DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Decatur, IL 62522	Sterile 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 (I) (WE) OBSERVED:

PRODUCTION SYSTEM

OBSERVATION 1

Deviations from written production and process control procedures are not recorded and justified.

Specifically,

Investigation 14-14-01453 was initiated 26NOV2014 for Line (b) (4) Media Fill failure (Media Fill Batch (b) (4)). The most probable root causes of contamination were attributed to the following:
• Slower than routine production ((b) (4)) leading to issues in stoppering;
• A (b) (4). media fill leading to operator fatigue where commercial fills are limited to a maximum of (b) (4).;
•(b) (4) table and (b) (4) loading cart malfunctions requiring the (b) (4) unloading of (b) (4) and use of a vial (b) (4)
A broken bolt on the (b) (4) table (b) (4) and frame required personnel to (b) (4) lift and secure the vial (b) (4) mechanism (b) (4). This led to operators leaning over filled, partially-stoppered vials to clear jams, which would have led to the full clearance and reject of units during a commercial production run.

1) Section 5.3 of SOP AA204, "MEDIA FILL PROCESS SIMULATION PROGRAM" (current rev. 45, eff. 26APR2016), specifically states that media fills should only be aborted under the same circumstances as commercially filled product. As such, conditions for the abortion of a media fill are identical to those required for abortion of commercial production batches, as defined by SOP QA101, "BATCH RECORD REVIEW: PRODUCT RELEASE/CLOSEOUT MEDIA REVIEW/CLOSEOUT" (current rev. 25, eff. 22MAR2016). Section 5.12 identifies aborted batches as those in which formulation is initiated not filled or formulated and partially filled, but does not identify specific conditions that would warrant Quality's decision to abort filling.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	in absence of Investigator Shields	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE Decatur, IL 62522	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

Despite the equipment malfunctions and (b) (4) unloading of (b) (4) during Media Fill Batch (b) (4) which management stated would normally require abortion of a commercial production batch, the media fill was allowed to proceed in violation of Section 5.3 of SOP AA204.

2) Section 5.5 of SOP AA204 states that "All operations taking place in the cleanrooms shall be performed identical to a commercial run for a media fill utilizing proper aseptic technique, per SOP AA143". Section 5.10 of SOP AA143 in use at that time (rev. 22, eff. 14JUL2014), "ASEPTIC TECHNIQUE", specifically required the (b) (4) Instead, production personnel failed to reject these exposed units and (b) (4) unloaded units for fear of not meeting media fill yield requirements in violation of SOPs AA204 and AA143.

3) No occurrence log was in use for (b) (4) Room (b) (4) and the (b) (4) failure/intervention in Room (b) (4) was not observed by Quality or Production Oversight during the media fill. While SOP AA238, "FILLING MACHINE (b) (4) AREA OCCURRENCES" (rev. 10, eff. 20MAY2013) requires (b) (4) (b) (4) operators failed to do so during Media Fill Batch (b) (4) The lack of documentation requires reliance on the consistent, independent interviews of operators to identify the timing and activities of the intervention(s) corresponding to the contamination of units from Media Fill Batch (b) (4)

QUALITY SYSTEM

OBSERVATION 2

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

Specifically, there are no means of accounting for the total number of pages of forms used to document batch control and test results issued against the total number of pages used, discarded, or copied and the issuance of each control/test data form is not reconciled in Batch Records. For example:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	10JUN2016 10 JUN 2016 10 JUN 2016	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Decatur, IL 62522	Sterile Drug Product Manufacturer

1) The (b) (4) day visual inspection of (b) (4) ampoule Media Fill Batch (b) (4) was observed on 08JUL2016. Results of media fill visual inspections for each tray are documented on a (b) (4)-DAY INSPECTION WORKSHEET" of Packaging Control Records, with additional pages documented on a (b) (4) (rev. 11/01). The (b) (4) additional (b) (4) used to document the (b) (4) and (b) (4) day post-incubation visual inspections of media fills are printed uncontrolled as attachments to media fill batch records. Each of the (b) (4) (b) (4) used to document the (b) (4) day post-incubation visual inspection of Media Fill Batch (b) (4) were printed on plain white paper, with no "Page # of #" documented at the time of issuance. No means of accounting for the total number of pages issued against the total number of pages used, discarded, or copied and are not reconciled in Batch Records.

