April 2012 Inspectional Observations (form 483)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

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NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Paul E. Austin, PhD, Vice President Industrial Operations

FIRM NAME

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TYPE OF ESTABLISHMENT INSPECTED

Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

1. Sterility for all BCG lots manufactured in Building -(b)(4)- since the firm's last successful Sterility Test Validation in 2001 cannot be assured in that:

A. Protocol B006293 was conducted as a re-validation of the firm's sterility test method for BCG. The failure of the re-validation test resulted in failure of the method to detect yeast and mold in the bacteriostasis/fungistasis testing and questions the ability of the firm's current test method to detect yeast and mold, if present, in sterility test samples. Protocol B006293, was conducted to validate the sterility test method of BCG using the -(b)(4)- --------(b)(4)----------.

B. There have been no less than 58 deviations relating to the isolation of mold within the aseptic operations areas of Building -(b)(4)- (Grade -(b)(4)-) including, but not limited to, ----------(b)(4)---------- ---------- filling, and freeze drying since August 2010. The samples were isolated from operator gloves and gowns, viable air sampling, and surface sampling. There is a lack of assurance that if this mold were to have an adverse effect on product, it would be detected using the current sterility test method. Examples of mold deviations include, but are not limited to, the following:

i. Deviation #700014981 (dated 10/6/11) documents a failed glove touch plate where mold was isolated from the operators

gloves after the operator had completed aseptic product manipulations during filling of batch -(b)(4)- in Room -(b)(4)- of Building -(b)(4)-.

ii. Deviation #700014774 (dated 9/14/11) documents a failed gown sample where mold was found on the forearm of an operator working in the Grade -(b)(4)- area of Room -(b)(4)- in Building -(b)(4)-.

iii. Deviation #700014363 (dated 7/20/11) documents a failed active viable air sample when a fungal organism was detected in Room -(b)(4)- in Building -(b)(4)-.

iiii. Deviation # 700012212 (dated 9/7/10) documents an "objectionable organism" when mold was detected from a floor sample in Room -(b)(4)- in Building -(b)(4)-.

C. The container closures for ---(b)(4)--- produced cultures are ---------(b)(4)---------- in the grade -(b)(4)- ----------. There is a lack of assurance that contamination would be noticed in the --(b)(4)-- in that monitoring in this Grade -(b)(4)- area takes place only --(b)(4)-- (see observation 17A)

D. There are currently 26 BCG lots released to the U.S. market that are within expiry as of April 25, 2012.

2. Failure to assure that disinfection of manufacturing areas, including but not limited to, aseptic processing areas is adequate in that

A. The disinfectants used in the BCG-IT area have not been shown to be effective against mold spores on all surfaces in this area. Validation studies were only conducted using -------(b)(4)------- mold. The disinfectant effectiveness studies as documented in Report C017795 entitled "Year 2010 Re-Evaluation of the Approved Disinfectants / Sporicidal Agents" did involve the use of mold spores but was only conducted using ----(b)(4)---- carriers.

B. Sporicidal agents used to clean manufacturing surfaces and equipment are used at a minimum of --(b)(4)-- -----. This includes areas where mold is frequently isolated during environmental monitoring. For example, no less than 58 deviations relating to detection of mold is documented as being isolated from processing areas in Building -(b)(4)-. Most of these deviations relate to aseptic processing areas.

C. Corrective actions for mold detection in aseptic processing areas does not always result in additional cleaning with a sporicidal cleaning agent.

D. The firm experienced a media fill failure during room re-qualification for the BCG ---(b)(4)--- that had been ----------(b)(4)----------, the firm discovered mold under the original floor. The floor was replaced, equipment was placed back into service, the room was cleaned and disinfected with the sporicidal agents and a media fill was performed to re-qualify the room. The failed media fill included both bacterial and mold contamination.

