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

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 6000 Metro Drive, Suite 101<br>Baltimore, MD 21215<br>(410)779-5455 Fax:(410)779-5707 | 3/19/2018-4/12/2018*<br>FEI NUMBER<br>1110315 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kimberly L. Kupec, Head of OSD Quality Morgantown

| FIRM NAME | STREET ADDRESS |
|---|---|
| Mylan Pharmaceuticals Inc. | 781 Chestnut Ridge Rd |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Morgantown, WV 26505-2730 | Finished Drug Product Manufacturer |

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

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically,

Specifically, we observed numerous instances of a lack of appropriate oversight by the Quality Unit and a failure to follow your procedure, "*Organization of the Quality Unit*" (Document Number: MPI-SOP-ADM-ALL-0004, Version 7.0, Effective 30 OCT 2017). The observations that follow demonstrate ways in which the Quality Unit:

- Was not always "involved in the approval of change controls, as applicable to commercial product" (Section 6.13)
- Did not adequately "review and approve equipment and facilities associated with the manufacture, packaging, labeling and holding of drug product" (Section 6.14)

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- Did not properly "approve … validation protocols/reports for production processes, analytical methods or electronic systems that may impact the strength, quality, safety, efficacy, identity or purity of the finished drug product or API" (Section 6.15)
- Did not "along with Senior Management … ensure continuing suitability and effectiveness of quality systems through governance including, but not limited to, Trending Review Board, Annual Product Review, Self-Inspection, and Quality Site Council" (Section 6.29)
- Did not ensure "compliance with all applicable regulations" (Section 6.30)

FACILITIES & EQUIPMENT SYSTEM

**OBSERVATION 2**

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

Specifically,

A. Your Quality Unit (QU) failed to adequately validate the cleaning processes of all manufacturing equipment and utensils shared between your 230 oral dosage drug products (potent and non-

potent) to ensure no cross-contamination of active ingredients and detergent occur between products. Manufacturing equipment and utensils are shared between non-potent and potent drugs including Fentanyl Citrate (potent opioid), Liothyronine Sodium (hormone), Prednisolone Sodium Phosphate (steroid), (b) (4) Cabergoline (potent dopamine agonist), and (b) (4) as well as low-therapeutic range drugs such as Levothyroxine Sodium. Some of the deficiencies include but are not limited to:

1) The Cleaning Validation Reports for the worst-case drug products for each category type (i.e. immediate release tablets, extended-release tablets, immediate release capsules, extended release capsules, mixed products, high potent, powders, and high volume products) were limited to (b) (4) swab test results from at least (b) (4) pieces of equipment including (b) (4) equipment for different drug products manufactured between 2010 and 2016 without any documented rationale for their selection to represent validation of the cleaning process. In addition, results were documented only as "Pass" or "Fail" for the selected equipment, and there was no interpretation of the impact of the entire manufacturing equipment train against the residue limits in the finished drug product. For example, Report for Cleaning Validation/Verification Program Utilizing (b) (4) (MPI-SOP-QAS-CLV-0004)-2010 approved on 10/5/16 includes a listing of ten (10) drug products identified by your firm as high-risk products for which test results for "Chemical" and "Micro" were reported as "Pass" or "Fail" for (b) (4) pieces of equipment per product that were swabbed between 2010 and 2013. There was no documented rationale for their selection and an evaluation of the overall residue detected across the manufacturing equipment train.

2) According to the 2016 Annual Cleaning Validation Program Review, approved a year

late on 2/28/18, trends for inadequate cleaning were identified for (b) (4) departments that were evaluated; (b) (4) (b) (4) No trends were identified for the (b) (4) departments; however, during the inspection, significant deficiencies in the cleaning process of the (b) (4) encapsulator were identified. Your Quality Unit's conclusion in this report that "*interim controls have been implemented for each identified department and therefore sufficient control exists to ensure product safety*" was not supported by the cleaning execution failure trends identified in most departments. In addition, significant deficiencies found during this inspection in cleaning procedures, cleaning validation, swabbing procedures and testing, and inadequate investigations do not support your conclusion that sufficient controls exist to ensure product safety.

3) Similarly, according to the Morgantown Cleaning Validation: 2017 Annual Program Review approved on 3/16/18, your firm continues to experience about a (b) (4) % swab failure for cleaning [68 out of (b) (4) initial swabs taken from selected manufacturing equipment during Jan-Dec 2017 produced aberrant results (41 failures and 27 inconclusive results)] indicating that corrective action has not been effective. Furthermore, the 68 cleaning failures documented in the report did not include 52 visual cleaning failures that occurred in Manufacturing since March 2017 for which a swab or an investigation were not performed. In addition, swab results that generated an unknown or extraneous peak were categorized as "inconclusive" and invalidated if a re-swab in another location of the equipment yielded passing results. Your Quality Unit's decision for invalidating swab results with extraneous peaks based on re-swab results in another location of the equipment lacked sound scientific rationale.

