamethasone repository (betamethasone sodium phosphate and betamethasone acetate). The MABP accompanied us during most of the inspection at the request of HFM-330.
The current inspection involved sampling of NECC products from within the New York and New England District areas. Sample results revealed that the firm has sterility and potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP).

On 2/10/03, at the close of this inspection, an FDA-483, Inspectional Observations, was issued to Barry Cadden, R.Ph. The FDA 483 Observations pertained to the following: 1) inadequate documentation to verify sterile drug products distributed meet set standards (such as specifications and/or USP limits if applicable) or the assigned shelf life, 2) failure to maintain complaint files, including written procedures pertaining to the handling of complaints, and 3) lack of documentation for the reported adverse events associated with lot 05312002@16 of methylprednisolone acetate which includes handling and disposition of reports of patient problems, complaints, adverse drug reactions, and drug product or device defects.

(SEE CONTINUATION SHEET for Reason for Inspection, History, and Voluntary Corrections)

CLASSIFICATION: OAI; referral to Massachusetts State Board of Pharmacy. Recommend firm be prohibited from manufacturing until they can demonstrate ability to make product reproducibly and dependably. If state is unwilling to take action, recommend firm be enjoined for GMP deficiencies.

DISTRIBUTION:
Orig: CF
C/S &EIR: FMD-145, MA Bd Pharm thru Compl Br for FOI clearance
C/S &483: WSB, Souza
CC (C/S, EIR, 483, EXH & ATTCH): MCL, HFM-330 (Kathy Anderson)

Endorsement Location: NWE-DO CF

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
[redacted]	03/07/2003 06:49 AM ET	[redacted]	03/07/2003 05:36 PM ET
	03/07/2003 06:49 AM ET		03/07/2003 05:30 PM ET
	03/06/2003 01:08 PM ET		ET
	03/06/2003 12:46 PM ET		ET
	03/06/2003 08:46 AM ET		ET
	03/05/2003 02:50 PM ET		ET

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877 **Inspection Start Date:** 10/24/2002 **Inspection End Date:** 02/10/2003

Firm Name & Address: New England Compounding Center , 697 Waverly Street Framingham, MA 01720 US

Related Firm FEI: **Name & Address of Related Firm:**

Registration Type

There are no Registration Types

Registration Dates

Establishment Type

M	Manufacturer
M	Manufacturer

Industry Code

60	Human and Animal Drugs
64	Human and Animal Drugs

District Use Code:

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877 **Inspection Start Date:** 10/24/2002 **Inspection End Date:** 02/10/2003

Firm Name & Address: New England Compounding Center , 697 Waverly Street Framingham, MA 01720 US

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56D015	Manufacturer	64 L C K			Surveillance	Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	03/07/2003	Referred to State (RTS)	[redacted]	NWE-DRUGS

Remarks:

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002	Manufacturer	64 L C K			Surveillance	Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	03/07/2003	Referred to State (RTS)	[redacted]	NWE-DRUGS

Remarks:

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877 **Inspection Start Date:** 10/24/2002 **Inspection End Date:** 02/10/2003

Firm Name & Address: New England Compounding Center , 697 Waverly Street Framingham, MA 01720 US

Products Covered

Product Code	Est Type	Description	Additional Product Description
64 L C K 07	Manufacturer	Betamethasone Sodium Phosphate (Glucocorticoid); Human - Rx/Single Ingredient; Sterile Liquid	in amber vial
64 L C K 45	Manufacturer	Methylprednisolone Acetate (Glucocorticoid); Human - Rx/Single Ingredient; Sterile Liquid	in amber vial

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
[redacted]	INV	NWE-DO	56D015	Manufacturer	64 L C K	200
	INV	NWE-DO	56D015	Manufacturer	64 L C K	35
	INV	NWE-DO	56002	Manufacturer	64 L C K	20
	INV	NWE-DO	56002	Manufacturer	64 L C K	15
					Total Hours:	270

Inspection Result

EIR Location
NWE-DO CF

Trips Num

Inspection Summary
REASON FOR INSPECTION: The investigation of New England Compounding Center (NECC) was conducted in response to an assignment (dated 8/2/02) received from HFM-330, Office of Compliance, Division of Prescription Drug Compliance and Surveillance, Center for Drug Evaluation and Research. The investigation was done in accordance with HFM-330 assignment/guidance and CPG 460.200 (Pharmacy Compounding). A limited inspection was performed which included covering aseptic processing procedures used at NECC. Sections of the current USP were used as a reference.
FACTS #332851.

The initial assignment requested an investigation to obtain information regarding three MedWatch reports associated with the use of methylprednisolone acetate preservative free 80mg/ml that was compounded by NECC in May of 2002. Per supervisory request, this assignment was changed to conduct an inspection during December 2002. The HFM-330 assignment requested answers to the following questions: 1) have any other patients experienced adverse events from the compounded product and 2) has the pharmacy conducted follow up to determine whether there is a problem with the compounded product.

HISTORY: The last FDA inspection of NECC was in April 2002. The inspection was classified VAI and a FDA-483 (List of Observations) was issued to Mr. Cadden citing sterility issues and lack of lot accountability. The practices that were cited on the previous FDA 483 were not in place and therefore the correction of these items was not an issue.

VOLUNTARY CORRECTIONS: n/a

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals:

Samples Collected

Sample Number
167876
167877
169126
169127
169128
169129
169130
169131
169132
169133
208553

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?: Y **483 Location:** NWE-DO CF

Response Type	Response Mode	Response Date	Response Summary
Further review needed	Letter	02/26/2003	Response outlined corrective actions; referred to MA State Bd of Pharmacy.

Footnotes
49 – 65, 83

New England Compounding Center
697 Waverly Street
Framingham, MA 01702

FACTS #332851
KMJ/DAD

FEI# 3003623877
EI Start: 10/24/02
EI End: 2/10/03

SUMMARY

The investigation of New England Compounding Center (NECC) was conducted in response to an assignment (dated 8/2/02) received from HFM-330, Office of Compliance, Division of Prescription Drug Compliance and Surveillance, Center for Drug Evaluation and Research. The investigation was done in accordance with HFM-330 assignment/guidance and CPG 460.200 (Pharmacy Compounding). A limited inspection was performed which included covering aseptic processing procedures used at NECC. Sections of the current USP were used as a reference.

