**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| One Montvale Avenue<br>Stoneham, MA 02180<br>(781)587-7500 Fax:(781)587-7556 | 1/11/2016-1/27/2016* |
| | FEI NUMBER<br>1000120535 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Stephen P. Berube , General Manager

| FIRM NAME | STREET ADDRESS |
|---|---|
| New England Home Therapies, Inc | 337 Turnpike Rd |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Southborough, MA 01772-1760 | Producer of Sterile Drugs |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Specifically:

- Gowns / coveralls with integral booties, face masks, and hair covers worn by personnel working in the ISO 5 zones (b) (4) Laminar Flow Hoods (b) (4), (b) (4) Laminar Flow TPN Hood (b) (4), and (b) (4) ) are not sterile.

- Chemical protective splash resistant gowns (knee length) donned by personnel working in Chemo Room ISO 5 (b) (4) and (b) (4) for preparation of cytotoxic sterile products are not sterile.

- Personnel were observed not to wash their hands prior to entry to the ISO 7 Anteroom and beginning to don cleanroom gowning components. Additionally, personnel apply non-sterile (b) (4) to hands prior to donning sterile gloves in preparation to work in ISO 5 hoods and (b) (4)

## OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed .

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Specifically:

- Drug production supplies such as (b) (4) and syringes (sterile (b) (4) ) are not sanitized prior to entry to ISO 5 zones in Hoods (b) (4) and (b) (4) used to produce sterile drugs. These supplies are removed from manufacturer's plastic lined corrugate boxes and bagged in the uncontrolled warehouse for subsequent passage into cleanrooms and use within ISO 5 zones.

- On 01/13/2016 we observed a Pharmacy Technician place a non sterile cleanroom (b) (4) beneath the aseptic operations to produce Methotrexate 31mg/1.24ml NS syringe, Qty: 2, in the ISO 5 (b) (4) in the Chemo Room. (b) (4) was observed in the ISO 5 TPN (Total Parenteral Nutrition) Hood (b) (4) (b) (4) .

- Personnel engaged in cleaning and aseptic processing in ISO 5 zones reach with their arms into Hoods (b) (4) and (b) (4) to manipulate equipment and components while wearing non sterile gowns.

**OBSERVATION 3**

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically:

- Staining was observed on the HEPA filter in use on ISO 5 (b) (4) Laminar flow Hood (b) (4) used to produce sterile drugs. The HEPA filter had approximately 2" x 1" and 1" round pale yellow stains centered on the lower right quadrant.

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- Staining was observed on the HEPA filter in use on ISO 5 (b) (4) Laminar flow Hood (b) (4) used to produce sterile drugs. The HEPA filter had an approximately 8" x 3" coffee colored stain on the lower right quadrant bottom edge. The stain was said to be from a spill of (b) (4) ) which occurred on or about August 2015. Although the hood was said to be currently removed from service due to the staining there was no documented or visual indication of the operational status of the hood.
  Additionally, there was no documented evaluation of the condition of the hood HEPA filter and the potential impact on the environment inside and adjacent to the hood or any plan for corrective actions.

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**OBSERVATION 4**
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically:

- Viable Air and Surface Environmental monitoring results are not representative of routine operating conditions. In (b) (4) in 2015 environmental monitoring was performed on the (b) (4) of cleanrooms and equipment. On the (b) (4) environmental monitoring (b) (4) by (b) (4) and bacteria and mold (Cladosporium spp.) was recovered in an active air sample taken on (b) (4) in the (b) (4) .

- (b) (4) Personnel Monitoring (finger tips (b) (4) ) is performed (b) (4) and does not test personnel under routine or worst case conditions following aseptic processing activities.

- Differential pressures between ISO 7 cleanrooms, ISO 5 Hoods, and ISO 5 (b) (4)

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(b) (4) to adjacent spaces are routinely monitored only (b) (4) and not on a more frequent basis during use for producing sterile drugs.

- Total airborne particulates are routinely monitored in the (b) (4) zones (b) (4) and not on a more frequent basis during production of sterile drugs.
- You do not follow your internal procedure CLIN-PH307, Effective: 03/01/2007, Environmental monitoring of the Clean Room. For example:
  - (b) (4) such as (b) (4) are not sampled (b) (4) (b) (4) (b) (4).
  - Personnel (fingertips) are not sampled (b) (4) (b) (4).
  - (b) (4) to sample the (b) (4) in the area (b) (4).