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4) Manufacturing investigations of cleaning failures did not extend to other batches. For example, Manufacturing Investigation Report (MIR) # 1415886 was opened on 1/10/18 (still open) to investigate yellow powder residue observed in the encapsulation machine (b) (4) # 2090 in NEX 374 after the encapsulation campaign of (b) (4) batches of Verapamil HCl ER Capsules (white powder). The previous drug product, Nitrofurantoin Mono/Macro Capsules USP 100 mg, consists of two yellow Mono tablets and one orange macro tablet. According to your investigation, the yellow powder dust coming from the mono tablets is a fine powder that may adhere to surfaces and accumulate on exposed areas of the machine. During an AQL inspection, this yellow powder was observed on the (b) (4) of the (b) (4) and on the (b) (4) that (b) (4) the (b) (4); this is located above the (b) (4) where capsules are filled. Most significantly, the yellow powder residue was observed after a (b) (4) between products, (b) (4) (b) (4) between strengths, as well as multiple visual inspections by manufacturing and QA after every clean. The root cause was identified as inadequate cleaning procedures (MPI-SOP-MFG-ENC-0008) that did not require removal of the (b) (4) and (b) (4) for thorough cleaning, as well as the failure of manufacturing and QA personnel to perform thorough visual inspections of the equipment before release. Your firm failed to extend this investigation to all batches manufactured in this and similar encapsulation equipment that could not be cleaned adequately as per the cleaning procedures. A review of the Cleaning and Maintenance Log Book for (b) (4) # 2090 between November 2016 and January 2018 showed numerous batches of different drug products including Nutrofurantoin Monohydrate/Macrocrystals Capsules, Amlodipine/Benazepril HCl capsules, Tolteridone Tartrate ER Capsules, and Verapamil HCl ER Capsules that were previously encapsulated in this equipment, but your QU did not extend the investigation to these batches.

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5) Your firm lacked written procedures and adequate controls to track use of major and ancillary equipment required to be swabbed for active residue after manufacturing potent and high-risk drug products to ensure they were always swabbed and had passing results prior to release

1. For example, on 02/09/16, you processed a batch of a developmental product called (b) (4) on (b) (4) (b) (4) Encapsulator #2090. At that time, this product was not evaluated as required by your written procedure titled "(b) (4) (b) (4) " (Document Number: MPI-SOP-QAS-GEN-0001, Version 5.0, Effective 15 Jan 2016). No cleaning verification was performed prior to releasing the equipment for use to encapsulate other commercial products. The next product processed on this equipment was Amlodipine/Benazepril HCl Capsules USP 10mg/20mg Lot #3074852 on 02/25/16.

   Currently your cleaning validation (b) (4) ranks this product as your (b) (4) product in terms of cleaning because of its (b) (4) and (b) (4) coupled with (b) (4) At the time of this event, (b) (4) Encapsulator (b) (4) were not being fully (b) (4) in the process of cleaning these pieces of equipment.

2. The Quality Unit fails to document cleaning verification swab samples submitted to the QC laboratory for analysis. Based on this deficiency, we

were unable to assess the entirety of cleaning verification swab samples taken and analyzed. In addition, several employees mentioned that there have been multiple instances in which swab samples were "missed", in which equipment was not swabbed but was used to further manufacture subsequent products. The equipment not swabbed but used to further manufacture likely includes batches distributed within the US. Since a system has not been established to track cleaning verification swab samples, we could not determine the potential impact of the missed swabs.

6) The 2013-2014 cleaning validation recovery studies associated with the recovery of cleaning agent (b) (4) from (b) (4) including (b) (4) (b) (4) have not been completed and reviewed as required, and no subsequent such studies were presented. These cleaning agent recovery studies were initiated to validate the methods to support acceptable removal of detergent after cleaning. (b) (4) is currently and routinely used for equipment cleaning activities at this site.

   For example, after production of Fentanyl Citrate buccal tablets 100mcg, lot X17-MTS-043, tablet press #617 was cleaned with (b) (4). This same tablet press was subsequently used in production of Liothyronine Sodium Tablets 5mcg lots 3081575, 3081576, and 3081577.

   This same press was also later used in production of the Fentanyl Citrate buccal tablet PPQ batches.

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B. During the walk-through of the manufacturing area on 03/27/2018 we observed the following instances of inadequate equipment cleaning after the equipment and room had been released by the Quality Unit:

1) An unknown crystal-like yellow residue was visually observed on the product support screen of the (b) (4) (Equipment ID #7560) in Room NEX 409. According to the "(b) (4) Cleaning Sheet", the equipment cleaning was completed on 03/22/2018 and released by Quality on 03/22/2018. Despite the operator performing the cleaning having prior knowledge that the effectiveness of the cleaning would be evaluated with cleaning swabs on 03/21/2018 and the swabs having passing results, the equipment was observed to not be visibly clean at the time of the walkthrough on 03/27/2018.