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On 10/24/02, Investigator [redacted] showed credentials, and issued an FDA 482, Notice of Inspection (including the attachment Resources for FDA Regulated Businesses), to Barry J. Cadden, Owner and Director of Pharmacy. On 10/24/02 Inv. [redacted] was accompanied by [redacted] of the Massachusetts Board of Pharmacy (MABP). On 12/12/02 FDA Credentials were shown, and a second FDA 482 was issued to Mr. Cadden by Investigators [redacted]. On 12/12/02 Inv. [redacted] were accompanied by [redacted] Investigator, and [redacted] Quality Assurance Surveyor, from the MABP. On 12/18/02 Investigators [redacted] returned to the firm accompanied by [redacted] On 1/14/03 Inv. [redacted] showed credentials, and issued an FDA 482 to Mr. Cadden for the purpose of sample collection. On 1/15/03 Inv. [redacted] showed credentials, and issued another FDA 482 to [redacted] Educational Coordinator, for the purpose of picking up a sample of vial caps. On 2/10/03 Inv. [redacted] showed credentials, and they issued another FDA 482, since they had not been at the firm for about three weeks.

This inspection covered the firm's compounding processes for sterile injectable steroid products which included the following: methylprednisolone acetate and betamethasone repository (betamethasone sodium phosphate and betamethasone acetate). The MABP accompanied us during most of the inspection at the request of HFM-330.

The current inspection involved sampling of NECC products from within the New York and New England District areas. Sample results revealed that the firm has potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP).

On 2/10/03, at the close of this inspection, an FDA-483, Inspectional Observations, was issued to Barry Cadden, R.Ph. The FDA 483 Observations pertained to the following: 1) inadequate documentation to verify sterile drug products distributed meet set standards (such as specifications and/or USP limits if applicable) or the assigned shelf life, 2) failure to maintain complaint files, including written procedures pertaining to the handling of complaints, and 3) lack of documentation for the reported adverse events associated with lot 05312002@16 of methylprednisolone acetate which includes handling and disposition of reports of patient problems, complaints, adverse drug reactions, and drug product or device defects.

ADMINISTRATIVE DATA

Post inspection correspondence should be sent to Barry Cadden R.Ph., Director of Pharmacy, at the below address.

Inspected Firm:	New England Compounding Center
Location:	697 Waverly Street Framingham, MA 01702
Phone:	[redacted]
FAX:	
Mailing Address:	697 Waverly Street Framingham, MA 01702
Dates of Inspection:	10/24/02, 12/12&18/02, 1/14-15/02, 2/10/03
Days in the Facility:	6
Participants:	[redacted] Investigator [redacted], Investigator

The EIR was written by [redacted]

FIRM INFORMATION

Pertaining to key firm personnel and their responsibilities no significant changes were made since the previous April 2002 inspection (see April 2002 EIR).

NECC holds a restricted license in the state of Massachusetts to operate as a compounding pharmacy. Essentially, MABP permits NECC to dispense only compounded pharmaceutical products. This is the second joint FDA and MABP investigation of the firm; the first was in April 2002 and was also a CDER assignment initiated by MedWatch complaints about the firm's betamethasone repository injectable

product. Please refer to the April 2002 EIR for the firm's hours and organizational structure. The MABP was present during the April 2002 investigation at the request of the FDA NWE-DO office per HFM-330 assignment.

On April 16, 2002 an FDA-483 was issued to Mr. Cadden citing sterility issues pertaining to the transfilling practices for betamethasone repository injection. Lot accountability was also cited for incomplete computerized record keeping of generated lot numbers. Mr. Cadden stated there is no lag in the transfilling time as noted in the 4/16/02 FDA-483. We were unable to verify this since compounding was not observed during this inspection. This inspection was classified VAI. No regulatory activities occurred as a result of the April 2002 inspection.

Since the April 2002 inspection, there have been significant changes to NECC's operations. One change is the acquisition of space previously occupied by a neighboring store. This space approximately doubled the firm's square footage which is currently being used for office space and a reception area. Mr. Cadden stated he now employs approximately twelve people in the following roles: 2 Pharmacists, 4 Pharmacy Technicians, 1 Bookkeeper, 2 Customer Service, 1 Receptionist and 2 Salespeople. He stated that the firm's employees make calls to out-of-state physicians and medical facilities and also maintain a web site.

Another change since the April 2002 inspection is the renovation of a previous reception area to accommodate the firm's new Class 10 hood. At the FDA inspectional closeout on 2/10/03, it was confirmed that the new hood is installed and certified. Mr. Cadden stated the new hood is not in use yet while he is awaiting the approval of the MABP.

NECC is planning on marketing and selling compounded products in all 50 U.S. states per Mr. Cadden. He stated he is in the process of applying to each state in order to do so. Currently he estimated he has permission to do so from approximately 13 states, though he could not recall which specific states. Mr. Cadden stated his firm employs individuals that telephone and/or send correspondence to prospective customers (physicians and medical facilities) found on the internet or in telephone books. He stated this is done to find prospective in-state and out-of-state customers. He also stated that he intends to have a representative from his firm travel the state of Massachusetts to promote the firm's services to potential customers. The firm also maintains a web site which advertises the firm's services and contains downloadable order forms. Mr. Cadden stated the NECC web site does not accept orders on-line.

COORDINATION WITH MASSACHUSETTS STATE BOARD OF PHARMACY

The Massachusetts Board of Pharmacy (MABP) provided three representatives who were each present intermittently throughout the inspection. The representatives were [redacted] Supervisory Investigator, [redacted] Investigator, and [redacted]

Quality Assurance Surveyor. To facilitate the sharing of information with MABP, one of the MedWatch complainants was contacted regarding directly reporting the adverse events to the MABP. MABP representatives were present throughout the majority of the inspection, which further facilitated MABP and FDA communications.
In early 2002 the MABP designated a committee to formulate compounding regulations for the State. Currently these regulations are under review by MABP. MABP anticipates implementing these new regulations sometime in 2003. Mr. Cadden is a member of the committee assigned by MABP.

