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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CBER/OC/DIVISION OF INSPECTIONS AND SURVEILLANCE, HFM-650 US FOOD AND DRUG ADMINISTRATION 1401 ROCKVILLE PIKE, SUITE 200-NORTH ROCKVILLE, MD 20852, (301) 827-6748/FAX (301) 827-6748 Industry Information: www.fda.gov/oc/industry	SEPTEMBER 08-15, 2011
	FEI NUMBER 30002689389

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: NAWAL (NMI) OUZREN, FACILITY QUALITY MANAGEMENT REPRESENTATIVE & QUALITY OP. DIRECTOR

FIRM NAME	STREET ADDRESS
BAXTER BIOSCIENCE MANUFACTURING SARL	ROUTE DE PIERRE-A-BOT 111
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
CH-2000 NEUCHATEL, SWITZERLAND	MANUFACTURER

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

1A. Advate (b) (4) lot # (b) (4) and # (b) (4) that did not meet the licensed in-process specification for (b) (4) of (b) (4) with a result of (b) (4) were further processed into final drug products and released into US market without CBER notifications as follows:

i) Advate drug substance lot # (b) (4) and final container drug product lot # (b) (4) and expiration date of 01/2012 and (b) (4), expiration date of 12/20/2011.

ii) Advate drug substance lot # (b) (4) and final container drug product lot #s: (b) (4), expiration date of 01/30/2013 and (b) (4), expiration date of 06/20/2012.

1B. There is no documentation that any of the above two drug product lots or drug substance lots were placed on stability studies.

2. The firm's LIMS (Laboratory Information Management System) specifically, (b) (4), has been in use since 2006 and from 2006-2011, (b) (4) software applications/modifications were made to the LIMS. Also, one modification via Change Control #CT09-1107 for the implementation of (b) (4) (b) (4) were made to the (b) (4). There are no assurances that the (b) (4) LIMS software applications have been adequately qualified and/or documentation that LIMS has been re-evaluated for re-qualification for its intended users' applications. For example:

i) Per EF 11-0263 dated May 16, 2011, there was program configuration error into the system (b) (4) (b) (4) (b) (4). As such, finished Advate batch # (b) (4) that was on hold was released by LIMS. The root cause was identified as (b) (4) due to lack of verification prior to the implementation in the system.

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ii) 15 batches of Advate drug substance and one Advate final batch status in LIMS were noted as "ready for release" as one (b) (4) result is "on line" in the system (b) (4) for the 15 batches. The root cause was noted as error due to the (b) (4)

B. Per EF #11-0315 dated June 14, 2011, wrong calculation was conducted on the control used for the (b) (4) (b) (4) The calculations were performed by LIMS on the (b) (4) measurement instead of (b) (4) (b) (4). The root cause was attributed to the LIMS calculation error.

C. Per EF #11-0116 dated March 03, 2011, SDS PAGE stability results for 2 (b) (4) samples of (b) (4) (b) (4) tests were entered and approved in LIMS under a false ID task. The root cause was that the LIMS procedure for approvals (b) (4) did not specify that the approval person must verify that the Task ID corresponds to the ID referenced. Also, the LIMS users interface software application failed to prevent the approval of the incorrect sample ID number.

3. Failure to correlate deviations/exceptions to better identify the root cause(s) and implement effective measures to correct and prevent the reoccurrence of these events in a timely manner, for example:

A. The (b) (4) column has been experiencing Pressure Increase Events (PIE) and High Pressure Events (HPE) since 2008, and 2 CAPAs (NE-CAPA-0009 and NE-CAPA-0017) were opened. However, these CAPAs are ineffective in that no action has been proposed to definitively address the fundamental problem of precipitation of protein(s) in the column.

B. NE-CAPA-0010 was opened as a result of Exception 08-0378 for the use of unqualified (b) (4) (b) (4) columns. After the CAPA was closed on 18 June 2010, EF #11-0388 and EF #11-0429 occurred related to the use of manufacturing area and equipment of inappropriate status. Yet, these exceptions were concluded as "not concerned by CAPA NE-CAPA-0010". If these equipment and areas had been clearly identified and labeled, the above referenced deviations would most likely not have occurred.

C. NE-CAPA-0020 was opened in June 2011 as a result of high percentages ((b) (4)) of production manufacturing deviations that are attributable to human factors since 2008. More immediate actions are recommended to reduce the number of such incidents while the investigation is in progress. For example:

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i. Per EF # 11-0452 dated August 08, 2011, during the filling of final container lot # (b) (4), some products flowed from the (b) (4) into the (b) (4). The incidence involved a (b) (4) which was left opened by the operation system right before the commencement of filling. The (b) (4) remained opened during the (b) (4) (b) (4) and was responsible for product loss that foamed onto the Class (b) (4). The filling process was stopped and the area was cleaned before filling continued. (The affected product lot is currently put on hold.)

D. Assessments of the qualification procedure of raw materials are not initiated after deviations related to the quality of raw materials had occurred. For example:

i. NE-CAPA-0012 related to the use of (b) (4) in cell culture.

ii. NE-CAPA-0014 related to the 7 (b) (4) batches that were out-of-specification for the (b) (4) (b) (4).

iii. EF# 10-0137 related to use of specific lots of (b) (4) that led to cell lysis which in turn resulted in the presence of the (b) (4) batches from (b) (4) at this facility. (b) (4).