   The last product manufactured with the equipment was Verapamil HCl SR Tablets, 240mg, Process #3096325 on 03/15/2018. Additionally, this equipment is used, but is not limited to the manufacturing of Verapamil HCl Tablets, Diltiazem HCl ER Tablets, (b) (4), and Zolpidem Tartrate Tablets.

2) Residue was observed on the capsule transport parts and powder dosing parts of the (b) (4) Encapsulator (Equipment ID #3992) located in Room #NEX 372. The equipment is used in the manufacturing process of Diltiazem HCl ER Capsules in various strengths including 120mg, 180mg, and 240mg. According to the "(b) (4) (b) (4) Encapsulation Room/Equipment Cleaning Checklist", the cleaning was completed on 03/22/18 and released by Quality on 03/22/18. Note: Refer to additional 483 observations related to cleaning and cross contamination concerns related to (b) (4)

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Encapsulators.

3) Black particles were observed inside the Coater (Equipment ID #653) located in Room #BB-206. According to the (b) (4) Coater – Room and Equipment Cleaning Checklist", the cleaning of the equipment was completed on 03/27/2018 and released by Quality on 03/27/2018. Your firm's Head of Plant Operations explained the particles were from a gasket that was removed from the Coater to reach an area with water spots. The Coater is used in the manufacturing process for various products such as, but not limited to Ciprofloxacin ER Tablets, Perphenazine and Amitriptyline Tablets, and Albuterol.

## OBSERVATION 3

Written procedures are not followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

During a walkthrough of the facility on 3/19/18, room NEX438 was observed to be ready to clean following milling of Verapamil HCl 240mg SR Tablets (Lot #3096325). On 3/20/18, cleaning swab samples were collected from the (b) (4) (#23494) used to process this batch after it was cleaned. A laboratory investigation (LIR #1477185) was opened to document the cleaning swab failure for the active ingredient, Verapamil. The swab failure location was on the (b) (4) of the (b) (4)

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On 3/21/18, a manufacturing investigation (MIR #1478099) was opened. The investigation states that residue was observed on the equipment after the active swab failure on the (b) (4) #23494 in NEX438. Photographs of the equipment taken during the investigation shows residue on various product contact parts and the stainless-steel product contact surfaces are pitted and scraped. The gasket was found to be torn.

Your written procedure titled "(b) (4) (Document Number MPI-SOP-MFG-FTZ-0002) requires in Section 8.1.1 that the cleaning checklist be completed when performing a complete clean.

The cleaning checklist, completed on 3/19/18, failed to document any concerns with the equipment. The second person sign off failed to document any problems with the equipment. The QA check on the equipment failed to document any concerns with the state of the equipment.

Section 8.1.3 of the procedure states that "area leads will inspect any damaged gaskets when necessary and if the gasket damage appears to have occurred during processing then an investigation into potential product impact will be initiated…"

The tear in the gasket was not identified until after a cleaning swab test result was found to be positive and an investigation was opened.

## OBSERVATION 4

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Procedures for the cleaning and maintenance of equipment are deficient regarding inspection of the equipment for cleanliness immediately before use.

Specifically,

C. Your firm's written procedure titled '(b) (4) (b) (4) ' (Document Number MPI-SOP-QAO-OPS-0032) is deficient in that it does not require an investigation to be opened when equipment is found to be not visibly clean upon AQL inspection.

After it is determined that a full re-clean is needed to clean the equipment and/or room is a Cleaning Effectiveness Form completed. However, section 9.2 of the procedure states that "near misses will also be tracked".

After equipment is initially cleaned, a second person visually inspects the equipment. If the equipment is found to be not visually clean during the second person check, then the equipment is re-cleaned. The number of times that equipment needs to be re-cleaned after the second person check is not recorded, tracked or trended. Section 3.3.1 of the procedure states that it is site leadership responsibility to "review and communicate cleaning effectiveness tracking and trending metrics".

Since March 2017, there have been a total of 52 instances of equipment or processing areas found to be not visibly clean upon AQL inspection. Additionally, the packaging department has not tracked or reported cleaning data as part of this program.

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Since 01/05/2017, there have been 21 instances where equipment was found to be not visually clean after the initial clean, second person check, and AQL inspection had already been performed. These instances were detected only when equipment was about to be swabbed for cleaning verification or the cleaning swabs tested positive for active or detergent residues.

6 of the 21 instances, were for active ingredient detection of products considered to be either (b) (4) and/or classified as a high cleaning risk (based on (b) (4) or a (b) (4) (b) (4) product including, but not limited to, Paliperodine, Levothyroxine, Prednisolone, and Buprenorphine.

These instances occurred despite operators that perform the cleaning being aware that cleaning swabs would be collected prior to them cleaning the equipment.