3. The in-progress investigation (under Deviation 700015642) and associated corrective actions (under CAPA PR# 199616) regarding the safety test failure (active Type 3 Poliovirus detected during testing as per SOP 2ST-032 entitled "Poliovirus Testing – Test For the Absence of Active Virus") of Poliovirus ----------(b)(4)--------- Lot ----(b)(4)--- does not include the following:

A. An evaluation of the impact of the failure on all Poliovirus ----------(b)(4)---------- lots, Poliovirus ---(b)(4)--- ---------- lots, Poliovirus ----------(b)(4)--------- lots, and DTaP-IPV lots that may have contacted post-inactivation manufacturing equipment that also (as described at the end of this observation) may have come in contact with Poliovirus ----------(b)(4)--------- Lot -----(b)(4)----- or Poliovirus ----------(b)(4)---------- Lot ----(b)(4)-----. This Type 3 lot was the lot used in Poliovirus -----(b)(4)------ Lot ----(b)(4)----.

B. An evaluation of the need for precautionary remedial actions in the non-live viral manufacturing areas of Buildings -----(b)(4)----- that potentially (as described at the end of this observation) may have been exposed to live Poliovirus.

C. A thorough evaluation of the Building -(b)(4)- containment issues including those issues discussed under Observation #4.

Although Deviation 700015642 was open at the time of the current inspection, it was only open pending the results of ongoing investigational testing. No definitive root cause was identified for the safety test failure. Deviation 700015642 identified "first conclusions" as atypical chromatography profiles associated with a period of increased -(b)(4)- levels at the ----------(b)(4)---------- or the potential of low level cross contamination in the QC laboratory. Poliovirus ----------(b)(4)---------- Lots ----------(b)(4)-------- had atypical profiles and increased ----------(b)(4)---------- and were used in the manufacture of Poliovirus ----------(b)(4)---------- Lot ----(b)(4)---- which was used in the manufacture of Poliovirus --(b)(4)-- ---------- Lot ----(b)(4)----. As per Report C020127 entitled "Evaluation of the Impact of Atypical ---(b)(4)--- Profiles and -(b)(4)- Alert Limit Excursion Levels on the Positive Absence of Active Virus Test" "…There is a theoretical probability that the process observations (i.e. atypical profile at ----------(b)(4)---------- ----------) may influence the safety test via incomplete inactivation. The associated impact is expected to be very low based on the quality attribute (----------(b)(4)---------- --------(b)(4)-------- and safety test at inactivation) and ---(b)(4)--- analysis. Any link is highly theoretical in terms of an impact to the inactivation process and corresponding link to the observed safety test excursion."

4. The following containment issues apply to the activities conducted in, or in support of, Building -(b)(4)- where live Poliovirus is grown for use in the manufacturing of Poliovirus Monovalent Inactivated or Buildings -(b)(4)- (Poliovirus Monovalent -(b)(4)- Concentrate manufacturing) or -(b)(4)- (Poliovirus Trivalent Concentrate manufacturing and DTaP-IPV formulation). Buildings --(b)(4)-- house non-live virus manufacturing activities:

A. The effectiveness of the disinfection (specifically for Poliovirus) of the Building -(b)(4)- facility, equipment (including electronic equipment such as air samplers), and outer IPV Poliovirus Monovalent Inactivated containers by ----------(b)(4)---------- solution as conducted under SOP 1ES-428

or SOP 1ES-429 or SOP 16FM-201 entitled) has not been validated under the actual conditions of use. The only validation conducted for these practices was a review of a literature articles including an article in which the effectiveness ----------(b)(4)---------- solution was evaluated against -(b)(4)- Poliovirus on a --(b)(4)--. This observation also applies to the -----(b)(4)----- disinfectants used to disinfect containers received in Building -(b)(4)- from Building -(b)(4)- as described in SOP 1ES-489.