Correspondence to the MABP should be sent to the following address:

The Commonwealth of Massachusetts
Division of Professional Licensure
Office of Investigations
[redacted]

MEDWATCH COMPLAINTS

This investigation was conducted per the HFM-330 assignment issued to the New England District Office. The assignment requested the collection of information and samples of NECC products in association with MedWatch complaints. Three MedWatch reports were received by the FDA detailing adverse events that occurred in two patients in July 2002 at the (b) (6), (b) (7)(C). See **Attachment #1** for the HFM-330 assignment and three MedWatch reports. In the MedWatch reports, the complainant attributed the adverse reactions to a compounded methylprednisolone acetate preservative-free 80mg/ml injectable prepared by NECC in May 2002. The MedWatch complaints were reported by a physician and the Chief Pharmacist at (b) (6), (b) (7). The Chief Pharmacist and Quality Supervisor from (b) (6) were both contacted regarding the MedWatch reports and events surrounding the adverse reactions.

On 9/30/02, [redacted] spoke with the Chief Pharmacist (b) (6), (b) He stated that after the adverse reactions occurred, he instructed his staff to remove all the methylprednisolone acetate injectable with the affected lot number from the hospital floors. The collected vials were then turned over to the hospital's Quality Assurance personnel. The MedWatch report from the pharmacist stated samples were available.

On 9/4/02, 11/1/02 & 3/3/03 [redacted] spoke with (b) (6), (b) (7)(C), Quality Supervisor at (b) (6), (b) (7). On 9/4/02, [redacted] confirmed with (b) (6), (b) (7)(C) that samples were available. (b) (6), (b) (7)(C) stated that she had received the unused vials from the pharmacy department. Arrangements were made with the FDA New York District to collect the sample vials (b) (6), (b) (7)(C)

(b) (6), (b) (7)(C) was able to describe the adverse events and surrounding incidents. She stated that both patients were given injections on (b) (6), (b) (7)(C) from the same lot (05312002@16) and both experienced pain and headache and were hospitalized with meningitis-like symptoms. Both patients received antibiotic therapy. Cultures of both patients' cerebrospinal fluid (CSF) were negative. Since both patients were on antibiotic therapy, the CSF cultures would be negative regardless of microbial growth prior to treatment. (b) (6), (b) (7)(C) did not have a hard copy of the CSF results. Both patients fully recovered. (b) (6), (b) (7)(C) confirmed the route of administration for both patients was intrathecal. One injection was intended as intrathecal and the other was unintended intrathecal (misplacement of needle into an unintended adjacent space).

One of the MedWatch reports stated the vials tested positive for gram negative organisms. Attached as **Exhibit #1** is the fax from (b) (6), (b) (7)(C) reporting results of the vial testing performed by (b) (6), (b) (7). The lab results show initially there was growth (gram negative rods), but after 8 weeks incubation there was no growth seen. (b) (6), (b) (7)(C) stated she believes the vial tested was from lot 05312002@16 and that the lab results are under one of the patient's names, but she believes it was the vial tested, not patient fluids (ie., not cerebrospinal fluid). Since they are single-dose vials, the actual vials used on the affected patients were discarded and could not be located.

When asked about actions taken by (b) (6), (b) (7), (b) (6), (b) (7)(C) stated she first contacted Mr. Cadden at NECC to make him aware of the adverse events. She stated she spoke with Mr. Cadden on/about 7/23/02. She stated she does not believe (b) (6) returned any of the vials to NECC. She believes they were all retained for FDA sampling and hospital investigative purposes. After the adverse events occurred, a hospital committee (including infectious disease and anesthesiology) looked into possible causes and determined, for lack of another answer, that the adverse events were caused by the compounded product from NECC.

SAMPLE COLLECTION BY FDA NYK DISTRICT: SEPTEMBER 9, 2002

A sample (FACTS 193610) was collected on 9/12/2002 by the New York District. The sample consisted of sixteen (16) vials of methylprednisolone acetate preservative-free (80mg/ml) injectable with "same lot number suspected for causing adverse reactions" in MedWatch reports. The sample was sent to FDA NRL for sterility and endotoxin testing. NRL was unable to perform the sample analysis until 4 days after the compounded product's expiration date. See **Attachment #2** for the collection report.

NOTE: The NRL reported the vials collected at (b) (6) were from lot 051902@15, a different lot than the MedWatch reports. A NWE-DO Compliance Officer spoke with (b) (6), (b) (7), Quality Supervisor at (b) (6) on 12/12/02. (b) (6), (b) (7) was surprised that the lot sampled by FDA at (b) (6) was different than the lot indicated in the MedWatch reports. This issue was not resolved in their phone conversation.

On 12/11/02, the NRL reported positive results for sterility (gram negative organisms). On 12/12/02 Investigators [redacted] visited the firm to notify Mr. Cadden of

the positive sterility results found upon analysis of his compounded product (see below for full description of firm visit).

On 12/18/02, NRL reported that the organisms were identified as *Burkholderia cepacia* and *Sphinogomonas paucimobilis*. The following is an NRL Pharmaceutical Microbiologist's description of the organisms found in sample 193610:

"Description of each bacterium:

Burkholderia cepacia- Burkholderia are aerobic, non-spore-forming, gram-negative rods which are straight or curved. This type of bacteria are environmental organisms found in water, in soil, and on plants including fruits and vegetables."Because of their ability to survive in aqueous environments, these organisms have become particularly problematic in the hospital environment". "The genus Burkholderia contains two organisms frequently encountered as human pathogens, B. pseudomallei and B. cepacia"."B. c. is well recognized as a nosocomial pathogen causing infections associated with contaminated equipment, medications, and disinfectants including povidone-iodine and benzalkonium chloride". "B.c. is emerging as an important pathogen in two patient populations with genetic diseases, Cystic fibrosis, and chronic granulomatous disease"

Sphinogomonas paucimobilis- This group of bacteria is also an aerobic non spore forming , gram –negative rod. "The new genus Spingomonas was created for the organism formerly known as Pseudomonas paucimobilis and CDC IIk-1. The genus Sphingomonas presently contain 16 species, but only S.paucimobilis , which is designated the type species, is important clinically. Colonies grown on blood agar medium are yellow pigmented and slowly growing, with only small colonies observed after 24 hr of incubation. S.a. is widely distributed in the environment, including water, and has been isolated from a variety of clinical specimens, including blood, cerebrospinal fluid, peritoneal fluid, urine, wounds, vagina, and cervix and from hospital environment"

The source of the reference information was obtained from the Manual of Clinical Microbiology, 7th edition, 1999, published by the American Society for Microbiology".