D. During an inspection of the manufacturing area, we observed Encapsulation (b) (4) 2610 in NEX361 which was cleaned and in the process of being reassembled. We requested the previous cleaning verification swab data for this equipment but was informed by the cleaning validation team that there is no record of this piece of equipment being swabbed ever.

E. In review of the cleaning verification process we observed Divalproex Sodium ER Tablets compressed using (b) (4) Tablet Press #1920 and #60. At least 4 LIRs have been opened due to cleaning verification swab failures for this product using this Tablet Press #1920. We requested

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all cleaning verification swab data for (b) (4) Tablet Press#60 but was informed by the cleaning validation team that (b) (4) Tablet Press #60 was never swabbed. Tablet press #60 was used at least (b) (4) for over five different products including Divalproex Sodium ER Tablets.

LABORATORY SYSTEM

**OBSERVATION 5**

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

F. Laboratory analyses are repeated until passing results are obtained. In our limited review, we observed the following instances in which failures for cleaning verification tests for product or detergent residues were obtained. Investigations conducted in each instance included various actions (including re-cleaning and re-swabbing), but they failed to consider a thorough assessment of the adequacy of the cleaning procedure.

1) While reviewing swab sample analysis for active residue for Divalproex Sodium ER Tablets manufactured on the (b) (4) Tablet Press #1920 or (b) (4) #361, going back to

August 2016, we observed multiple instances of the components of both equipment units being re-cleaned and re-swabbed multiple times until passing results were obtained. For example:

1. Following the production of Divalproex Sodium ER Tablets batch# 3078594 in August 2016, cleaning and swabbing was repeated 2 times until passing results were obtained for the (b) (4) Tablet Press #1920.

2. Following the production of Divalproex Sodium ER Tablets batch # 3082027 in March 2017, cleaning and swabbing was repeated at least five times until passing results were obtained for some components. Two components, the (b) (4) and (b) (4) for the (b) (4) for (b) (4) Tablet Press #1920, were removed from production into the lab for further testing. There has still been no determination into the residues present on these components that were removed from production.

3. Following the production of Divalproex Sodium ER Tablets batch # 3085464 in June 2017, re-cleaning and re-swabbing was conducted multiple times until passing results were obtained for some components including (b) (4) and (b) (4) for the (b) (4) for (b) (4) Tablet Press #1920.

4. Following the production of Divalproex Sodium ER Tablets batch # 3090111 in August 2017, re-cleaning and re-swabbing was conducted multiple times for the (b) (4) #361. In

addition, multiple instances of visual failures were observed in the production area after the full re-clean. The investigation did not determine the source of the failure.

5. Following the production of Divalproex Sodium ER Tablets batch #3092516 in January 2018, re-swabbing was conducted multiple times for the (b) (4) for (b) (4) Tablet Press #1920 until passing results were obtained. Upon the initial failed swab results for the (b) (4) (b) (4) of this equipment cleaning validation management determined this part to be worn and unsuitable for continued use and was removed from service without determining the source of the inconclusive result.

2) During the (b) (4) analysis for detergent residues after the (b) (4) of product Paliperidone ER Tablets 1.5mg, Lot# 3093034, out-of-specification (OOS) results were obtained for the following product contact components: (b) (4). (b) (4) were re-swabbed and re-analyzed three additional times until a passing result was obtained. There is no information on whether cleanings were performed prior to the re-swabbing every time.

3) During the (b) (4) analysis for detergent residues after the (b) (4) of product Paliperidone ER Tablets 9mg, Lot# 3094332, OOS results were obtained for the following product contact component: (b) (4). The (b) (4) was re-swabbed and re-analyzed

two additional times until a passing result was obtained.

4) During the (b) (4) analysis for detergent residues after the granulation using the (b) (4) for product Verapamil Tablets 240mg, Lot# 3096325, OOS results were obtained for the following product contact component (b) (4) The component was re-cleaned and re-swabbed one additional time until a passing result was obtained.

5) During the (b) (4) analysis for detergent residues after compression of product Cyclobenzaprine Tablets 10mg, Lot# 3094889, OOS results were obtained for the following product contact component (b) (4) The (b) (4) was re-rinsed and re-swabbed one additional time until a passing result was obtained.

6) During the (b) (4) analysis for detergent residues after compression of product Ondansetron Tablets 4mg, Lot# 3095187, OOS results were obtained for the following product contact components (b) (4) The (b) (4) were re-cleaned and re-swabbed one additional time until passing results were obtained.