2) Non Conformance 22082 was initiated for Investigation of a positive, non-integral ampoule identified during the (b) (4) day visual inspection of Media Fill Batch (b) (4). Review of the batch record for Media Fill Batch (b) (4) identified 1 cracked ampoule rejected from Tray (b) (4) upon initial inspection, documented on a (b) (4) and the 1 contaminated, non-integral unit rejected upon (b) (4) day inspection from Tray (b) (4) documented on a Form (b) (4) (b) (4) used to document the initial container-closure integrity inspections of media fills are printed uncontrolled as attachments to media fill batch records. Each of the (b) (4) Form (b) (4) used to document the ampoule (b) (4) of Media Fill Batch (b) (4) were printed on plain white paper, with no "Page # of #" documented at the time of issuance.

OBSERVATION 3

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other drug products that may have been associated with the specific failure or discrepancy.

Specifically, AQL inspections are conducted according to SOP WQ102 (rev. 32, eff. 16MAY2016). (b) (4) Upon completion of 100% and AQL inspections of each sublot, sublotting is no longer distinguishable thru labeling, final packaging, and distribution of drug product batches.

1) Non Conformance 20101 was initiated 23NOV2015 upon AQL failures of Sublots (b) (4) of Clindamycin Batch (b) (4). The visual inspection process for Clindamycin 50mL vials is (b) (4) and the most probable cause

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	SK 10JUN2016 SK 10JUN2016 SK 10 JUN 2016	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016 FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Decatur, IL 62522	Sterile Drug Product Manufacturer

of failure to identify the critical (cracked vials)/major (foreign matter) defects was attributed to human error during the (b) (4) inspection. The initial 100% visual inspection of Sublots (b) (4) are indistinguishable in Packaging Records, and while subject to the same root cause for AQL failure of Sublots (b) (4), no 100% visual or AQL re-inspections of Sublots (b) (4) of Batch (b) (4) were performed.

2) Non Conformance 11501 was initiated 26JUN2015 upon AQL failures of Sublots (b) (4) of Clindamycin 50mL vial Batch (b) (4). Sublot (b) (4) initially failed AQL inspection for major defects (particulate matter) and Sublot (b) (4) initially failed AQL inspection for critical defects (cracked vials). Based on the location of the cracks identified in the body of vials and toward the bottom, the most likely root case for cracked vials was ascribed to the handling of glass during placement on the (b) (4) and in transit to the (b) (4) facility. Foreign matter was identified as a known process-related defect, yet no specific root cause for the particulate was identified. And the most likely root cause of failure to identify the critical/major defects during 100% visual inspection was identified as human error. The initial 100% visual inspection of Sublots (b) (4) are indistinguishable in Packaging Records, and while subject to the same root cause for failure of Sublots (b) (4) no 100% visual or AQL re-inspections of Sublots (b) (4) of Batch (b) (4) were performed.

3) Non Conformance 15130 was initiated 24AUG2015 upon AQL failure of Sublot (b) (4) and an out-of-specification total cumulative reject rate (29%) of Clindamycin 50mL vial Batch (b) (4). Sublot (b) (4) initially failed AQL inspection for major defects (red foreign matter), then failed a second AQL inspection for critical defects (cracked vials), and then failed a third AQL inspection for critical defects (cracked vials) before being rejected. The most probable source of the red foreign material was suspected to be a (b) (4) used in the manufacturing of Clindamycin, the most likely root cause for cracked vials was suspected to be due to a malfunction of the (b) (4) and excessive of handling of units. The most probable root cause of failure to identify the critical/major defects during 100% visual inspection was identified as human error. The initial 100% visual inspection of Sublots (b) (4) are indistinguishable in Packaging Records, and while subject to the same root cause for failure of Sublot (b) (4) no 100% visual or AQL re-inspections of Sublots (b) (4) of Batch (b) (4) were performed.

OBSERVATION 4

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	P.C.K. 10JUN2016 SSK 10JUN 2016 S.M.K. on Hehalf of A.M.S.	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE Decatur, IL 62522	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

Quality controls do not include a determination of conformance to written descriptions of sampling procedures for drug products.

Specifically, documentation of the AQL samples taken from each batch of sterile drug product provide no traceability to individual trays sampled or identification of the total quantity available when sampling is performed. There is no mechanism to verify that AQL samples (b) (4)) are collected(b) (4) throughout batches of finished drug products as required by SOP WQ102 (rev. 32, eff. 16MAY2016).

LABORATORY CONTROLS SYSTEM

OBSERVATION 5

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically,

1) Sterile drug product sampling is documented in individual batch records with general requirements for sample sizes described by SOP QA113 (rev. 8, eff. 23MAY2014). Based on minimum sampling quantities specified by USP <71> for batches in which >500 units are produced:
- in the case of low-fill products, n=40 units are sampled for sterility testing;
- for large-volume products, n=10 units are sampled for sterility testing;
- and for all other products, n=20 units are sampled for sterility testing.