Please refer to the following table for a description of NYK district samples collected and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
193610	Methylpredisolone AC (PF) 80MG/ML INJ	05192002@15	16	11/15/02	1/14= *Sphingomonas paucimonas* 4/14= *Burkholderia cepacia*

VISIT TO FIRM: OCTOBER 24, 2002

MABP Supervisory Investigator [redacted] accompanied [redacted] to the firm. Ms. [redacted] presented Mr. Cadden with a formal request for information. At that time she

informed Mr. Cadden that a copy of his response would be provided to the FDA. Please see **Exhibit #2** for the State's request for information and NECC written response.

Mr. Cadden stated he was telephoned by an employee from (b)(6) to notify him of the adverse reactions that were reported to MedWatch. He did not have the employee name, but did email that information to me the following day (**Exhibit #3**). (b)(6), (b)(7)(C) Quality Supervisor at (b)(6) notified Mr. Cadden about the adverse reactions associated with methylprednisolone acetate. Mr. Cadden stated (b)(6), (b)(7)(C) told him the adverse reactions were due to "administration errors" since the injections were administered intrathecally. The medication is not FDA approved for intrathecal administration. Mr. Cadden stated that the hospital had returned vials of the affected product to the firm and that NECC sent a sample of the returned product to its contract laboratory (Analytical Research Laboratories, Oklahoma City, OK (ARL) for testing. I viewed the laboratory results (received by lab on 8/20/02 and reported on 8/22/02). The results reported on 8/22/02 hard copy were negative for "endotoxin content and microbial contamination". I then viewed the initial ARL results (received by lab on 6/19/02 and reported on 6/20/02) for the affected lot, 05312002@16, which were negative for "endotoxin content and microbial contamination". See **Exhibit #4** for supporting documentation.

The following information was also obtained from Mr. Cadden:

1) Random sampling for finished compounds is as follows: for lots with small volume vials, 2-3 vials are tested and for lots of larger volume vials (ie., 10ml) 1 vial is tested for sterility and endotoxins.
2) NECC is still closed on Saturday and Sunday, but Mr. Cadden stated he often comes to work on Saturdays to make sterile compounds. Mrs. Cadden still works two to three days per week in an administrative role only.
3) Regarding the processing of sterile suspension injectable steroids: The compounding occurs in the "Clean Room". Once compounded, the suspension (in a beaker) is covered with 3 layers of aluminum foil, brought through the ante-room to the main compounding area and autoclaved. The suspension is then brought back through the ante-room into the "Clean Room". The suspension is brought to room temperature on a magnetic stirrer (approximately 2-4 hours) then the suspension is transferred to vials (various sizes) with a Baxter Repeater Pump. Mr. Cadden stated the bulk suspension is sterilized (versus sterilization in final vial container) because the properties of the suspension would not allow it to resuspend in the vials and the particle size would be too large. The steroid compounding formulas from Professional Compounding Centers of America, Houston, TX (PCCA) instruct him to compound the products in this way. Suspensions must be autoclaved since they cannot be filtered through a 0.22μ filter due to particle size.

[redacted] told Mr. Cadden that MABP discourages the use of "as directed" instructions on patient prescription labeling and that stock sold as "For Office Use Only" was not allowed in the state of Massachusetts unless the firm obtained a special permit.

VISIT TO FIRM: DECEMBER 12, 2002

On 12/11/02, NRL informed NWE-DO that the sterility results for sample 193610 showed a presumptive positive for four (4) of fourteen (14) vials. At that time it became a priority to visit NECC to inform Mr. Cadden of the results and determine what his intentions would be regarding the compounded product. On 12/12/02, Inv. Joyce and DeWoskin went to NECC and informed Mr. Cadden of these results. Mr. Emery and Mr. Chaput from the MABP were present. Mr. Cadden stated that NECC had conducted a recall of the product in August 2002 (without FDA knowledge) after the adverse reactions were reported to NECC by the MedWatch complainant hospital. Mr. Cadden did not share this recall information with the FDA at the October 2002 visit to NECC. He stated recall notification to customers was done via telephone calls. The only record of the recall process was a three page table listing customer names, returned product and lot numbers. Recall information was requested per NWE-DO Recall Coordinator guidance.

Mr. Cadden confirmed prior to the recall he was using 6 month expiration dates for sterile products with preservatives and was sterilizing the vials himself at NECC. He stated he conducted a recall after receiving the complaint from (b)(6) in July 2002. He stated he received 500-600 vials back from customers as a result of the recall. He retested one (1) of these vials for sterility and endotoxin and the results were negative. Mr. Cadden showed us ARL #24399 results (refer to Exh. #4, pages 3&4). I asked Mr. Cadden if he thought of testing a more representative quantity from the returned product (ie., not just one vial), but he stated he only tested one vial. Mr. Cadden stated the corrections he has made since the complaint from (b)(6) include the following actions: 1) expiration date was decreased from 6 months to 60 days for preservative free products, and 2) utilization of a contract facility (Eagle-Picher) to pre-sterilize vials for use in sterile products. See **Exhibit #5** for information from Eagle-Picher Industries, Inc. website (Miami, OK).

Mr. Cadden stated he had not received any other complaints associated with the use of NECC compounded sterile steroid injectables. Representative testing for sterility and endotoxin was discussed with Mr. Cadden. We explained to Mr. Cadden that the USP contains guidance on sample sizes in relation to lot quantities. We also discussed validation and verification of testing procedures performed by contract laboratories.

While at the firm, samples were collected of methylprednisolone acetate preservative-free (PF) injectable and betamethasone repository injectable. After seeking supervisory guidance, I collected 20 x 1 ml vials of methylprednisolone acetate PF (80mg/ml) and 10 x 5ml vials of betamethasone repository (6mg/ml betamethasone repository = 3mg betamethasone sodium phosphate + 3mg betamethasone acetate). These compounds were chosen because they were associated with the current and April 2002 MedWatch reports. Both products are sterile suspension injectable steroids and are compounded by similar methods according to Mr. Cadden. See **Attachment #3, 4, & 5** for the FDA-463a (Affadavit), FDA-484 (Receipt for Samples), and collection reports.