G. We observed the practice of conducting (b) (4) on HPLC and GCs prior to official analyses. This practice is a corrective action to an observation cited during the November 2016

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FDA inspection in which (b) (4) were being performed prior to official analyses. The corrective action of allowing for (b) (4) is not adequate because there is no defined procedure or limit for conducting (b) (4) In our limited review of chromatography data, we found instances in which (b) (4) were performed for as many as (b) (4) In one of the instances we observed, there were (b) (4) made within (b) (4) set for Atenolol USP API (Batch #402851)

H. The Quality Unit's retrospective review of (b) (4) on liquid chromatography systems, conducted as a commitment to the Agency, does not include a review of the (b) (4) in project folders not labeled with a product name. For example, the folders related to cleaning and method validations have not been included.

I. During an inspection of the Quality Control laboratories, we observed that the (b) (4) calibration for the (b) (4) does not include a check for accuracy on the (b) (4) (b) (4) used for standardizing the (b) (4) . Without a check of this value the (b) (4) used for (b) (4) the sample material may be inaccurate. This analysis is utilized to test more than (b) (4) APIs and more than (b) (4) finished products, including (b) (4) and Fentanyl Citrate Buccal Tablets. We observed at least 10 Laboratory Investigation Reports (LIRs) for assay samples which were out of trend (OOT) and required (b) (4) (b) (4)

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| Kimberly L. Kupec, Head of OSD Quality Morgantown | |
| FIRM NAME<br>Mylan Pharmaceuticals Inc. | STREET ADDRESS<br>781 Chestnut Ridge Rd |
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## OBSERVATION 6

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Specifically,

According to your firm's MPI-SOP-QAC-STB-0002 "*Finished Product Retention Samples*" rev. 5.0, the annual inspection of the reserve samples is limited to inspection of the labeling and container closure system without visually inspecting the drug product, i.e. tablets and capsules, for signs of deterioration.

PRODUCTION SYSTEM

## OBSERVATION 7

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

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A. Your firm lacks adequate process controls and procedures to ensure properly qualified tablet presses and validated compression parameters are used for each of the drug products (tablets) manufactured by your firm to ensure process consistency and compliance with in-process and finished product specifications. For example,

1) Your production department routinely transfers tablet presses (a total of (b) (4) presses of various models (b) (4) between production rooms depending on production scheduling needs. This can result in the table press being connected to a (b) (4) (b) (4) depending on the design of the production room. Your Quality Unit (QU) failed to:

   i. Evaluate the impact of (b) (4) on the (b) (4) of the powder blend of each drug product to demonstrate that no segregation occurs.

   ii. Establish written procedures to ensure the (b) (4) used during routine production is the same used during Process Performance Qualifications (PPQs) of each drug product.

   iii. Establish written procedures to re-qualify or evaluate the tablet presses after transfer to a different production room. For example, the Installation and Operational Qualification (IQ/OQ) for the (b) (4) (i.e. (b) (4) ) Tablet Press # 7666 was performed on 6/21/10 in Room NEX-160 and it was not identified as portable equipment. This tablet press was observed in Room NEX-135 during the compression of Diphenoxylate HCl/Atropine Sulfate Tablets, lot # 3094914 on 3/19/18. Your firm considers all tablet presses as portable equipment moved with

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forklifts but lacks written procedures for their control. No change control or documentation was provided to support this transfer.

2) Written work instructions MPI-DOC-MFG-COP-WI-0024 [(b) (4) (b) (4)] and MPI-DOC-MFG-COP-SET-0008 [(b) (4)] are not consistently followed by operators and potential critical parameters such as compression force and pre-compression force have not been established for each drug product in tablet form. For example, variability in target compression speeds and compression/pre-compression forces were observed when comparing the Compression Record Sheets for Diphenoxylate HCl/Atropine Sulfate tablets 2.5/0.025 mg as follows:

| Batch # | Target Speed Setting (RPM) | Main Compression Force (Actual) | Pre-Compression Force (Actual) |
|---|---|---|---|
| MPI-DOC-MFG-COP-SET-0008 (Approximate Press Start-Up Settings) | (b) (4) recommended speed) | Not specified | Not specified |
| (b) (4) (1/24/05) Validation | (b) (4) RPMs | Not documented | 0.2-3.0 |
| 3085839 (4/25/17) | (b) (4) RPMs (b) (4) | 7.9-8.9 | 0.0-0.9 |
| 3085840 (4/27/17) | (b) (4) RPMs (b) (4) | 8.3-10.4 | 0.0-0.10 |
| 3094914 (3/19/18) | (b) (4) RPMs (b) (4) | 4.9-5.20 | 1.0-1.8 |

In addition, during the tablet press set-up of Diphenoxylate HCl/Atropine Sulfate 2.5/0.25 mg tablets, lot # 3094914 on 3/19/18, we found that the press start-up settings for this

product as established in MPI-DOC-MFG-COP-SET-0008 "(b) (4) (b) (4) " were not followed because the tablet press being used (Equip. # 7666 (b) (4) was not listed for this product and therefore, there were no start-up settings established. Still, set-up for compression was initiated based on parameters used for a batch manufactured a year prior, and upon interview with the Compression Area Lead, it was found the operator was having issues achieving tablet hardness. Since February 2016, a total of (b) (4) batches of Diphenoxylate HCl/Atropine Sulfate 2.5/0.25 mg tablets have been compressed on a (b) (4) tablet press and released, even though start-up settings for this tablet press have not been established as per MPI-DOC-MFG-COP-WI-0024 and MPI-DOC-MFG-COP-SET-0008.