No additional sterility test samples are required to be collected following critical interventions in ISO Class 100 areas during batch production and there is no valid statistical rationale demonstrating that the minimum recommended sampling quantities from USP <71> are representative of the various batch sizes commercially produced.

No enhanced sampling for sterility testing is required upon over-action-limit recoveries from environmental

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Decatur, IL 62522	Sterile Drug Product Manufacturer

monitoring samples obtained during batch production and no statistical rationale for the sufficiency of these microbiological test sample sizes to support the sterility assurance of affected batches is included in excursion investigations.

2) Environmental monitoring of controlled areas of the Grand Ave. facility is described by SOP EM127 (rev. 30, eff. 12APR2016). For example, passive air monitoring for viable particulate is performed per SOP ML105 using (b) (4) settle plates. Evaluation of the firm's Microbiology Laboratory identified (b) (4) passive air monitoring samples per specified location, exposed for (b) (4). each during the production of at least (b) (4) commercial batches on Filling Lines (b) (4) and (b) (4) immediately prior to the inspection. Section 5.5.4 of SOP EM127 requires exposure time for a standard production fill to span only (b) (4) hours per location with a (b) (4) not exposed for more than (b) (4) yet filling operations are authorized for up to (b) (4)

3) Section 5.2. of SOP ML133, (b) (4) TESTING OF GLOVES AND GOWNS OF CLEANROOM PERSONNEL" (rev. 41, eff. 04APR2016), requires monitoring of all personnel that have entered the firm's ISO Class 10,000 and 100 filling areas (b) (4) Routine personnel (b) (4) monitoring is required (b) (4) per shift, (b) (4). Section 5.2.3 specifically states that "(b) (4) There is no requirement for monitoring of personnel following routine interventions and operator exposure to the ISO Class 100 filling areas which are simulated during media fills. Non-routine interventions require the initiation of investigations, (b) (4)

OBSERVATION 5

The suitability of all testing methods is not verified under actual conditions of use.

Specifically, sterility test method verification for Ephedrine Sulfate ampoules was conducted using Batch (b) (4), with (b) (4) units tested for each (b) (4) test organisms on 11JAN2011. No sterility testing of (b) (4) lots of Ephedrine Sulfate was performed to ensure the method is suitable for the detection of microbial organisms and no requirement for evaluation of more than (b) (4) batch is required by SOP ML102,

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	P.C.K. 10JUN2016 SSK 10JUN2016 P.C.K. in lieu of A.M.S.	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Regulatory Affairs/CER/Chicago District 5500 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 Tel: (312) 353-5863 Fax: (312) 596-4187 Industry Information: www.fda.gov/oc/industry	June 01 - 10, 2016
	FEI NUMBER 1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Johnathan D. Shoemaker, Vice President & General Manager

FIRM NAME	STREET ADDRESS
Akorn Pharmaceuticals, Inc.	1222 W. Grand Ave.
CITY, STATE AND ZIP CODE Decatur, IL 62522	TYPE OF ESTABLISHMENT INSPECTED Sterile Drug Product Manufacturer

"VALIDATION OF (b) (4) TEST METHOD" (rev. 22, eff. 21JUL2014), to demonstrate method repeatability.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 6

Control procedures are not established which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

1) Current general requirements for HEPA filter testing are described by SOP AA255 (rev. 15, eff. 18FEB2016). Data for (b) (4) at the (b) (4) of ISO Class 100 areas is currently being developed (b) (4)) to establish formal acceptance criteria. The requirement for evaluation of (b) (4) (b) (4) from (b) (4) was implemented with Revision 15 of SOP AA255, and the qualification of ISO Class 100 areas prior to the December 2015 re-qualifications evaluated (b) (4) (b) (4)" from HEPA filter (b) (4) only (SOP AA255, rev. 13, eff. 21SEP2015). However, the actual working level of ISO Class 100 Areas of Fill Lines (b) (4) and (b) (4) are (b) (4) " from HEPA filter (b) (4) respectively.

2) Current acceptance criteria for clean (b) (4) of HEPA filter panels installed in the (b) (4) (b) (4) the ISO Class 100 Area of Line (b) (4) are established in (b) (4) . Measures of (b) (4) (b) (4) at HEPA filter (b) (4) of the ISO Class 100 or 10,000 Areas of Line (b) (4) are not required and no acceptance criteria to demonstrate the sufficiency of (b) (4) to sweep particles away from the filling/closing area of Line (b) (4) are established.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Samina S. Khan On Behalf of Investigator Shields	Patric C. Klotzbuecher, Investigator Samina S. Khan, Investigator Anastasia M. Shields, Investigator	10JUN2016