Please refer to the following table for a description of samples collected on this date and the subsequent NRL results.

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)

VISIT TO FIRM: DECEMBER 18, 2002

A visit to the firm was conducted to request information regarding NECC recall procedures and collect samples. After conferring with NRL for sampling requirements, it was decided that further samples were necessary from NECC. See **Attachment # 6, 7 & 8** for the FDA-463a (Affadavit), FDA-484 (Receipt for Samples), and collection reports. Please refer to the following table for a description of samples collected on this date and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
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"

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

The following items were also discussed with Mr. Cadden:

1) Sampling of compounded products by NECC: The firm's sampling procedures were again discussed with Mr. Cadden. He stated he used the recommendations of his contract laboratory (ARL). I discussed with Mr. Cadden the USP recommendations for testing of sterile products. Mr. Cadden stated he would look at these recommendations and reconsider his testing procedures. A copy of the firm's sample log to ARL is attached as **Exhibit #6**.
2) Environmental Monitoring of "Clean Room": While discussing the firm's "clean room", Mr. Cadden stated that he has his laminar flow hood serviced yearly,

which includes HEPA filter testing (and replacement as necessary). I asked Mr. Cadden if he would know if the HEPA filter needed to be changed between yearly inspections and he stated no. I discussed with Mr. Cadden the impact that could have by possibly compromising the sterility of his product. I recommended NECC initially evaluate the life span of their HEPA filters (via more frequent monitoring) and compose a testing plan around that evaluation. Mr. Cadden stated that the firm changes the pre-filters every 4-6 weeks to prolong the life of the HEPA filter. Mr. Cadden stated another component of his yearly testing of the clean room is air sampling. I recommended Mr. Cadden consider expanding his environmental monitoring to include surface and wall sampling. I suggested guidance resources such as the USP.

3) Sterile compound preparation:
   a. Mr. Cadden stated that he uses a new set of disposable tubing for the Baxter Repeater Pump for each lot that is compounded.
   b. When asked what other sterile compounds are made by the firm, Mr. Cadden stated if he was able to filter the product that he would make the compound.
   c. Mr. Cadden stated the water source for sterile products comes from 1000 ml bags of Sterile Water for Injection.
   d. Mr. Cadden stated that NECC started to compound Prochlorperazine (Compazine) Injectable 2-3 weeks prior when he was able to access the bulk product.
   e. Mr. Cadden stated the firm does not dispense any medication to clients for office stock use. He stated that it would be a possibility in the future if Massachusetts state laws changed and allowed this of compounding pharmacies.
   f. [redacted] requested of Mr. Cadden the opportunity to observe production of sterile products in the very near future depending on his compounding schedule. On 12/23/02, [redacted] spoke with Mrs. Cadden who stated that compounding would not resume until after the start of the New Year since business was slow around the holidays.
   g. A copy of the NECC "Policies and Procedures for Compounding Sterile Products" and "Aseptic Compounding Policies and Procedures Manual" (SOP's) are attached as **Exhibit # 7 & 8**.
4) Recall Procedures:
   a. Health risk analysis: While discussing the lots made before August 2002 that were distributed with a 6 month expiration date, I asked Mr. Cadden if he had any intentions of recalling those products also since those products will continue to have expiration dates through February 2003. Mr. Cadden stated he did not have any intention of recalling products other than the steroid products recalled in August 2002. The firm's recall procedures in August 2003 consisted of calling clients who received the 05312002@16 lot of methylprednisolone and asking them to return any steroid product they had in stock. This means that clients who received lots other than the 05312002@16 were not notified of the recall or

possible problems with the products and will likely use those products until the expiration date of 6 months.

b. Mrs. Cadden stated she notified customers of the recall by telephone. We restated the information needed by FDA to process the recall. Please see the heading "Recall Information" for the information provided by NECC.

c. The returned products from the recall were still at NECC. Two large boxes were examined by [redacted] Lot numbers and product names were identifiable and it was confirmed that they were the products intended for the recall.

d. A copy of a FDA Talk Paper from 11/15/02 was given to Mr. Cadden and is attached as **Attachment #9**. This reference described current regulatory actions taken against compounding pharmacies.

VISIT TO FIRM: JANUARY 14, 2003 this section written by [redacted]

On 1/14/03, I [redacted] went to NECC. At the time of my arrival I showed my credentials and issued an FDA 482 to Barry Cadden. The purpose of this visit was to pick up a sample of sterilized vial stoppers and sterilized vials. The vial stoppers Mr. Cadden stated are bought pre-sterilized from Eagle Picher Environmental. Mr. Cadden provided CSO [redacted] with a sealed bag containing 100 vials from Eagle Picher Environmental which was submitted to Northeastern Regional Laboratory (NRL) for sterility and endotoxin testing. These vials are assigned Sample Number 167876. Also on this same date Mr. Cadden provided a sealed bag of vial stoppers which he stated he autoclaved. However, when I returned to the office, I noticed a tear in the bag; and therefore decided not to submit this sample. Instead I decided to go to NECC the following day for a new sample. When the tear was noticed I called the firm and notified [redacted] the Educational Coordinator, that I would be returning on 1/15/03 to collect some more autoclaved stoppers.

When I was at the firm on 1/14/03 Barry Cadden notified me that his lawyer ([redacted] Massachusetts – phone 617-964-2501) instructed him to tell me that he would provide me samples, but if I had any other requests or questions pertaining to any of their procedures and compounding activities, I was to put my requests or questions in writing. Mr. Cadden stated he would then submit my requests to his lawyer for review, and then get back to me. At the time I was talking to Mr. Cadden I requested the address and name of customers who received lot 05312002@16, methylprednisolone 80mg/ml injection which is a lot number of product that stated he told people to return to NECC due to a potential problem, when I returned to the office I sent Mr. Cadden an e-mail repeating this request. As of 2/10/03, the date that the FDA 483 was issued, a response to this e-mail request had not been received.