B. There are no written procedures as to how to conduct the ----------(b)(4)---------- (mentioned in Standard Work Instructions J005265 entitled “Safety and Containment procedures for -(b)(4)-, IPV” and described under SOP 16FM018) of Building -(b)(4)- equipment (such as --(b)(4)---) used in the live virus area that are sent off site for calibration and maintenance. Additionally no validation of this procedure has been performed.

C. Calibration and maintenance of equipment used in the Building -(b)(4)- live virus processing area (such as air samplers) that has been surface disinfected as described under Standard Work Instruction J005265 is performed in the Metrology Laboratory located in Building -(b)(4)-. Calibration and maintenance of equipment from other areas of the site are also performed in the same area by the same personnel however generally at different times. There are no written procedures requiring this temporal segregation of equipment while in Building -(b)(4)-.

D. The scrubs which are worn under Tyvek suits by employees who work in the live virus area of Building -(b)(4)- are not decontaminated prior to their pick up by an outside contactor for laundering. Additionally employees of the outside contractor have unsupervised access to non live virus areas of Building -(b)(4)- and other buildings on the site such as Building -(b)(4)-, Building -(b)(4)-, and Building -(b)(4)- (where non live manufacturing activities are conducted) in order to retrieve soiled scrubs and supply laundered scrubs. There are no written procedures for the contactor describing how these activities are to be performed. No evaluation regarding the need to decontaminate the scrubs prior to removing them from Building -(b)(4)- has been performed.

E. A wet/dry vacuum was observed in a janitorial area (Room -(b)(4)-) of Building -(b)(4)-. There were no records describing what the vacuum was used for, nor procedures describing its use.

F. During the time period surrounding the dates of manufacture of the Poliovirus Monovalent Inactivated lots (in Building -(b)(4)-) used in Poliovirus -------(b)(4)------- Lot ----(b)(4)---- (June-October 2010) over 10,000 facility monitoring alarms for differential pressure were recorded by the Facility Monitoring System for this building. There is no documentation that each of these alarms was evaluated for its impact on the manufacturing activities conducted. As per SOP 1ES-300 entitled “Routine Monitoring of Pressure Differentials in the Manufacturing Area” the production areas must investigate all pressure differential alarms promptly. Additionally there is no written procedure governing how the “--(b)(4)-- Review of Environmental Records –IPV” are performed. Review of these Building -(b)(4)- related trending records from July-October 2010 showed numerous differential pressure spikes for which there is no documentation of an investigation.

G. In April 2009 under Study Project No. 08608 the firm was provided with various recommendations as to how to reduce the number of alarms from Building -(b)(4)-. As of the date of this inspection none of the recommendations had been implemented.

5. Other Poliovirus containment issues:

A. On 2-22-12 an employee was directly exposed to live Poliovirus in Building -(b)(4)- and was taken to the site’s health center. No deviation was written for this incident nor was there any documentation indicating how the employee was decontaminated before being taken to the health center.

B. Tubing is ----------(b)(4)---------- area of Building ----(b)(4)---- ---------- of the Poliovirus Monovalent as per SOP 1ES-429 entitled “The Equipment and Material Flow Procedures for the IPV Production Facility, Building -(b)(4)-. This tubing is only disinfected with ------(b)(4)------.

C. On 4-14-12 personnel including a CSO were allowed, in the presence of Management, to enter a non live virus are of Building -(b)(4)- (which is -(b)(4)- to Building -(b)(4)-) after having been in the live virus testing area of Building -(b)(4)-. This is contrary to SOP 1PL-090 entitled “Personnel, Equipment and Material Flows”.

D. ----------(b)(4)---------- are used to ----------(b)(4)---------- and store -(b)(4)- filters used in Building -(b)(4)- and the live virus area of Building -(b)(4)-. Building -(b)(4)- is a live Poliovirus manufacturing facility. The tanks are---(b)(4)---- in Building -(b)(4)- after use.