B. Your firm failed to implement adequate process control parameters for the manufacturing of Metolazone 2.5 mg Tablets to ensure the drug product always meets finished product specifications. From March 2017 to October 2017, your firm opened five (5) Manufacturing Investigation Reports (MIRs) (PR#s: 1142941, 1188055, 1244747, 1248472 and 1344323) for OOT/OOS content uniformity results involving seven (7) batches (lot #s: 3079406, 3085880, 3082388, 3082389, 3082390, 3082391 & 3089248), of which one (lot # 3082388) was rejected for OOS content uniformity results. A product trend for atypical content uniformity results was identified on 6/9/17 as PR# 1225491. However, corrective and preventive actions (CAPAs # 1009442 & 1205749) such as (b) (4) (b) (4) (b) (4) have not successfully mitigated powder segregation in the blend and content uniformity issues in the finished drug product.

C. Your Quality Unit (QU) implemented changes outside of the approved specifications and processing parameters ranges for weight and hardness of Doxycycline Hyclate Delayed-release

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Tablets, USP 200 mg tablets (ANDA 090431) (PR # 918028) (b) (4) without adequate evaluation of the impact of the changes on this product over its shelf life. Your firm re-validated the process with the new formulation and parameters in July 2016 with (b) (4) (b) (4) but did not conduct accelerated stability studies. Instead, the (b) (4) validation batch was placed on long-term stability. During the stability study at (b) (4)-month (Aug 2017), the dissolution profile of the (b) (4) Validation Batch # 2007278 showed a downward trend of (b) (4)% between the (b) (4) results of the initial and (b) (4)-month test intervals which was attributed to normal processing and testing variability according to your investigations (LIR # 1288061 & MIR # 1288174). On 7/24/17, the (b) (4) manufactured batch (Lot # 3086421) showed "depressed dissolution results" within specifications during finished product testing but was rejected due to statistical analysis by your laboratory showing the batch would not meet dissolution specifications throughout its shelf life of 24 months based on the performance of the (b) (4) validation batch (LIR # 1265485 & MIR # 1304799). Your QU did not determine a root cause for the slower dissolution profiles and failed to extend the investigations to other potentially affected batches that were not placed on stability.

D. Written procedures including batch record instructions are not established for specified compression force ranges/limits to be maintained during tablet compression operations. Specifically, for the following pending application drug products, compression force range specifications had not been established and set forth in written instructions as supported by development data:

(b) (4)

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**OBSERVATION 8**

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically,

1. Your firm's Work Instructions such as MPI-DOC-MFG-COP-WI-0021 (b) (4) (b) (4) " MPI-DOC-MFG-COP-WI-0024 "(b) (4) (b) (4) " containing detailed instructions about compression set-up cannot be accessed by operators through your firm's electronic document system when conducting operations and they are not allowed to print them in order to be able to follow the specific steps.

2. At 0548 on 3/19/18, Clozapine 200mg Tablets (Lot# 3092858) started compression in Room #NEX138 on Tablet Press #2748. At (b) (4) on the same day, the machine was shut down due to tablets "sticking". At (b) (4) on the same day, (b) (4) separate in-process quality checks recorded in the room activity log that the machine was down.
At (b) (4), during a walk-through of the facility on the same day, it was observed that the in-process Clozapine (b) (4) which could be seen (b) (4) from outside the room, was stored uncovered and exposed to the room environment.

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It was determined that the product was left uncovered when the operator left for the shift change around the time the machine was shutdown. No operator was assigned to continue processing the product during the next shift. The (b) (4) subsequent QA in-process checks did not document that the product was exposed and did not resolve the problem by covering the product as required by your written procedure titled '(b) (4) (b) (4) ' (Document Number MPI-SOP-MFG-GEN-0009).

There was no documentation in the batch record or in any other record that the product had been left exposed to the room environment during this time.

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**OBSERVATION 9**

Changes to written procedures are not drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality control unit.