VISIT TO FIRM: JANUARY 15, 2003 (this section written by [redacted]

On 1/15/03, I [redacted] returned to NECC for the purpose of collecting a sample of sterilized vial rubber stoppers. I showed my credentials, and issued an FDA

482 to [redacted] Educational Coordinator. [redacted] said Mr. Cadden was at the facility but not available. At this time she provided me a sample of vial stoppers in a sealed bag which she stated were autoclaved within the last day. I observed that there were water droplets in this bag with the stoppers and that they were making water stains on one part of the white packaging material of the autoclave bag. I submitted these vial stoppers to NRL as Sample #167877. After I was provided the sample by [redacted] left the firm.

Please refer to the following table for a description of samples collected January 14-15, 2002 and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
167877	Sterile Vials	n/a	~100	n/a	"In progress" as of 3/4/03
167876	Vial stoppers	n/a	Unkn.	n/a	"In progress" as of 3/4/03

MEETING WITH THE MABP: FEBRUARY 5, 2003 (Boston, MA)

A meeting was held to discuss the appropriate course of action for NECC. **Attachment #10** contains the minutes of this meeting.

VISIT TO FIRM: FEBRUARY 10, 2003 (Closeout and issuance of FDA-483)

On 2/5/03, [redacted] telephoned and left a voice mail for Mr. Cadden to inform him that there were violative sample results for subpotency and that the close out meeting would be held on 2/10/03. On 2/6/03, [redacted] received a voice mail from Mr. Cadden stating his intentions to investigate and institute a recall of betamethasone repository (lot 12102002@11).

The purpose of 2/10/03 closeout meeting included issuance of the FDA-483 (List of Observations), to request recall information for the methylprednisolone acetate recalled in 2002, to inform the firm of the complete results for samples obtained 12/18/03, and to find out the firm's intentions with respect to the violative lot within expiry and surrounding lots of similar products.

The closeout meeting took place at NECC on 2/10/03. In attendance from NECC were Barry J. Cadden, NECC Owner and Director of Pharmacy, [redacted] Educational Coordinator, was present in a secretarial role for NECC. In attendance from MABP [redacted] and [redacted] In attendance from the FDA NWE-DO were Investigators [redacted]

The visit began with a tour of the newly completed room that houses NECC's new Class 10 hood. The hood was certified by Scientific Air Analysis, Inc. (47 Fatina Dr, Ashland, MA 01701, [redacted]. The room contains the Class 10 hood, autoclave, incubator, sink, dishwasher, computer station and office area.

Mr. Cadden stated NECC had plans to work with a consultant, [redacted], of the Preble Group. See **Exhibit #9** for the consultant information.

The following information was requested at the meeting:

1) For the recall of methylprednisolone acetate in 2002: distribution list (including addresses), reason for recall, recall strategy, time period of product distribution, total quantity distributed, total quantity returned in the recall, documentation of calls to clients, time period in which recall was conducted (start & stop), total quantity made and total put into vials, vial sizes and quantity of each that was made and product disposition.
2) For the pending recall of betamethasone repository (lot 12102002@11): all information above applicable to pre-recall period, copy of product labeling, recall initiation date, any complaints or adverse events reported and a recall contact.
3) Other Information: consultant CV, list of current stock on hand for all sterile injectable products, list of compounding that has taken place since 1/1/03 for all sterile injectable products and intentions with respect to similar products (ie., sterile injectable steroid suspensions).

[redacted] issued a new request for information from MABP dated 2/7/03. [redacted] provided a copy of the letter (**Exhibit #10**).

RECALL INFORMATION

On Friday, 12/13/02, the NWE-DO Recall Coordinator stated the district needed information from NECC to document and classify the recall of the methylprednisolone compounded product. I called Mr. Cadden that afternoon and discussed the need for recall information and to collect a larger quantity of vials for our sample (see below). He stated he would gather the information..

On Monday, 12/16/02, I called NECC to verify the receipt of the e-mail request for recall information and to answer any questions pertaining to the request. I left a message after I was told (by [redacted]) that Mr. Cadden was "in the clean room". Lisa Cadden returned my call and informed me that Mr. Cadden did not receive my email on Friday. I explained that I sent it as a reply to an email from Mr. Cadden and that I would resend the email the following morning. I also verbally stated the list of requested information for the recall so the firm would have adequate notice. This information was not provided to NWE-DO until after 2/10/03. On 2/14/03, NWE-DO Recall Coordinator received two faxes from [redacted] containing the information for the NECC recall of betamethasone repository injection (6mg/ml, lot 12102002@11). On 2/18/03, NWE-DO Recall Coordinator received a fax from [redacted] containing the information for the NECC recall of methylprednisolone acetate (preservative-free, all lots compounded before 7/16/02). Please see **Exhibit # 11 & 12** for these documents. On 2/21/03, the NWE-DO received additional information from [redacted] (via fax) informing the

FDA of NECC recall of further lots of betamethasone repository. This fax is attached as **Exhibit #13.**

CDER ASSIGNMENT & CPG 460.200 (PHARMACY COMPOUNDING)

The responses to the HFM-330 questions were obtained by inspectional visits and information provided by the MA State Board of Pharmacy (when followed by a *).

1) *Please determine from the Massachusetts Board of Pharmacy, whether NECC is operating in conformance with the applicable state law regulating the practice of pharmacy? Subsequent to the April 2002 joint FDA-State investigation, and referral to the Massachusetts Board of Pharmacy, what follow-up was done or what sanctions were taken by the Board?*

   There were no sanctions taken by the MABP against NECC following the April 2002 investigation. The Board is in the process of approving and adopting new regulations for pharmacy compounding firms. The MA applicable state laws reference the USP. Please see FDA-483 items for deficiencies observed at the firm.

2) *Does the NECC continue to fill patient specific prescriptions for each compounded product dispensed?*

   NECC dispenses and prepares products in bulk for administration to individualized patients pursuant to a receipt of a valid prescription from a prescriber. Bulk products produced in limited quantities at NECC are not compounded for third parties for resale. (*)

   Regarding patient specific information for filling non-sterile prescriptions: Mr. Cadden stated that NECC calls patients to ask them about their current medications for their computer patient profiles. He stated another reason to call the patient before making the compound is to verify the patient wants the compound since they are not usually covered under prescription insurance plans.