E. On 4-13-12 during the ----------(b)(4)---------- Testing (under SOP 2ST-012 entitled “Poliovirus ----(b)(4)---- Assay) of Inactivated Poliovirus Monovalent Lot -(b)(4)- in Room -(b)(4)- of the QC Virology, Live Virus Assay Laboratory located on the -(b)(4)- floor of Building -(b)(4)- a personal cell phone was observed on a desk in the same room. Standard Work Instruction J005428 Version 4.0 entitled “Cleaning/Disinfecting and Operational Requirements for Routine Laboratory Testing in All Areas of QC Virology” does not prohibit this practice however there are no procedures in place describing what disinfection if any is required for personal items taken in to this live Poliovirus testing area.

6. Samples of ----------(b)(4)----------, Lot -(b)(4)-, were used in study SS01-006-Rep(version 2.0) to demonstrate the robustness of the IPV safety test. The robustness study failed to include an evaluation of separate test results for Lot -(b)(4)- that included a positive test for Type -(b)(4)- virus with the -(b)(4)- sample.

7. Validation of the maximum --(b)(4)-- for the ------(b)(4)------ chromatography column used for purification of poliovirus monovalents has not been determined (SS01-027-Rep).

8. SOP 1ES-481, Personnel Conduct and Aseptic Technique for the Aseptic Processing Area-Filling and Packaging, Building

-(b)(4)- discusses procedures for operators to use when filling vaccine products in Room -(b)(4)-. During observations on 4/11/12 of aseptic filling for Daptacel® in room -(b)(4)-, the SOP was not followed in at least the following examples:

A. Operators were observed to reach across the open vials that are to be filled in order to remove downed vials from the accumulation table or stoppers that may be stuck in the stopper rail.

i. Deviation # 700015281, dated 11/14/11, documents the left forearm of a gown sample of a filling operator with an out of limit result of 9 CFUs.
ii. Deviation # 700013656, dated 3/28/11, documents recovery 3 CFUs of "objectionable organisms" from the gown of a filling operator.

B. -(b)(4)- used to dislodge stoppers and downed vials in the Grade -(b)(4)- area are not regularly sanitized. The ----------(b)(4)----------. Further, one operator was observed placing the -(b)(4)- used to remove downed vials directly onto the stainless steel surface of the filling suite.

9. The goggles worn by operators who perform the aseptic filling of all of the products filled at this site (on the aseptic filling line located in Building -(b)(4)-) are not rendered sterile prior to use. As per SOP 1PL-402 Version 5.0 entitled "Aseptic Processing Area Gowning and Controlled Area Garments" they are sanitized. Additionally these goggles are not routinely monitored as part of the monitoring of the aseptic filling operators.

10. The following changes were not reported to the Agency:

A. Change Control 2037829 was closed on 03 December 2010. This change was for the addition of identity testing on Fluzone and PRP-T.

B. Change Control 2038691 was closed on 5 August 2011. This change was for the extension of expiry dating of the current in-house reference vaccine (Lot -(b)(4)-) for ----------(b)(4)----------.

C. Change Control 2062497 was closed on 08 September 2011. This change was for the extension of expiry dating for the positive control vaccine -(b)(4)- Lot -(b)(4)-.

11. Failure to notify CBER of significant changes in the manufacture of IPV intermediates:

A. Changes made to the IPV process (change control 2020065) resulted in demonstrated higher levels of -(b)(4)- in --------(b)(4)---------. Change control 205779 subsequently rescinded one of these changes.

B. Changes made in the procurement of ----------(b)(4)---------- (change control 2007-0552) used in the IPV safety test were not reported.

12. There is no SOP for personnel conduct and aseptic technique for the aseptic processing of BCG areas in Building -(b)(4)-. These aseptic operations include, but are not limited to, ----------(b)(4)----------, filling, and freeze drying.