**OBSERVATION 5**

The operations relating to the processing of penicillin are not performed in facilities separate from those used for other drug products for human use.

Specifically, your cleanroom design and operational procedures do not provide adequate segregation of ß Lactam antibiotics and cytotoxic products from general drugs produced in your facility as follows:

- ß Lactam antibiotics are processed (b) (4) For example on 01/13/2016 you produced (b) (4).

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Additionally, you do not have a written spill plan for cleanup of ß Lactam antibiotics.

- Your Anteroom is a common space (b) (4) and may contribute to transfer of contamination throughout your facility. For example: Personnel don a chemical protective splash resistant gown (knee length) and new sterile gloves over their cleanroom gown upon entering the Chemo Room for processing. When finished, these personnel remove the chemical protective gown and gloves (b) (4). Then they (b) (4) so the foot covering contacts all spaces transited (Chemo Room and Anteroom).

- On 01/14/2016 a wheeled cart was observed standing over the sticky mat located on the Anteroom side of the Chemo Room door. There is potential for hazardous materials handled in the Chemo Room to be carried out of the area on the feet of personnel exiting the Chemo Room. The first contact point of personnel outside the Chemo Room is on the sticky mat. Potential hazardous substances may be transferred to the cart wheels and distributed through the Anteroom and adjacent areas.

- Written procedures do not restrain personnel from working in the buffer room following the aseptic processing of cytotoxic sterile products and do not require donning a new cleanroom coverall before such work.

**OBSERVATION 6**

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Buildings used in the processing of a drug product are not maintained in a good state of repair.

Specifically:

- The window between the ISO 7 Buffer Room and the ISO 7 Anteroom and the window between the ISO 7 Buffer Room and unclassified Pharmacy have wood frames and trim. Painted trim of both windows observed in the ISO 7 Buffer room was chipped down to bare wood. The painted trim of the window in the ISO 7 Anteroom was also observed to be chipped exposing bare wood.
- During the walkthrough of the facility on 01/11/2015, the following conditions were observed:
  - A gap under the door separating the facility's pharmacy area from the adjacent, uncontrolled warehouse
  - Gaps under and around the uncontrolled warehouse shipping and receiving bay doors, as well as gaps along the sides of the loading bay dock levelers
  - Apparent spider webs around the shipping and receiving bay doors in the uncontrolled warehouse
- The firm lacks an effective pest control plan, including controls for flying insects in the uncontrolled warehouse adjacent to the pharmacy area. The uncontrolled warehouse is used to [redacted (b) (4)]. The outer packaging of these components is not sanitized before entry to ISO 5 hoods and [redacted (b) (4)].

**OBSERVATION 7**
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

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Specifically:

- Non-sterile wipes are used in the ISO 5 critical zones to clean and sanitize equipment surfaces with (b) (4) and other sanitizers. Additionally, non-sterile (b) (4) are used to (b) (4) and (b) (4) beneath aseptic connections.

- Procedures do not specify the concentration of (b) (4) in the (b) (4) (b) (4) solution, (b) (4) for use in cleanroom and equipment sanitization in ISO 5 zones. Also, procedures do not specify the contact time necessary for surface disinfection where (b) (4) is used as a sanitizing agent. Additionally, unlabeled spray bottles said to contain (b) (4) were observed in the Buffer Room and Anteroom. The date of preparation of the solution in the unlabeled bottles was not recorded to ensure the (b) (4) was still effective.

- Cleaning and sanitization procedures lack sufficient detail for cleaning the wheeled carts to effectively prevent the spread of contamination between the Chemo Room, Buffer Room, and Anteroom. Procedures do not detail the cleaning and sanitization of cart wheels.

- A sink used by personnel for hand washing during gowning is located in the Anteroom common space transited by personnel and equipment moving to and from the Buffer Room and Chemo Room.

