DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	09/02/2011 - 09/27/2011* FEI NUMBER 2917293

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Andrea J. Goddard, Senior Director and SSF Site Quality Head

FIRM NAME	STREET ADDRESS
Genentech Inc	1 DNA Way
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
South San Francisco, CA 94080-4918	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

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not include the conclusions and follow-up.

THIS IS A REPEAT OBSERVATION FROM 06/2011

Specifically,

A) During our review of Deviation Report #506273 on 09/02/11, opened due to disintegrating (b) (4) (b) (4) gaskets on the vial washer in Area (b)(4) on February 21, 2011, we noted that the investigation failed to include instructions to compare particulates isolated from culled Avastin finished drug product vials (packaged Lot #(b) (4) ; Fill Lot #(b) (4)) with the disintegrating (b) (4) gasket material identified and recovered after identification of the discrepancy.

The investigation report, dated 07/26/11, states that a total of 12 isolated particulates from (b)(4) filtered Avastin vials were sent for analytical analysis (b) (4) and/or (b) (4)). However, the investigation failed to include analysis and comparison with the recovered disintegrating (b) (4) gasket material, in order to rule out potential (b) (4) contamination of this lot, which is currently in Quarantine status due to failing "Total Critical Particulates" via Automated Inspection.

B) During our review of Deviation Report #464179 on 09/12/11, opened due to an Area (b)(4) capper power outage during the fill of Avastin Lot #(b) (4) , (Packaged Lot #879296) on July 21, 2010, we noted that the investigation failed to describe:

1) Actions taken to address the capper oil leak discovered during the investigation
2) Disposition of the in process vials on the manufacturing line during the (b)(4) hour shutdown and repair period

There is no documentation to provide assurance that the capper oil leak was addressed/repaired prior to the resumption of manufacturing. Additionally, there is no documentation to provide assurance that the in-process filled/stoppered vials were discarded, as required per section 11.0 of SOP 1630.011.

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OBSERVATION 2

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

Specifically,

There is no data to provide assurance that the conveyance and capping of product-filled Avastin vials is performed in a "Controlled Primary HEPA filtered Area", as described in section 3.2.P.3.3 of your firm's Bevacizumab BLA (#125085).

The current design of the capping area, as observed during our tour of Area (b)(4) on 09/21/11, appears to allow a gap between the end of the HEPA filter coverage and the semi-permanent plastic barriers. This gap appears to permit the influx of air from the Class (b)(4) work environment, which would then be passed over the vials during the conveyance and capping process.

Additionally, your firm uses displaced stopper detector (DSD) equipment located upstream of the vial capping equipment in Room (b) (4), to verify the displacement between the stopper and vial. The parameter settings for the DSD equipment were derived from Document No. TR10-050 vol 1, titled "Defining the Reject Limit for the Displaced Stopper Detectors for (b) (4) 3" and microbial challenge studies performed by a contract laboratory. Your firm lacks adequate documented evidence to support the integrity of the microbial challenge studies performed by your contract laboratory. For example, during microbial challenge studies, (b) (4) were used to implement a pre-defined displacement between stopper and vial of study vials. There is no assurance that the thickness of the (b) (4) as reported were verified and accurate.

OBSERVATION 3

There was a failure to handle and store closures at all times in a manner to prevent contamination.

Specifically,

There is no data to provide assurance that the Avastin vial caps, manufactured by a contract facility in (b) (4) (USA) and/or (b) (4) , are "suited for packaging lyophilized and sterile liquid products", as described in section 3.2.P.3.3 of your firm's Bevacizumab BLA (#125085). These caps are listed in the BLA as "primary packaging components".

There is no data to provide evidence that the current procedures and practices in place, including the contract manufacturing, shipment, handling, and administration of the caps do not result product adulteration.

Notably, these caps are received in "folded" plastic bags (b) (4) caps/bag) inside cardboard boxes. The firm has no data and/or controls to provide assurance that this shipment in non-sealed plastic bags does not adversely affect the cap integrity, specifically with regard to cap bioburden.

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OBSERVATION 4

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

Specifically,

A) During our review of the media fill Lot #(b) (4) reconciliation form (FN2502), we noted that a total of 81 vials were rejected as "Line Clearance", and were put to waste (not incubated). However, according to section 3.0 of SOP QS00031, titled "Aseptic Media Fill Program", line clearance vials are to be "segregated, capped, and incubated".

There is no documentation to describe why these 81 vials were not incubated and examined for microbial growth, as required per your firm's procedures.

B) During our visual observation of the Aseptic filling operations for Avastin Lot #(b) (4) on 09/06/11, we observed one of (b) (4)operators resting his gloved hands on his midsection near the gown zipper. Per our request, this operator was counseled by his supervisor regarding proper Aseptic Technique during our tour. However, following the discussion with his supervisor, the operator resumed the practice of resting his gloved hands on his midsection near the gown zipper. We observed this operator performing and assisting in multiple line interventions during our tour.

Your firm's current SOP 1640.004, titled "Aseptic Techniques for GPMF Critical/Controlled Areas", lacks instructions for maintaining distance between gloved hands and the sterile gowning during filling operations.

C) During our tour of the portable pooled bulk tank in Area[(b)(4)] Room (b) (4) on 09/06/11, we visually examined the connection between the (b) (4) transfer tubing and stainless steel valve (attached to the pooled bulk tank). This valve is attached to the bulk pooled tank via (b) (4) . This (b) (4) transfer tubing and stainless steel valve are used to transfer product from the pooled bulk tank to the Area[(b)(4)] filler.

During our visual examination, we observed a buildup of condensate on the on the neck of the stainless steel valve, which was being fed by (b) (4) into the connection point between the valve (b) (4) transfer tubing, which was being held in place by (b) (4) . The procedure describing this connection is found in Figure 1 of SOP 1630.007, titled "Portable Tank to Filler Transfer Line [(b)(4)] (GPMF, Room (b) (4)", which states: "(b) (4) ". However, there are no specific instructions regarding the details of this connection (b) (4) .), in order to ensure the integrity of this connection and prevent the ingress of liquid condensate.

Notably, during our review of media fill Lot (b) (4) , we noted the following comment regarding the portable pooled bulk tank, "Technician… observed Transfer Tank pressure at (b) (4)". This comment suggests that the pooled bulk tank may occasionally experience negative pressure, potentially aiding the ingress of liquid condensate.

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*** DATES OF INSPECTION:**
09/02/2011(Fri), 09/06/2011(Tue), 09/07/2011(Wed), 09/08/2011(Thu), 09/09/2011(Fri), 09/12/2011(Mon), 09/14/2011(Wed), 09/15/2011(Thu), 09/19/2011(Mon), 09/20/2011(Tue), 09/21/2011(Wed), 09/22/2011(Thu), 09/27/2011(Tue)

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