REASON FOR INSPECTION

This investigation was initiated from HFD-330, Division of Prescription Drug Compliance and Surveillance. HFD-330 requests follow-up of 2 MedWatch Adverse Event Reports. The assignment was entered into FACTS under ID #298826 as a domestic investigation to be conducted under PAC 56D015. The assignment also requests working jointly with the Mass Board of Pharmacy.

HISTORY

There is no pervious investigational/inspectional history on file for New England Compounding (NEC) Pharmacy Inc., Framingham, MA 01702. The Mass Pharmacy Board has inspected NEC in the past.

SUMMARY OF FINDINGS

This investigation of New England Compounding Pharmacy Inc., Framingham, MA 01702 revealed that the subject lot, 02012002@27 identified in MedWatch Forms, could not be traced through NEC Pharmacy records. The owner of NEC, Barry Cadden, R.Ph could offer no definitive explanation/or records. According to Mr. Cadden lot #02012002@27 did not exist. A review of the compounding operations was accomplished and areas of concern regarding sterility were discussed. An FD-483 was issued regarding sterility issues and lack of lot accountability.

The Mass Board of Pharmacy performed their own independent inspection while the FDA investigation was in progress.
Note: Mass Board of Pharmacy was invited to participate by the FDA NWE-DO, per Headquarters' assignment.

PERSONS INTERVIEWED/AREAS OF RESPONSIBILITY

On 4/9/02 credentials were displayed and a Notice of Inspection was issued to Barry J. Cadden R.Ph, Owner & Director of the Pharmacy.

Mr. Cadden coordinated all the information for this report. Mr. Cadden is the Owner of NEC. He identified his wife Lisa Cadden R.Ph as Vice President of NEC. Mrs. Cadden was introduced on the second day of the inspection.

Mr. Cadden was informed that the purpose for the inspection was a follow-up to adverse events involving the compounded product Betamethasone acetate/betamethasone sodium phosphate. (The drug was administered via an epidural injection in the adverse event reports.) Note: Per instruction from HFD-330, detailed information such as lot number & MedWatch Reporter was not shared with Mr. Cadden for confidentiality reasons.)

Mr. Cadden stated there are (b) (4) employees, (b) (4) of whom are involved in compounding. Mr. Cadden is the only individual that compounds sterile product. NEC has been in business about 4 years.

On the first day of inspection. Mr. Cadden was cooperative & supplied some documents. The second day of inspection, Mr. Cadden had a complete change in attitude & basically would not provide any additional information either by responding to questions or providing records. Mr. Cadden challenged FDA jurisdiction/authority to be at his pharmacy. He indicated he had consulted with his lawyer. From that point on it was essentially "talk to my lawyer".

JURSDICTION

Section 704(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act describes the nature of FDA inspectional authority with regard to retail pharmacies. In particular, this section states that the "provisions of the second sentence of paragraph (1) shall not apply" to pharmacies operating in the retail capacity. The sentence being referred to is contained in Section 704(a)(1)(B). It provides the authority during factory inspections of firms that manufacture, process, pack, or hold prescription and nonprescription human drugs an (restricted) devices for access to "records, files, papers, processes, controls, and facilities" bearing on whether these products are in violation of the Act. In summary, our inspectional authority at pharmacies operating in a retail capacity consists of being able to:

- enter, at reasonable times (Section 704(a)(1)(A), and
- inspect, at reasonable times, and within reasonable limits and in a reasonable manner (Section 704(a)(1)(b), the establishment and its equipment and operations

However, the owner of the pharmacy is not obligated to furnish records, as is normally the case when a facility that processes drug products is being inspected.

On the first day of the inspection (April 9) we were allowed to review and were furnished with copies of records related to the compounding of Betamethasone Repository Injection. Later the same day, Mr. Cadden raised as an issue the precise nature of FDA's authority to inspect retail pharmacies. However, at this time he did not express any reservations about having allowed us to review any of these records.

However, it became clear, upon our return on the following morning, that Mr. Cadden had reconsidered this matter. He presented us with a printed copy of Title 21 of the United States Code, Section 374 (the codified version of Section 704 of the Act) that he had apparently downloaded from the Internet (www4.law.cornell.edu/uscode/21/374.html), with paragraph (2)(A) of Section 374 highlighted. Mr. Cadden stated that he was no longer willing to provide us with any additional records, unless we would identify the specific lot of Betamethasone Repository Injection that was the focus of this investigation. Since we had been specifically directed by CSO Richman (CDER/OC/Division of Prescription Drug Compliance and Surveillance) not to divulge this lot number, we were not in a position to comply with Mr. Cadden's request. From this point on, no additional records were provided or collected.