**OBSERVATION 8**

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, you do not have adequate written investigations into failures and discrepancies that have the potential to adversely impact drug sterility and other quality attributes. Your investigations do not

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include an assessment of the root cause of failures and discrepancies and they do not present any appropriate corrective and preventive actions. For example:

- Environmental sampling performed on 05/20/2015 recovered 3 CFU bacteria (Lactococcus spp.) and one mold (Cladosporium spp.) in an air sample (b) (4) taken in the (b) (4). You did not conduct a documented investigation to include evaluation of the potential impact on drugs produced in the area and determine the root cause of the findings and any appropriate corrective actions. Your response was limited to retrieval of drugs produced in the area, repeat (b) (4) of cleanroom facilities and equipment surfaces, and resampling.

- Environmental sampling performed on 10/13/2015 recovered one mold (Cladosporium spp.) in an air sample (b) (4) taken in the (b) (4). You did not conduct a documented investigation to include evaluation of the potential impact on drugs produced in the area and determine the root cause of the findings and any appropriate corrective actions. Your response was limited to retrieval of drugs produced in the area, repeat (b) (4) of cleanroom facilities and equipment surfaces, and resampling.

- On (b) (4) your cleanroom air systems contractor discovered during routine (b) (4) certification that Hood (b) (4) (Chemo Room – (b) (4)) failed the Inflow Velocity test (said to be found at 90 FPM). After replacing a booster fan in the duct servicing (b) (4)(b) (4), Hoods (b) (4), Inflow Velocity was within the specification (b) (4) during retesting on (b) (4) Your response to this event failed to adequately investigate the potential impact on cleanrooms and drug products especially considering any potential to contaminate with cytotoxic drug compounds as follows:

    - You did not have a report of as found results to enable thorough assessment of the performance of Hood (b) (4) prior to repair.

    - You did not document an investigation to consider potential impact on compounded drugs.

- You did not document an investigation considering that (b) (4) of the Chemo Room air exhaust is through the (b) (4) and the effect of potentially lower velocity and volume of air drawn through the (b) (4) on the air balance relative to adjacent rooms. Lacking such an investigation, you did not provide assurance that the designed pressure cascades were maintained to prevent the release of cytotoxic drug compounds in your cleanroom facility.

**OBSERVATION 9**

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

Specifically:

- Air flow pattern testing (smoke studies) performed in ISO 5 zones do not include dynamic assessment of (b) (4), Hoods (b) (4), used to produce sterile cytotoxic drugs.
- You do not document review of the manufacturer's certificate of analysis, including growth promotion data, and acceptance of each lot of media used to validate the aseptic simulations (media fills) supporting your aseptic process controls.

**OBSERVATION 10**

Routine calibration of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance.

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Specifically, you do not have a calibration program to include routine calibration of equipment critical to operation of the cleanrooms and support of aseptic processing. For example:

- Mechanical manometers used to monitor performance of ISO 5 Hoods (b) (4) and (b) (4) used to produce sterile drugs are not calibrated on any routine interval.

- Mechanical manometers used to monitor the differential pressures and pressure cascade between the Buffer Room, Anteroom, Chemo Room, and the Pharmacy are not calibrated on any routine interval.

- The (b) (4) thermometers used to (b) (4) in incubators including Incubator (b) (4) are not calibrated on any routine interval. Incubator (b) (4) is used for incubation of environmental and personnel monitoring samples and media fills.

**OBSERVATION 11**

Procedures describing the handling of written and oral complaints related to drug products are deficiently written or followed .

Specifically:

- Adverse Drug Reactions (ADR) are not investigated and finalized on a timely basis. During the period Jan 2015 to Aug 2015 there were nine ADR's reported. At least two of those were open for nearly one year and two were finalized after six months.

- ADR investigations do not include an adequate assessment or determination of root cause. Your investigations fail to consider the potential or rule out product quality or drug production defects,

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such as contamination or incorrect potency, to cause adverse reactions experienced by patients. All cases reviewed during the inspection, including those reporting fever and injection site rash, were considered to be the result of patient allergic response or common not unexpected side effects.

***DATES OF INSPECTION**

1/11/2016(Mon),1/12/2016(Tue),1/13/2016(Wed),1/14/2016(Thu),1/27/2016(Wed)

1/27/2016

X Jonathan G Matrisciano

Jonathan G Matrisciano
Investigator
Signed by: Jonathan G. Matrisciano -S

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