4) Corrective and preventive actions are not instituted in a timely manner to prevent reoccurrences. For example:

A) No corrective and preventive actions have been instituted into several equipment leaks and associated systems that occurred since September 2009 in the cell culture area that could result in product contaminations, i.e., leaks on the (b) (4); leaks at (b) (4) and leaks on the (b) (4). (b) (4) the firm manufactures (b) (4) Advate: 32 equipment leaks occurred in 2009, 30 in 2010 and 30 so far in 2011.

B. (b) (4), several deviations of leaks that could result in the contamination of products were documented during the Advate purification processes: (b) (4) columns and equipment during the purification processes. For example: forty nine (49) leaks in 2009, forty five (45) leaks in 2010 and thirty four (34) leaks so far in 2011. No formal investigation and/or CAPA have been opened to

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address these leaks.

C. The corrective and preventive actions to prevent reoccurrences into observation of clumps noted during the (b) (4) was not conducted in a timely manner. Per Deviation #EF11-0264 dated May16, 2011 after opening of (b) (4) for production activities, a technician observed a light, reddish coloration on the (b) (4) column, located on the top of the bed about 1cm of the bed height. For example:

i) Per Deviation #EF11-0086, the deviation occurred on February 02, 2011, and the clumps were not sent to a contract lab for identification until August 2011.

ii) Although Event Form #11-0086 has been initiated, there is no documentation of investigation into the root cause of the clumps.

5. Corrective and preventive actions are not always implemented to prevent reoccurrences. For example:

A. Per EF #11-0422 dated August 05, 2011, it was stated that no corrective action and preventive action (CAPA) was needed as the result of the generation of iron filings during the intervention to dismantle the (b) (4) (b) (4) on June 28, 2011 that affected 27 drug substance lots. During the dismantling process, iron filings were introduced into (b) (4) and accumulations of the iron filing were noted on the (b) (4) when the (b) (4) was dismantled on June 28, 2011. The deviation report noted that the metal filings were visible to the naked eye and that the (b) (4) (b) (4) the metal filings from these batches. The lack of the institution of CAPAs failed to consider: (b) (4)

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i) The larger sizes of metal filings that were noted on August 2011 were the larger sizes that cannot (b) (4) (b) (4) and were the ones found (b) (4). The smaller filings may have (b) (4) the process and cause product contaminations.

ii) Although per the deviation report, the manufacturing incident and deviation was an isolated incident, and no need for CAPA, however, per the EF #11-0422, there is a high probability that the intervention carried out near (b) (4)

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(b) (4) on February/June generated the iron filings. There is no documentation that the observation of light reddish coloration on the (b) (4) Column (b) (4) per EF #11-0264 dated May 16, 2011 was reviewed and considered for corrective and preventive action.

iii) No documentation of the institution of preventive action to check, flush and clean the (b) (4) before use in production, whenever an intervention is conducted.

6. There is no qualification data to justify the (b) (4) maximum mixing time limits for (b) (4) of the batch record. Per the Validation Summary Report #2004-SD-PQ1/VER 1, only (b) (4) mixing time has been validated.

7. During the observations of the Advate filling and formulation processes the following deficiencies were note:

A) Curtains between the aseptic filling Class (b) (4) areas were observed covered with streaks of white film marks running down the entire curtains.

B. There are no assurances that the environmental monitoring conducted in the Advate Class (b) (4) formulation area is representative of the environmental conditions during the formulation process. For example:

i) The non-viable air monitoring equipment and viable air monitoring plate were observed to have been placed too far away from the activities that were occurring during the formulation processes, i.e., (b) (4) (b) (4)

ii) There is no documentation of viable bioburden floor sampling of high personnel traffic areas during Advate drug product formulation process. The only one floor location sampled during the observed bulk formulation activities was the sample floor area (b) (4) where no personnel movements were observed throughout the formulation.

iii) There is no documentation that formulation personnel monitoring was conducted after the formulation process.

8) The corrective and preventive actions instituted as a result of previous 2009 FDA-483 observations are inadequate as follows:

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A. The corrective actions instituted as a result of previous FDA-483 Observation #2 into Advate complaints of reconstitution difficulties and losses of vacuum during use are inadequate. For example:

i) Advate complaints of reconstitution difficulties and lack of vacuum have increased from 9 complaints per (b) (4) in 2010 to 43 complaints per (b) (4) so far in 2011.

ii) No additional investigations and corrective and preventive actions have been instituted to address the increase in these complaints in 2011. Complaints of reconstitution difficulties and lack of vacuum have been on the increase since 2006. The firm has instituted CAPAs, as recently as 2010, none of which have been completely successful in reducing the numbers of these complaints.

B. Inadequate corrective action was instituted as a result of previous FDA-483 Observation #4A (i) regarding the lack of upper mixing time validation of the (b) (4) (b) (4) of the batch record. Per the firm's response to the observation: the firm promised to validate the upper mixing time and implement accordingly in relevant Advate batch records. The validation has not been conducted as promised, instead a study titled: (b) (4), dated October 06, 2009 was provided for review.

C. Inadequate corrective action was instituted as a result of previous FDA-483 Observation #7 regarding the inadequacies of qualification of the (b) (4) storage of cell culture media used for (b) (4) in bottles. The previous hold time qualification study failed to meet (b) (4) criteria of (b) (4) at the beginning and end of the study. The hold time study was re-qualified as corrective action to the cited observation per Final Report 2009-(b) (4) dated May 27, 2010. Although the (b) (4) was documented for the start of the hold time study as (b) (4), there was no documentation of the (b) (4) of the media at the end of the (b) (4) hold time qualification.

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