MEDWATCH ADVERSE EVENTS

Per HFD-330 Assignment, 2 Adverse Events, reported through the MedWatch system were identified to the NWE-DO for follow-up. The information contained in these reports were not openly shared with NEC nor with Mass Board of Pharmacy. Both MedWatch reports were from the same Reporter and involved the same lot number of Betamethasone.

Note: An inspection/subsequent action of a [redacted] (b) (4) Compounding Pharmacy for Betamethasone was revealed during a telecon with HFD-330 while the NEC investigation was in progress. (The information was not included with the NWE-DO assignment.) Very similar operational problems existed with the [redacted] (b) (4) Compounding Pharmacy that were encountered with NEC. The action for the [redacted] (b) (4) Compounding Pharmacy was taken by the State Pharmacy Board. See Attachments to this report for the FD-483 and State Board of Pharmacy, [redacted] (b) (4) Case [redacted] (b) (4) Accusation.

The NWE-DO FDA Investigators conducted the NEC MedWatch follow-up investigation by requesting a printout of the Betamethasone Compounded Product for the year 2002. The subject lot number was listed on this printout, i.e., lot #02012002@27. See Exhibit #1 for this printout.

From this printout, lot #'s 02152002@10 and 02012002@27 were selected for review. Formula Worksheets for lot #02152002@10 were provided, see Exhibit #2. No records for lot #02012002@27, (the MedWatch lot number), were provided. Mr. Cadden indicated that there were no Compounding records for this lot. When he accessed the database, the only document generated was a Prescription log with a "date made", of 2/1/02 for 1000 ml. See Exhibit #3.

Mr. Cadden expressed his belief that the Betamethasone was never compounded under lot #02012002@27. However he could not provide any documents to support his belief, such as a cancelled lot etc.

Due to MedWatch confidentiality restrictions, the status of the subject lot could not be pursued via this avenue.

Note: Complaint files are not maintained per se. Mr. Cadden stated that complaints are kept within a Customer file. FDA could not reveal the Complainant to Mr. Cadden.

The FDA Investigators then contacted the MedWatch Reporter in an attempt to verify the existence of lot #02012002@27. The Reporter, (b) (6), (b) (7)(C) was contacted by phone. The contact person was identified to FDA as (b) (6), (b) (7)(C).

(b) (6), (b) (7)(C) stated that a total of probably 5 incidents occurred after using subject Betamethasone on patients. The two more recent incidents were reported via MedWatch. Refer to MedWatch Reports for details. They are Assignment Attachments to this report.

(b) (6), (b) (7)(C) said he had no product remaining, all had been returned to NEC. He stated that he spoke to '(b) (6), (b) (7)' by phone describing the incidents but did not tell him he was reporting adverse events on MedWatch Forms.

(b) (6), (b) (7)(C) reviewed his paperwork, including PO Invoice, Return Goods, but could not find any paperwork specifically identifying the subject lot.

(b) (6), (b) (7)(C) stated he would provide copies of these documents to the FDA NWE-DO. They were faxed the same day and hard copies would be mailed overnight. See Attachments for these records. Note: There is no lot number identified on any of the records provided by (b) (6), (b) (7)(C)

was asked specifically if FDA could share the MedWatch Reports with Mr. Cadden. (b) (6), (b) (7)(C) said he would not want the information shared.

Note: A follow-up assignment at the [redacted] (b) (6), (b) (7)(C) location should be considered if HFD-330 deems it appropriate.

Due to jurisdiction/confidentiality restrictions, this FDA investigation could not proceed to any definitive resolution of issues raised in the Headquarter's assignment. HFD-330 Assignment contacts, Fred Richman and Kathy Anderson were fully informed of problems/barriers that were encountered throughout the inspection. NWE-DO Compliance Director, David Elder and NWE-DO Drug SI, Ellen Madigan were also made aware of the situation.

Prior to concluding the investigation, poor practices and areas of concern were discussed via Conference Call with HFD-330 and NWE-DO Management. The FDA Investigators were encouraged to issue an FD-483 to NEC.