13. Environmental monitoring is insufficient in the filling suites and other Grade (b)(4) areas: Examples include:

A. Active viable air monitoring is conducted ----------(b)(4)----------. Shift times vary for different operations but shifts in filling last for -(b)(4)-. For example, according to the firm, a filling shift in Building -(b)(4)- would be approximately -(b)(4)-. The active viable air monitoring takes place during the regular shift at -(b)(4)- locations for approximately -(b)(4)- per sample. The total of the -(b)(4)- samples would account for approximately ---(b)(4)--- total active viable air sampling time for an -(b)(4)- shift. A similar scenario takes place during filling operations in the BCG filling area in Building -(b)(4)-.

B. Passive viable monitoring is not representative of the operations taking place in some Grade -(b)(4)- areas. For example, there is ----------(b)(4)---------- passive air monitoring during the filling operations and is located ---------(b)(4)----------. Areas where most dynamic activity (loading of stoppers, manipulation of vials or stoppers) takes place are not represented for viable monitoring.

14. There is a lack of document control for procedures in a category referred to as "Standard Working Instructions" (SWI). There is an excess of 200 versions of SWIs used throughout the firm. The firm defines these documents in SOP 1PL-100 (version 12), Management of Master GxP Documents. It states in part that the SWI are sequential instructions that explain a precise description of each work activity and is intended to describe the processes, associated tasks and responsibilities to create, review, approve, distribute and archive. The document further defines SWI stating "SWI's shall be sequenced in the order of operations accurately reflecting the requirements and relevant activities. SWI's state the "how" and further support SOPs and/or Policies. Standard instructions can be SWI's if they also meet the following criteria:
a) Not explicitly required by GMP regulations
b) Not a license requirement
c) Validation or stability have not identified its instructions as a critical control parameter
d) Not required by company policies
e) Form in document not required to be reviewed by Quality Rep

For example:

A. SWI J005428, Cleaning/Disinfecting and Operational Requirements for Routine Laboratory Testing in All Areas of QC Virology, is used to describe routine cleaning/disinfecting procedures for routine laboratory testing in all areas (including live virus areas) of QC Virology. This includes sections entitled: Initial Operational Requirements before Entering the Laboratory; effective use of a Laminar Flow Biosafety Cabinet; Planning for Testing; Performing Procedures (including use of aseptic

technique); Waste Disposal Procedures (including biohazard waste both bacterial and viral); Final Operational Requirements in the Laboratory; Dealing with Spills, and Dealing with Broken Glass.

B. SWI J005084, Aseptic Techniques, describes the aseptic techniques used to maintain the sterility and purity of vessels or cultures under various conditions in the Diphtheria and Tetanus Department to aid trained Fermentation personnel with the necessary steps required to perform aseptic techniques.

15. Failure to ensure that the Stability program is sufficient and accurate:

A. The polio potency test (D-Antigen ------(b)(4)------) which is performed on both ---(b)(4)--- Bulk and reconstituted Pentacel has no specifications and is not a licensed test. This is a repeat observation.

B. Stability indicating parameters on reconstituted Pentacel (Diphtheria Potency, Tetanus Potency, and component pertussis mouse immunogenicity) are only being tested at the ---------(b)(4)--------- shelf life.

16. Keys are not being stored in a controlled manner in at least the following areas:

A. Reference standards such as Tetanus Antitoxins, Diphtheria Antitoxins, and Tuberculin Standard are being stored in a ----------(b)(4)----------. The keys to -(b)(4)- are stored in Room -(b)(4)- in a -(b)(4)-. The keys to the -(b)(4)- are being stored in an ---(b)(4)--- in Room -(b)(4)-

B. BCG --------(b)(4)------- seeds are being stored in locked freezers (----------(b)(4)----------) in Building -(b)(4)-, Room -(b)(4)-. The keys to these freezers are being stored in a --------(b)(4)--------. During a walk through of the facility on 12 April 2012, the -(b)(4)- was observed to be open. According to the firm, the -(b)(4)- was left opened all night and that they were unsure for how long.