3) *What types and strengths of sterile products does the pharmacy compound? What quantities are being compounded? Is the pharmacy compounding copies of commercially available FDA-approved products (ie.,- products that have the same active ingredient, dosage form, and strength)? (typical batch size follows where known).*

   - Hyaluronidase 150u/ml- Discontinued by manufacturer (5,000 ml)
   - Triamcinolone Diacetate 40mg/ml- When unavailable (500 ml)
   - Methylprednisiolone Acetate PF 40mg/ml and 80mg/ml-
     Special order when unavailable (1,000 ml)

- Betamethasone Repository 6mg/ml and PF 6mg/ml- Special order when unavailable. (1,000 ml)

* Refer to Exh.#17 & 18 for other products compounded by NECC.

4) *Does NECC continue to assign unsubstantiated beyond-use dates? (designate expiration dates without basis)*

Mr. Cadden stated that beyond use dates are included on each formulation obtained from PCCA. Drug substances received, stored, or used at NECC are obtained only from FDA registered facilities. He stated he uses 6 month expiration dates for sterile products with preservative and 60 days for preservative-free.

It should be noted that samples obtained on 2/18/02 show that sample #169128 of methylprednisolone acetate preservative free (40 mg/ml x 1 ml, lot 11262002@5) had an expiration date of 1/10/03, which is approximately 45 days, not 60 days as stated by Mr. Cadden.

5) *Please obtain formulation information that will enable us to compare the compounded product formulations with the FDA-approved formulations. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a product that is only slightly different than a FDA-approved product that is commercially available (such as to remove a preservative or coloring agent for an individual patient with an allergy problem). In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the formulation for the particular patient. Does the pharmacy have documentation from the prescribers that demonstrates the medical need for the particular variation of the formulation for each individual patient?*

Please see **Exhibit#14** for "Logged Formula Worksheets" utilized by NECC

6) *Does NECC compound drug products (including sterile products) in anticipation of receiving prescriptions? If so, what quantities are compounded on that basis? How do the amounts compare to the amount compounded after receiving valid prescriptions?*

Mr. Cadden stated *sterile products* are compounded *before* prescriptions are received. In general, approximately a 30 day supply would be maintained by NECC. The exception to this would be sterile products that can be filtered, such as ophthalmic products, which are compounded after receipt of a prescription. We did not have the opportunity to verify quantities compounded versus quantities dispensed on a monthly basis.

Mr. Cadden stated *non-sterile products* (creams, ointments, capsules, etc) are compounded *after* prescriptions are received.

7) *Does NECC use commercial scale manufacturing or testing equipment to compound drug products? What are the specific batch sizes that are prepared for each type of sterile product and how often is each batch prepared?*

In January 2003, NECC completed installation and certification of a "Class 10" Isolator biological hood. Mr. Cadden plans to begin utilizing this new area once he receives MABP approval. Refer to question 2 for typical batch sizes.

8) *Does NECC compound any products that have been removed or withdrawn from the market for safety reasons? If so, please obtain documentation.*

Mr. Cadden denies the firm compounds any products that have been removed or withdrawn from the market for safety reasons

9) *Has NECC instituted a formal written complaint system since the April 2002 FDA-State inspection?*

NECC does not have a formal written complaint system to date per Mr. Cadden. He stated complaints are still filed under specific facility or patient.

10) *Has NECC performed any corrective actions in response to the FDA 483 List of Observations issued at the conclusion of the April 2002 inspection?*

Mr. Cadden told us the only changes made were in response to the (b) (6), (b) (7) (C) adverse reactions and entailed the following: 1) expiration date was decreased from 6 months to 60 days for preservative free products, and 2) utilization of a contract facility (Eagle-Picher) to pre-sterilize vials for use in sterile products. See **Exhibit #5** for information from Eagle-Picher Industries, Inc. website (Miami, OK).

11) *Annually, how many prescriptions for compounded products does the NECC dispense?*

Mr. Cadden estimated NECC dispenses 20,000 prescriptions per year.

12) *Does NECC ship compounded products out of state? Was any of the lot of methylprednisolone acetate PF80mg/ml referenced in the MedWatch report shipped out of state?*

According to Mr. Cadden, NECC does ship compounded products out of state. The lot of methylprednisolone acetate PF referenced in the MedWatch was shipped out of state. On 2/5/03, [redacted] from MABP provided the states

NECC is licensed in as SC, FL, VA, ME, RI, NH, ID, NE, KS, VT, OH, MO, MT and CT (pending).

13) Does the NECC maintain a website concerning the products they compound?

Yes, the firm advertises services on the intranet at neccrx.com. The contents of the website, www.neccrx.com as of 10/11/02 are attached in **Exhibit #15**. Mr. Cadden states they do not accept online orders.

14) Please document the processes used to make the Methylprednisolone Acetate Preservative Free 80mg/ml product, including production scale, and any in-process controls.

See "Logged Formula Worksheet" provided by Mr. Cadden (**Exhibit #16**). This is the formula NECC obtained from PCCA to compound Methylprednisolone Acetate. Production scale varies according to what Mr. Cadden anticipates as need for the compounded product. There are no in-process controls per Mr. Cadden.

15) What quantity of compounded sterile products, including methylprednisolone acetate PF 80mg/ml are on hand for sampling?

We obtained samples of sterile injectable compounds on 12/12 & 18/02. Refer to **Exhibit #17** for a list of current inventory as of 2/11/03.

OBJECTIONABLE CONDITIONS

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 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

E. immediate area while product is exposed to the environment, such as during filling and prior to container closure).

F. 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 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.

Discussion of FDA 483 Observation 1

Mr. Cadden stated he did not have documentation of established standards or specifications for finished sterile products compounded by NECC. This included the verification that the above items (A thru M) have been addressed by NECC to ensure the quality of products compounded by NECC.

Mr. Cadden stated he was unable to provide data to support the assigned shelf life for finished sterile products compounded by NECC. Mr. Cadden stated that he utilized the recommendations on the product compounding formulas ("logged formula worksheets") received from PCCA. After learning of the the adverse reactions to methylprednisolone acetate in July 2002, Mr. Cadden stated he shortened the shelf life of preservative-free products from 6 months to 60 days. There was no product specific data available to support the use of either shelf life.

Mr. Cadden stated that he purchased Standard Operating Procedure (SOP's) from PCCA. After review of the SOP's, it was determined that they have not been revised for use at NECC. It was also noted that NECC does not follow the SOP's. Mr. Cadden stated he does not follow all of the SOP's. Refer to **Exhibit #8** for the NECC SOP's.

