DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
New England District Office One Montvale Avenue Stoneham, MA 02180 Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry	7/12, 7/16-7/18, 7/20, 7/24-7/26, 8/6/2012
	FEI NUMBER 3006568549

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Claus Weisemann, Ph.D., Senior Vice President Corporate Quality and Compliance

FIRM NAME	STREET ADDRESS
Alexion Pharmaceuticals, Inc.	100 Technology Way
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Smithfield, RI 02917	Therapeutic Drug Substance 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:

1. The firm's investigations into Soliris (b) (4) microbiological contamination events are inadequate. For example:

   a. Risk assessments (b) (4) and (b) (4) for release of Soliris drug substance lot (b) (4) (drug product lots A75445C and A75445D), and the release for forward processing of Soliris drug substance lot (b) (4) are not sufficient justification alone for lot release. Soliris lot (b) (4) contained a count of TNTC (too numerous to count)/10 mL at the (b) (4) step in April 2011 and Soliris lot (b) (4) contained counts of TNTC/10 mL and 40 cfu/1 mL at th (b) (4) (b) (4) step in March 2012. The isolates were identified as *Bacillus thuringiensis* and *Acinetobacter radioresistens* for lot (b) (4) and as *Bacillus thuringiensis* for lot (b) (4). The potential impurities generated, i.e. non-host cell by-products, were not quantified and the process impurity clearance was not calculated. Specific analytical testing beyond routine release and stability has not been performed for these Soliris drug substance lots to verify whether potential impurities, i.e. non-host cell by-products, generated at the (b) (4) step were removed during the purification process.

   Additionally, a BPDR has not been filed for Soliris drug substance lot (b) (4) (drug product lots A75445C and A75445D), as it exceeded its filed specification of (b) (4) at the (b) (4) with a result of TNTC/10 mL.

   b. In the past 15 months, the Soliris drug substanc (b) (4) process has experienced 7 contamination events. Five contamination events occurred in 3 bioreactors and 2 (b) (4) contamination events occurred at the (b) (4) The firm has not adequately investigated to determine whether these contamination events are linked and has not adequately prevented reoccurrence of microbial contamination in the Soliris (b) (4) manufacturing process.

   Three bioreactor microbial contamination events occurred between October 2011-January 2012 for lots (b) (4) Two (b) (4) contamination events occurred in April 2011 for lot (b) (4) and in March 2012 for lo (b) (4). Each aforementioned contamination event isolated *Bacillus thuringiensis* as the contaminating microorganism, however the QC Microbiology Department has not confirmed whether the bioreactor contamination events and the (b) (4) contamination events were the same strain; only two of the bioreactor contamination events were analyzed for, and confirmed as the same strain.

   Two additional bioreactor contamination events occurred in July 2012 for Soliris lots (b) (4) and (b) (4) lot (b) (4) was contaminated with *Lysinibacillus boronitolerans* and lot (b) (4) was contaminated with *Bacillus thuringiensis*. Investigations are ongoing for these events.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Megan A. Haggerty	Megan A. Haggerty, Investigator	08/06/2012

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In all 5 of the bioreactor microbial contamination events, bioreactor (b) (4) and/or (b) (4) were in use when the contamination occurred. Although the firm believes the cause of the three October 2011-January 2012 bioreactor microbial contamination events were due to faulty high-high limit switches, the firm has not ruled out whether there is another root cause for the contamination events. In the (b) (4) microbial contamination events, three potential root causes were identified but a definitive root cause was not confirmed.

c. The adequacy and effectiveness of the routine CIP cycle has not been evaluated as part of the bioreactor contamination events, for example where *Bacillus thuringiensis* has been isolated. The cycle was validated with the intent for use in routine cleaning; it is not validated or effective for when bioreactors are subjected to bioburden exceeding upper in-process specification limits or for post decontamination events. For example:

1. Following a confirmed *Bacillus thuringiensis* contamination in bioreactors (b) (4) and (b) (4) for Soliris lot (b) (4), on January 14, 2012, a routine CIP cycle was executed for (b) (4) on January 18, 2012. Although the post-CIP visual inspection indicated a passing result on January 18, 2012, a bioreactor entry confirmed the CIP cycle was not effective as a soil was observed at the liquid level of the bioreactor. The firm has not evaluated the effectiveness of their routine CIP cycle with bioburden counts that exceed upper in-process specification limits.

2. Following a confirmed *Bacillus thuringiensis* contamination in bioreactor (b) (4) for Soliris lot (b) (4) on July 18, 2012, the decontamination of bioreactor (b) (4) was executed, followed by a routine CIP cycle. Although the post-CIP visual inspection indicated a passing result on July 20, 2012, a bioreactor entry occurred on July 21, 2012, where confirmation of the CIP cycle failure occurred when visual residue was observed. The firm has not evaluated the effectiveness of the post-decontamination CIP cycle, which is the same cycle run for routine operations, with preceding decontamination procedures executed a (b) (4)

Additionally, post-CIP visual inspection procedures are not sufficient in determining whether CIP cycles are effective. For example, the post-CIP visual inspection following production of Soliris lot (b) (4) in bioreactor (b) (4) on January 18, 2012 passed although upon subsequent vessel entry, soil was observed at the normal operating liquid level of the bioreactor.

d. The firm has not adequately assessed necessitation for an increased frequency of a sporicidal agent throughout the clean rooms, particularly to address environmental monitoring isolate *Bacillus thuringiensis*. *Bacillus thuringiensis* has been isolated in 4 Soliris bioreactor contamination events and 2 (b) (4) events between April 2011-July 2012.

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2. Deviation 3324 was initiated due to a leak on the interior of the drywall in a column in the cell culture area (b) (4) A tent was constructed prior to cutting into the drywall to investigate the leak which was observed to have caused mold on the column drywall interior. This deviation was not adequately investigated for the following:

   a. The deviation did not list in-process batches in (b) (4) uring the work or assess whether there was any impact to the batches manufactured in the cell culture area (b) (4) he deviation assumed since the cell culture operations are closed that there was no impact to batch quality.

   b. Increased environmental monitoring sampling, e.g. augmented site sampling and/or frequency, did not occur during the construction of the tent in the controlled cell culture suite, during the Facilities Department's activities within the tent, and during the deconstruction of the tent to verify the environment was not compromised due to these non-routine activities.

   c. Prior to execution, the Quality Unit did not approve the cleaning plan performed by Manufacturing following deconstruction of the tent.

   d. The Facilities Department lacks specific instructions on cleaning procedures prior to deconstruction of the tent.

3. The procedure "Quality Control of Microbiological Media" SOP QC-0201, version 5.0 is used for growth promotion o (b) (4) used in the environmental monitoring program. The procedure does not specifically describe how to select environmental isolates to be used in growth promotion. The firm has selected (b) (4)

4. Deviations are not required to be initiated for all visual inspection failures, for example post CIP visual inspection failures. For example, pooling was observed on July 26, 2011 following a CIP cycle fo (b) (4) . A deviation was not initiated; subsequently a second CIP cycle was performed. Additionally, the Quality Unit does not review the bioreactor use and cleaning logbooks, therefore they are not required to be notified of such failures.

5. The Quality Unit has not ensured verification of whether current sampling procedures for larger drummed raw materials could potentially contaminate the room in which they are sampled or other raw materials. Raw materials sampled in larger drummed containers are taken in an unclassified room which is not a controlled, qualified, or certified area. Additionally,

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the cleaning procedure following raw material sampling is not specific on how to clean the area where sampling occurs on the floor.

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	Megan A. Haggerty	Megan A. Haggerty, Investigator	08/06/2012