Specifically,

Special instructions for manufacturing operators (e.g. using (b) (4) (b) (4) (b) (4) are entered into the LIMS system as a result of investigations or CAPAs approved by the Quality Unit (QU) but without going through your change control system as required by MPI-SOP-QAC-CHG-0005 (b) (4) *Change Management Procedure for Non-Regulatory Changes*, MPI-SOP-QAC-CHG-0004 (b) (4) *Change Management Procedure for Regulatory Changes*, and/or MPI-SOP-QAS-EQV-0001 *Change Control Procedures for Mylan cGMP Equipment and Systems*. In addition, your QU was not able to provide a listing of all manufacturing changes made within the LIMS system without a change control since November 2016 as these changes are not tracked, reviewed or

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approved. For example, CAPA PR# 1205749 was opened on 5/18/17 (not closed yet) to determine controls to mitigate content uniformity issues in Metolazone 2.5 mg tablets. (b) (4) identified included (b) (4) (b) (4) (b) (4) and (b) (4) press speed to (b) (4) (qualified speeds (b) (4). These changes were not captured within the change control system and no training was provided to operators to follow these changes from established procedures.

**OBSERVATION 10**

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically,

Your QU assigns a (b) (4) day hold time (Out-Date) for each manufacturing phase ((b) (4) (b) (4) of your drug products without evidence of their stability. Furthermore, this hold time was frequently exceeded by your production department. From 11/1/16 thru 11/19/18, your QU opened 462 investigations as per MPI-SOP-QAO-OPS-0011 "*Exceeded Out-Dates*" for exceeding the hold time but no effective corrective and preventive action has been implemented.

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QUALITY SYSTEM

**OBSERVATION 11**

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

1. The decision to authorize the approximately (b) (4) batch reduction for Carbidopa/Levodopa, 25mg/100mg, lot 3092534 (b) (4) under Manufacturing Investigation # PR 1407468 did not include a documented assessment of the impact of the batch reduction including (b) (4) capacity changes on the validated process for this same product. In addition, no change control notification was initiated for this batch reduction. This batch was later subject to an LIR for dissolution failure and was pending final assessment and disposition.

   In further review, adjustments to written batch manufacturing instructions including dispensing adjustments affecting the final batch size are permitted at this site as part of a deviation investigation per written procedure, "Instructions for (b) (4), (b) (4) due to a Processing Deviation" (MPI-SOP-MFG-GEN-0035) without a documented assessment of the impact of the change on process validation. Over the last year, 16 events were provided in which batch size reductions were authorized under a deviation without

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an adequate and documented process validation assessment of the change. These include the reduction to Atorvastatin Calcium 80mg lot 3088548 that was subsequently subject to another deviation investigation for 'excessive broken tablets'. This lot was released for distribution.

2. On 02/15/18, you received a complaint for two lots (3091569 & 3091571) of Carbidopa/Levodopa 10mg/100mg tablets having a high percentage of "specks" on the tablets. The investigation (PR#1446914) states the spots were only on the surface. There was no evaluation of the inside of the tablets to determine if the spots were present throughout the tablet.

   The investigation did not evaluate the potential for the specks to have been caused by cross contamination from previous products made on the same equipment. The investigation does not identify the type of equipment, equipment number or the location where the product was made.

3. On 05/11/17, you received a complaint for Carbidopa/Levodopa 25mg/100mg (Lot #3076689) having blue/dark spots on the tablets. The tablets are normally yellow in color.
   The investigation concluded by analytical analysis that the dark spots contained trace metals associated with stainless steel. The report did not adequately evaluate the equipment used in the production of this product as a potential source of the metal instead concluding that a "likely point of introduction cannot be determined".

The investigation did not evaluate this complaint for the specific equipment used to manufacture the product and did not evaluate if there were other similar complaints for metal in other products made on the same equipment.

4. Your Quality Unit (QU) opened Manufacturing Investigation Reports (MIRs) # 1071629 and 1106258 on 12/12/16 and 1/25/17, respectively, and Trending Assessment Form # 1165047 (3/31/17) to investigate higher than expected (b) (4) assay results and high variability results (OOT) for content uniformity for (b) (4) batches of Prednisolone Sodium Phosphate Orally Disintegrating Tablets 10 mg (b) (4) According to your investigations, the root cause of the OOT results was determined to be untrained or inexperienced operators that did not properly (b) (4) (b) (4) (b) (4) Your root cause was not supported by evidence because all involved operators were experienced and had documentation of training in performing the (b) (4) method. In addition, your investigation was not adequate in that all potential root causes for powder segregation and heterogeneity of the blend were not ruled out. For example, (b) (4) (b) (4) were not evaluated as potential root causes. Furthermore, your QU lacked hold time studies for this product to demonstrate powder segregation does not occur during (b) (4)

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5. During our review of Atenolol, USP API (b) (4) Assay testing, we observed Laboratory Investigation (LIR 1464472), which has been opened since March 6, 2018 based on OOS results for (b) (4) of Atenolol USP obtained the day before, on March 5, 2018. A re-analysis of samples from the (b) (4) resulted in OOS results for (b) (4) (b) (4) on March 7, 2018. During the investigation, the firm's Quality Unit attributed these additional failures to the samples being outside the solution stability time range (b) (4) hours). Employees informed the FDA investigators of the same on the first day of the current inspection (March 19, 2018). Based on a review of the original sample solution stability study at the request of the FDA investigators on March 19, 2018, the firm's Quality Unit found that the samples were stable for 13 days. On the same evening, the firm's Quality Unit created and approved a report that samples for Atenolol USP analysis are stable for 13 days, and opened a Pre-Market Supply Incident (PMSI) notifying the supplier of Atenolol USP of the (b) (4) total OOS batches.