Observation #2

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

Discussion of FDA 483 Observation 2

Mr. Cadden stated that no formal complaint files are maintained by NECC. NECC has not established adequate written procedures for the handling of complaints and adverse events reported to the firm.

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.

Discussion of FDA 483 Observation 3

Mr. Cadden stated he did not have documentation of an investigation or the subsequent changes made by NECC in response to the adverse events associated with methylprednisolone acetate lot 05312002@16. No written records were available to rationalize or confirm the implementation of shorter expiration dates and the use of pre-sterilized vials. There was also no written documentation to show follow up actions were being taken to ensure the effectiveness of corrective actions taken by the firm.

DISCUSSION WITH MANAGEMENT (2/10/03)

It was explained to Mr. Cadden that at this point the FDA is considering NECC a pharmacy compounder and not a drug manufacturer. Mr. Cadden stated he had retained the services of a pharmaceutical consultant. The consultant is supposed to meet with Mr. Cadden within the next week to determine a course of action.

[redacted] presented the FDA-483 to Mr. Cadden. Each item was reviewed with Mr. Cadden. Mr. Cadden was asked if he understood each point, to which he answered yes. Mr. Cadden was asked if he had any questions about each of the observation items, to which he answered no. [redacted] stated he was very familiar with the observations and would be able to assist Mr. Cadden in his written response.

Further details pertaining to this closing discussion is in this report under the heading entitled: "Visit to Firm: February 10, 2003". [redacted] stated they planned to have a written response to the FDA within two weeks. After the FDA-483 was issued and discussed, the inspection was concluded.

REFUSALS

Though information was not made readily available, there were no direct refusals from the firm.

ADDITIONAL INFORMATION

Guidance was received from HFM-330 throughout the entire investigation, including a teleconference on 12/16/02. During this teleconference, guidance was given regarding

samples to be collected and the composition and issuance of the FDA-483 (List of Observations).

On 1/23/03, NWE-DO received information that NECC had retained the services of [redacted] (Washington, DC) to represent him in regulatory matters. [redacted] requested available information through FOI. [redacted] discussed with the NWE-DO Compliance Branch that he would be representing NECC and Mr. Cadden; communication between the FDA and NECC from that point on (excluding the closeout on 2/10/03) occurred between [redacted] and NWE-DO Compliance Branch.

On 3/3/03 [redacted] of MABP related to Inv. Joyce that NECC had retained separate counsel to handle MABP related matters; however, he still retained [redacted] to handle FDA related matters.

At the time of this report, [redacted] stated MABP had not received a reply from NECC for their request for information dated 2/7/03. NECC requested and was granted an extension for submitting this information to MABP.

The list of current stock on hand for all sterile injectable products was received by fax on 2/11/03 (**Exhibit#17**). The list of compounding that has taken place since 1/1/03 for all sterile injectable products was received by email on 2/14/03 (**Exhibit #18**). [redacted] response to [redacted] questions on 2/10/03 regarding FDA regulations was received by NWE-DO on 2/21/03 and is attached as **Exhibit #19**.

The documents obtained from NECC to support the sample collections on 12/12 & 13/02 are attached as **Exhibit #20**.
Since the opportunity to observe production did not occur, no photographs were taken by the investigators.

ATTACHMENTS

FDA-482 Notice of Inspection (Dated 10/24/02)
FDA-482 Notice of Inspection (Dated 12/12/02)
FDA-482 Notice of Inspection (Dated 1/14/03)
FDA-482 Notice of Inspection (Dated 1/15/03)
FDA-482 Notice of Inspection (Dated 2/10/03)

1) CDER HFM-330 Assignment (Dated 8/2/02, 10 pages)
2) Collection Report for NYK Sample 193610 (4 pages)
3) FDA 463a Affadavit (Dated 12/12/02, 1 page)
4) FDA-484 Receipt for Samples (Dated 12/12/02, 2 pages)

5) Collection Reports for NWE Samples 12/12/02 (6 pages)
6) FDA 463a Affadavit (Dated 12/18/02, 1 pages)
7) FDA-484 Receipt for Samples (Dated 12/18/02, 2 pages)
8) Collection Reports for NWE Samples 12/18/02, 21 pages)
9) FDA Talk Paper (Dated 11/15/02, 2 pages)
10) Minutes of Meeting between MA State Board of Pharmacy and FDA NWE-DO (with attachments) (Dated 2/24/03, __pages)
11) FDA-483 Inspectional Observations (Dated 2/10/03, 3 pages)

EXHIBITS

1) Fax from (b) (6), (b) (7)(C) of (b) (6), (b) (7)(C) (Dated 11/1/02, 2 pages)
2) MABP Request for Information (10/02) and NECC response (Dated 11/18/02, 10 pages)
3) Email from NECC (dated 10/25/01, 1 page)
4) Analytical Research Laboratories Results for methylprednisolone lot 05312002@16 (4 pages)
5) Eagle-Picher Industries, Inc. background information (6 pages)
6) NECC sampling log to ARL (1 page)
7) NECC "Policies & Procedures for Compounding Sterile Products" (3 pages)
8) NECC SOP Manual (179 pages)
9) Curriculum Vitae of NECC Consultant (Fax Dated 2/11/03, 5 pages)
10) MA State Board of Pharmacy Request to NECC (Dated 2/7/03, 3 pages)
11) NECC Recall information (dated 2/14/03, 9 pages)
12) NECC Recall information (dated 2/18/03, 7 pages)
13) NECC Recall Information to NWE-DO Recall Coordinator (Dated 2/21/03, 7 pages)
14) Logged Formula Worksheets (21 pages)
15) NECC website information (Date accessed 10/11/02, 7 pages)
16) Methylprednisolone acetate "logged formula worksheet" (1 page)
17) NECC current inventory (dated 2/11/03, 2 pages)
18) NECC lots compounded since 1/1/03 (dated2/14/03, 2 pages)
19) NECC Response to 503A statement by [redacted] (Dated 2/21/03, 2 pages)
20) Supporting documents for sample collections (24 pages)

[redacted]
NWE-DO

[redacted]
NWE-DO