DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place Dr., Suite 5900 Detroit, MI 48207 313-393-8100 Industry Information: www.fda.gov/oc/industry	06/23/2015 - 07/09/2015*
	FEI NUMBER 1810189

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Robert J. Betzig, Interim Site Leader

FIRM NAME	STREET ADDRESS
Pharmacia & Upjohn Company LLC	7000 Portage Rd.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Kalamazoo, MI 49001	Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

QUALITY SYSTEM

OBSERVATION #1

Documented investigations into discrepancies and out-of-specification results are not fully investigated.

Specifically,

A. Non-confirmed OOS investigations do not include documentation to support that an adequate investigation has been performed prior to batch release. In certain instances, the LIR record and (b) (4) lot result records do not include a summary of the aspects of the manufacturing process that may have caused the problem as well as the results of a documentation review from this perspective. For example, LIR 1089785 documents a non-confirmed OOS release result for methylprednisolone in Solu-Medrol lot L57022 with a result of 86.6%. The investigational measurements protocol revealed no definitive laboratory error. A further analysis protocol consisting of (b) (4) retesting did not confirm the original result and the average of the retests was reported in (b) (4) The (b) (4) lot result record does not adequately document an appropriate manufacturing investigation as part of the lot release process. Additional examples include a non-confirmed OOL release result for free hydrocortisone in Solu-Cortef lot L41543 documented in LIR 1055593 and a non-confirmed OOS release result for pH in Depo-Medrol lot H28452 documented in LIR 706021.

OBSERVATION #2

Annual product reviews do not include a review of all appropriate data to evaluate quality characteristics indicative of potential trends.

Specifically,

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		Jeffrey D. Meng, Investigator Andrew J. Idzior, Investigator Rebecca E. Dombrowski, Supervisory Investigator Thomas J. Cosgrove, Director, CDER, OMQ	07/09/2015

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The 2015 Annual Product Review for Cleocin Ovule Suppository 100 mg with review period ending 2/18/15 did not include an evaluation of content uniformity data on a (b) (4) basis as part of the Trend Review Summary section to ensure the detection of potential adverse trends.

FACILITIES & EQUIPMENT SYSTEM

OBSERVATION #3

Equipment used in the manufacture, processing, packing, or holding of drug products is not of appropriate design to facilitate operations for its intended use, cleaning, and maintenance.

Specifically,

A. During filling of lot M13447 on 6/29/15, (b) (4) Grade (b) (4) monitoring probes were observed near the north and south trayers of line (b) (4) where vials with partially seated stoppers are transported via belt and manual tray loading occurs. These (b) (4) continuous (b) (4) monitoring probes were observed approximately 2 feet above the working surface and do not appear to represent potential product exposure to the environment.

B. A slight residue on a HEPA filter grate determined to be rouging was observed on 6/23/15 within the (b) (4) boundary of the Grade (b) (4) area in Room (b) (4) Activities within this area include the aseptic addition and blending of sterile API for suspension formulation, including Depo-Medrol lot L80068 on 6/17/15.

C. On 6/23/15, an autoclave cart in the autoclave prep area was observed with apparent surface discoloring and roughening due to rouging. These autoclave carts are used to load material into the autoclaves and then exit the autoclave into the Grade (b) (4) aseptic storeroom area.

D. Exposed sprinkler heads observed on filling line (b) (4) and line (b) (4) in the Grade (b) (4) spaces were observed to consist of an older design with surfaces that are not easily cleanable.

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OBSERVATION #4

Individual logs for major equipment do not include written records of cleaning.

Specifically,

Equipment logs for major equipment such as (b) (4) and (b) (4) do not include written records of within campaign cleanings.

MATERIALS SYSTEM

OBSERVATION #5

Written procedures are not followed for identification, handling, and storage of components.

Specifically,

Containers of material that were torn, leaking, and associated with an investigation of a rodent infestation were not taped off, placed in an area identified for rejected materials, and labeled or marked as rejected material according to written procedures. These materials included approximately (b) (4) bags of soy flour, (b) (4) bags of granulated sucrose, (b) (4) bags of material ID R000180340, and (b) (4) bags of material ID R000130405. Additionally, containers of (b) (4) Buffer stored with material containers approved for use in cold storage were not identified with unique (b) (4) labels according to written procedures.

PRODUCTION SYSTEM

OBSERVATION #6

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not

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written and followed.

Specifically,

A. The rationale for the selection of representative processes for demonstration during media fill simulations within SOP 10554, Media Fill Program, does not include an assessment of the risks associated with various filling line speeds to capture worst case scenarios for aseptic processing lines (b) (4) [redacted] In addition, filling line speed during media fills are not specified or recorded for evaluation at the time of fill. For example:

Media Fill lot W417J was filled on line [redacted] simulating [redacted] mL (b) (4) [redacted] vials. The line speed limits in the batch record are (b) (4) [redacted] containers per minute (cpm) with no specified setting stated or recorded. Data pulled from the automated line historian indicates the line was running at approximately (b) (4) [redacted] (cpm) for most of the batch.

Media Fill lot W411F was filled on line [redacted] simulating [redacted] mL (b) (4) [redacted] vials. The line speeds limits in the batch record are (b) (4) [redacted] cpm with no specified setting stated or recorded. Line speed data for this lot was not available from the historian.

B. The program for managing aseptic processing personnel participation in media fills does not ensure that a person's participation is representative of their routine responsibilities. For example, a "technician" is responsible for the majority of critical filling line setup tasks and typically performs the majority of the major interventions required during routine processing. However, technicians (b) (6) [redacted] did not participate in setup activities or perform major interventions in any media fills since (b) (6) For example, (b) (6) [redacted] media fill participation history consisted primarily of manipulating vials with forceps.

LABORATORY SYSTEM

OBSERVATION #7

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug product meet appropriate statistical quality control criteria as a condition for their approval and release.

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Specifically,

An appropriate statistical evaluation of lot release data was not performed to assure the acceptability of individual lots with an appropriate confidence and probability. For example,

Depo-Medrol lot #L39677 with a total of (b) (4) units tested for content uniformity with a resulting AV of (b) (4) average of (b) (4) and an RSD of (b) (4)

Depo-Medrol lot #H15529 with a total of (b) (4) units tested for content uniformity with a resulting average of (b) (4) and an RSD of (b) (4)

OBSERVATION #8

Drug products not required to be sterile are not examined to prevent objectionable microbiological contamination.

Specifically,

API products such as Phenytoin Sodium, Toceranib Phosphate, Triazolam are not examined to ensure they are free from objectionable microbiological contamination.

*Dates of Inspection:
06/23/2015 - 06/26/2015, 06/29/2015 - 07/02/2015, 07/06/2015 - 07/09/2015

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