6. Laboratory investigation (LIR 1416727) which was opened based on an OOS result for batch #549048 of Clomipramine HCl, USP API assay testing resulted in OOS results for an additional batch #549046 during a (b) (4) During the investigation, the firms' Quality Unit attributed these additional failures to the sample being outside the solution stability time range (b) (4) hours). However, there is no data to support this hypothesis as the solution stability study indicates it was only conducted up to the (b) (4) hour timepoint. Additionally, the Quality Unit accepted data during this investigation on an instrument that they later designated to be out of service due to a performance issue

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## OBSERVATION 12

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

Specifically, your Quality Unit failed to review and close all LIMS investigations opened during the compression or encapsulation processes of numerous batches before their release as required by MPI-SOP-QAO-REV-0011 "Review of Quality Assurance Folders from Manufacturing to AQL Management." These brief investigations are opened when issues such as out-of-limit or out-of-specification results are obtained during in-process checks that require supervisory intervention. According to a list of LIMS investigations generated during the inspection on 3/28/18, 4,279 out of 25,432 LIMS investigations were not closed by QA prior to batch release. Of these open investigations, 1,945 investigations were for in-process results that were out of specifications.

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| | James M Mason, Investigator<br>Marcus A Ray, Investigator<br>Melissa T Roy, Investigator<br>Atul Agrawal, Non Reporting User<br>Ileana Barreto-Pettit, National Expert<br>Rebecca E Dombrowski, FDA Center Employee<br>or Employee of Other Federal Agencies<br>Ko U Min, Chemist/Biologist<br>Alison N Stieg, Chemist/Biologist | X James M Mason<br>Investigator<br>Signed By: 2000408308<br>Date Signed: 04-12-2018 14:33:24 | 4/12/2018 |

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 6000 Metro Drive, Suite 101<br>Baltimore, MD 21215<br>(410)779-5455 Fax:(410)779-5707 | 3/19/2018-4/12/2018* |
| | FEI NUMBER<br>1110315 |

| NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED | |
|---|---|
| Kimberly L. Kupec, Head of OSD Quality Morgantown | |
| FIRM NAME<br>Mylan Pharmaceuticals Inc. | STREET ADDRESS<br>781 Chestnut Ridge Rd |
| CITY, STATE, ZIP CODE, COUNTRY<br>Morgantown, WV 26505-2730 | TYPE ESTABLISHMENT INSPECTED<br>Finished Drug Product Manufacturer |

**OBSERVATION 13**

Written records of investigation of a drug complaint do not include the follow-up.

Specifically,

Complaint investigation under PR 1194778 received on May 4, 2017 for "10 broken tablets" reportedly observed by a pharmacist from a bottle of Benazepril HCl/HCTZ tablets 20mg/12.5mg, lot 3080983, resulted in a review of the retained sample for this lot that also confirmed a broken tablet in the retained, 100 count bottle. The complaint investigation concluded that the root cause of the complaint event was manufacturing. Market action assessment was not documented in this closed complaint investigation, and a FAR had not been filed for this lot as of 3/29/2018.

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***DATES OF INSPECTION**

3/19/2018(Mon), 3/20/2018(Tue), 3/21/2018(Wed), 3/22/2018(Thu), 3/23/2018(Fri), 3/26/2018(Mon), 3/27/2018(Tue), 3/28/2018(Wed), 3/29/2018(Thu), 4/10/2018(Tue), 4/11/2018(Wed), 4/12/2018(Thu)

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

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kimberly L. Kupec, Head of OSD Quality Morgantown

| FIRM NAME | STREET ADDRESS |
|---|---|
| Mylan Pharmaceuticals Inc. | 781 Chestnut Ridge Rd |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Morgantown, WV 26505-2730 | Finished Drug Product Manufacturer |

X Marcus A Ray
Investigator
Signed By: 2001597816
Date Signed: 04-12-2018 14:34:32

X Melissa T Roy
Investigator
Signed By: 2001550773
Date Signed: 04-12-2018 14:35:22

X Ko U Min
Chemist/Biologist
Signed By: 2001622356
Date Signed: 04-12-2018 14:36:09

X Alison N Stieg
Chemist/Biologist
Signed By: Alison N. Stieg -S
Date Signed: 04-12-2018 14:36:47

X Atul Agrawal
Non Reporting User
Signed By: Atul J. Agrawal -S
Date Signed: 04-12-2018 14:38:15

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Investigator
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DATE ISSUED
4/12/2018