The FDA Investigators impressed upon HFD-330 and NWE-DO Management that due to limitations on information gathering and access to records, the FD-483 observations could not/would not be supported with documentation. The FDA Investigators were directed to issue the 483 (even in light of the lack of documentation).

The FD-483 was faxed to HFD-330 for review and comment prior to issuance. Fred Richman and Kathy Anderson deleted 3 of the 7 Observations and modified one observation, (#5) by removing the lot number identification.

A conference call involving NWE-DO Investigators, HFD-330 Fred Richman, Kathy Anderson and CDER FOI Specialists Andrea Mascialea and Roy Castle was held on 4/15/02. FOI Specialists had no problem including the lot number on the observation. This was based on the fact that the suspect lot number was never revealed to NEC as the suspect lot number on the MedWatch Form.

The modified 483 was issued on 4/16/02 with 4 observations listed. Numbers 1-3 involved sterility issues. Observation 4 essentially described lack of lot number accountability. Refer to List of Observations for details, an attachment to this report.

OPERATIONS

The firm is a compounding pharmacy. The hours of operation are [redacted] (b) (4) All information was obtained from Mr. and Mrs. Cadden. There are [redacted] (b) (4) employees total, including [redacted] (b) (4) Registered Pharmacists, [redacted] (b) (4) data entry, [redacted] (b) (4) secretarial staff, and [redacted] (b) (4) pharmacy technicians. Pharmacists and Technicians receive Compounding Technique Certification [redacted] (b) (4)) from [redacted] (b) (4)

Formulations for compounding are obtained from (b) (4) The firm's prescription software (b) (4) is from (b) (4) Raw materials are obtained primarily from (b) (4) with alternate source (b) (4). Certificates of Analysis are provided with (b) (4) products. COA's were provided with (b) (4) products on request. See Exhibit #'s 4(a-b) for representative examples. Sterile compound product samples are sent to (b) (4) for sterility and endotoxin testing.

Medications are compounded pursuant to written/telephone/fax prescriptions from physicians/licensed facilities. The firm deals directly with patients, physicians and institutions. The firm states they fill patient specific prescriptions only, and that they have no wholesale functions. See Exhibit #5 for a representative Order Form. Mr. Cadden states that he is the only employee who compounds sterile products.

Leslie Doyle, R.Ph, from the Massachusetts Board of Pharmacy conducted her own independent audit on the second FDA on-site inspection of 4/10. Ms. Doyle was made aware of our concerns/findings regarding the Betamethasone Repository 6mg/ml injectable. Investigator Joyce accompanied Ms. Doyle for a State general inspection. Additional findings included:

1) Absence of DEA license on premises
2) Absence of DEA Class II Narcotic inventory on premises
3) Medication refrigerator contained employee beverages
4) Medications (ketoprofen, specifically) are commonly transferred from large bulk container to smaller (ketoprofen) container for ease of dispensing (therefore medication would be transferred to smaller container with incorrect lot and expiration date).
5) No reverse distributor for disposal of unused/unacceptable materials

The firm compounds betamethasone product both with (multi-dose vial) and without (single dose vial) preservative. Limited information about the compounding process was obtained. Mr. Cadden states he uses a Log Formulation Worksheet (LFW) (Exhibit #2) which outlines the steps taken in compounding the betamethasone. We were denied a copy of the (b) (4) formulation used to derive the Log Formulation Worksheet (LFW). A copy of the firm's "Policies & Procedures for Compounding Sterile Products" was obtained (Exhibit #6). The medication name on this document is (b) (4)", but Mr. Cadden claims this document applies to all sterile products. It outlines controls for the facility, equipment, maintenance, personnel, quality assurance/control, and dispensing. The lot in question from the MedWatch reports was lot #02012002@27, which contained preservative according to firm records. See Exhibit #1 for lot number printout.

Mr. Cadden states when compounding the product, he accesses the LFW in the computer. The computer assigns a lot number based on the date and order of compounding (i.e.: 02012002@27 would've been the (b)(4)th item entered in the computer for compounding on February 1, 2002). He then determines the quantity to compound and prints the LFW. The product is made according to the quantities and directions on the LFW. The location where raw materials are mixed is unclear. Mr. Cadden stated that he then (b) (4) (the autoclave is located outside of the clean room). Then he brings the (b) (4) The vials are labeled with self made computer labels. See Exhibit #7 for a representative example of a label. A sample is sent to (b) (4) for sterility and endotoxin testing. Mr. Cadden states he waits for acceptable lab results before dispensing product.

Mr. Cadden stated on/about 3/19/02 through 4/6/02 he received (b) (4) results positive for endotoxin ((b) (4)). See Exhibit #'s 8(a-d) for Test Results. He stated these lots (about 4 lots total) were awaiting disposal at his facility. After research, Mr. Cadden decided to change the suspending agent (b) (4). After making a lot on 4/6/02, Mr. Cadden stated he sent his samples to (b) (4) then left the product beaker covered with aluminum foil on the magnetic stirrer in the hood awaiting lab results. Mr. Cadden told us it could take anywhere from seven to ten days to obtain lab results. This beaker was observed in the laminar flow hood on 4/9/02. When questioned about this practice, Mr. Cadden stated he didn't want to waste the money on vials or the effort in transfilling the vials if the 4/6/02 lot failed testing. He stated he would transfill the vials upon receiving satisfactory lab results. It was discussed with Mr. Cadden that this was not an acceptable process for maintaining product sterility. Upon returning to the firm 4/10/02, the hood was clean and Mr. Cadden was asked the whereabouts of the 4/6/02 lot. He stated he received negative lab results the night before and had transfilled the lot into vials that morning. He accredited the positive endotoxins to the previous suspending agent. When asked if he had intentions of dispensing the lot, he said yes. The FDA investigator suggested to Mr. Cadden that he retest the 4/6/02 lot again after transfilling the vials since the product sat in a beaker for 5 days before transfilling into vials. The risks and impacts of non-sterile product to patients and his firm were discussed. Mr. Cadden agreed to retest the lot to confirm sterility and lack of endotoxins.

AREAS OF CONCERN

1) No accessible system for retrieving complaints/ADR reports. The firm claims that these documents are filed under patients or institutions, so they cannot be retrieved without that specific information. This prohibits the firm from identifying and tracking problems with individual medications or lot numbers.

2) Beyond use dating not substantiated. Preservative and Preservative Free product both receive the same expiration date of six months. There is no indication as to why/how this date was chosen and if laboratory data confirms these expiration dates.

3) Preservative vs. preservative free: The only label differentiation between the two is"***MDV***" and "PF".

4) Batch formula worksheets contain expired products. Mr. Cadden states they use in date materials, but probably have not updated their computer with correct lot numbers and dates. If raw materials were to be recalled, the firm would have trouble recalling their correct products since it is not apparent what lots are used for compounding medications.

5) Recordkeeping poor; lot numbers exist with no prescriptions linked as being dispensed. This would again prohibit timely recall of product to patients.

6) Positive endotoxin source still definitively unknown.

7) Non-sterile laminar flow hood environment: On the first day of the investigation, the clean room was observed. The laminar flow hood contained a beaker covered with aluminum foil on a magnetic stirrer. To the left of the beaker sat two-three bags of vial caps. To the right of the beaker sat a plastic (Rubbermaid-like) tray with miscellaneous items. When asked about this practice, Mr. Cadden acknowledged that there were unsterile items placed in the hood, but that he tried to wipe them down with alcohol before placing them inside the hood.

8) Autoclave: there is no SOP in place for use of or maintenance of the autoclave. Mrs. Cadden says the machine is "cleaned/flushed" [redacted] (b) (4) [redacted]. There is no documentation to support this statement, which was also noted by the state representative.

ASSIGNMENT QUESTIONS

The following represents information gathered to address specific questions included in the assignment. (Refer to the Assignment for the list of questions.) The information is supplied in the same sequence as the questions are asked in the assignment.

#1 This question is to be answered by the Mass Board of Pharmacy.

#2 yes

#3 •they sometimes have a [redacted] worth of product on hand
•[redacted] compounded
•dispension timeframe varies

#4 no, supposedly they do not sell wholesale

#5 •they do not dispense directly to patients
•yes, they provide to institutional pharmacy for dispensing to patients

#6 •they dispense [redacted] Rx's per month
•about [redacted] out of state

#7 see EIR

#8 not provided

#9 refer to EIR, some COA's on file

#10 no formal written complaint system
Supposedly complaints are kept within a Customer File.

DISCUSSION WITH MANAGEMENT

At the conclusion of inspection, an FD-483 List of Observations was issued to Barry J. Cadden, R.Ph, Director of Pharmacy & Owner of NEC. Also present was Beverly Gilroy, Administrative Assistant. Ms. Gilroy was present on 4/10/02 and at the closing on 4/16/02. Essentially Ms. Gilroy's presence was as 'note taker'.

All 3 FDA Investigators were present. The Observations included:

Observation #1 **Betamethasone Repository Injection (Betamethasone Acetate and Betamethasone Sodium Phosphate Suspension 6 mg/ml, a product which is intended to be sterile, is sampled for sterility and endotoxin testing immediately after sterilization of the bulk compounded product in [redacted] (b) (4) beaker. Individual vials of Betamethasone Repository are not filled until the test results for sterility and endotoxin (pyrogen) are received from the contract testing laboratory, a process which can take up to one week after the sterilization and sampling of the bulk product have occurred. While laboratory test results are pending, the [redacted] (b) (4) beaker and its contents are stored in the firm's laminar flow hood. The only other measure taken during this period to prevent recontamination of the bulk suspension is the use of a covering of multiple layers of aluminum foil over the mouth of the beaker.**

In response to item #1, Mr. Cadden stated it was not his usual practice to wait for up to one week before filling individual vials. He stated the practice of transfilling the vials normally occurs within a few hours after autoclaving, once cooling of the beaker with product mixture is complete. He stated the delay (of up to one week) in transfilling only occurred during the period in which product samples were testing positive for endotoxin, and it was for that reason he did not want to transfill the vials unless the sample received satisfactory laboratory analysis. It was explained to Mr. Cadden that these observations were discussed with him during the investigation, but Mr. Cadden declined to provide documentation showing this was not his normal practice. Mr. Cadden also stated that the beaker with product witnessed by FDA investigators actually didn't contain the betamethasone repository. Mr. Cadden was reminded of the contradictory information he provided to the investigators during the investigation.

Observation #2 **The samples taken immediately after completion of the autoclave sterilization cycle [redacted] (b) (4)) are not representative of product that remains in the original [redacted] (b) (4) beaker for up to one week past the time of sampling.**

In response to item #2, Mr. Cadden stated it was incorrect because item #1 was incorrect per above.

Observation #3 **The firm's validation of the autoclave cycle does not take into account the fact that the autoclaved bulk product is not transfilled into a final container/closure system (vials) for a period of up to one week.**

In response to item #3, Mr. Cadden stated it was incorrect because item #1 was incorrect per above.

Observation #4 **On at least one occasion, a lot number (Lot 02012002@27) was generated in the firm's computerized recordkeeping system, for which no associated records could be retrieved. It cannot be determined whether:**

- **this lot was distributed and records covering its preparation were never created or are no longer in existence, or**
- **the preparation of this lot never proceeded, but no record of its cancellation was entered into the recordkeeping system**

See Exhibit #'s 1 and 3 to support this observation.

In response to item #4, Mr. Cadden stated he agreed with this observation. He also stated that of the two possibilities, he agreed with the latter the most.

Mr. Cadden indicated he would consider a written response to the 483 Observations but was basically non-committal.

The inspection was concluded.

This investigative report was prepared by all 3 FDA Consumer Safety Officers. Primary responsibility for Headings included:

- C. DeSimone CSO, MedWatch Section
- K. Joyce, CSO, Operations Section
- M. Lookabaugh, Compliance Officer, Jurisdiction Section

EXHIBITS

#1 2002 Betamethasone lot number Printout
#2 Representative Formula Worksheet
#3 Prescription Log, 1 page
#4 Certificates of Analysis
(a) (b) (4)
(b) (b) (4)
#5 Representative Order Form
#6 Policies & Procedures, Sterile Products
#7 Representative Vial label
#8 (b) (4) Results
(a) #21119 (c) #21178
(b) #21162 (d) #21179

ATTACHMENTS

FD-482 Notice of Inspection
FD-483 List of Observations
FACTS Assignment ID #298826
HFD-330 Assignment dated 4/4/02
HFD-330 FAX dated 4/9/02, 18 pages
Related MedWatch Information sent to NWE-DO from Reporter

Constance DeSimone, CSO
US FDA NWE-DO

Kristina Joyce, CSO
US FDA NWE-DO

Mark Lookabaugh, CO
US FDA NWE-DO

CDS/KJ/ML/lcj:4/19,22,23,24/02 a:/NECPI.EIR

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