17. During an inspectional walkthrough of the BCG Facility in Building -(b)(4)- on 11-12 April 2012, the following was observed:

A. BCG-IT is a sterile product manufactured using aseptic processing from the ----------(b)(4)----------. The cell culture ----------(b)(4)----------. In addition, the product ----------(b)(4)----------.

B. There is no usage logbook for the ----------(b)(4)----------.

C. The SOP was not present during observation of the propagation of BCG Cultures on 11 April 2012.

18. Propogation of BCG is described in SOP 13BC-638 version 9.0 and Batch Production Record (BPR) -(b)(4)- ----- version 5. The following discrepancies were noted in these procedures:

A. ----------(b)(4)----------

B. ----------(b)(4)----------

19. BCG ----------(b)(4)---------- seeds are not always stored in a controlled manner.

A. The BCG -(b)(4)- seed (Lot -(b)(4)-) which was to be stored in a --(b)(4)-- in the Manufacturing Distribution Center (Building -(b)(4)-, Freezer -(b)(4)-) could not be located for a period of about 45 minutes. The seed was eventually found on a shelf with other materials in -(b)(4)-.

B. SOP 1PL-150, Requirements and Maintenance of Sanofi Pasteur Seedstock, The ----------(b)(4)----------, Bldg -(b)(4)-, states that the movement of seed banks is tracked by the Inventory Transfer Form. The Inventory Transfer Forms do not reconcile for BCG -(b)(4)- seed (Lot -(b)(4)-) stored in Freezer -(b)(4)- The Inventory Form (dated 20 December 2010) states that the current balance is -(b)(4)- vials. However, the Inventory Form (dated 19 December 2011) states the previous balance is -(b)(4)- vials. There is no documentation or written explanation for the discrepancy of 2 vials on the Inventory Forms.

C. SOP A004253, Management of Seed Lots and ------(b)(4)-----, states that seeds must be inventoried in -(b)(4)-. The Inventory Transfer Form states that -(b)(4)- vials are withdrawn from the ----(b)(4)---- on 20 December 2010 for stability purposes. -(b)(4)- shows that -(b)(4)- vials are withdrawn from the ----(b)(4)--- on 20 December 2010.

D. SOP A004253, Management of Seed Lots and ------(b)(4)-----, states that the seed inventory should be reconciled a minimum of -(b)(4)- times per year and presented to the Site Seed Committee for review and verification. The documentation presented for the reconciliation does not compare what is in inventory compared to what should be in inventory.

20. Deficiencies in training include:

A. Operators ---(b)(6)--- performed part of the propogation of BCG Culture on 11 April 2012. These operators were trained according to SOP 1QA-058, Training Log and Lesson Plan for Bulk Manufacturing, BCG Production, Building -(b)(4)-. The training procedure does not provide detailed instructions on how training is to be performed such as the number of -(b)(4)- to be inoculated. Training of Operators --(b)(6)-- documented 24 -(b)(4)- were inoculated during training but -(b)(4)- are inoculated during routine production.

B. Operators --(b)(6)-- routinely perform Purification of Tetanus Toxoid Using Ammonium Sulphate Fractionation. Both operators were trained on versions of the SOPs that do not reflect normal manufacturing (Deviation 7000143365). Operator

-(b)(6)- was trained by Operator -(b)(6)- under the current training procedures on 02 February 2011. SOP 26PL-002 states that trainers should have sufficient documented evidence of qualification, knowledge, and/or skill in the subject area that they perform training. Training for Operator -(b)(6)- was documented to have been performed on 09 July 2004. This was determined to have not been his official training but was a batch manufactured during normal processing. This was allowed since Operator -(b)(6)- was previously trained and because he was “grandfathered” in to the new training program. SOP 26PL-003 version 2.0 which was effective at that time does not state that this was allowed.

C. Shop Floor Quality Personnel (--(b)(6)--) perform review of Batch Production Records for Tetanus Purification (BPR -(b)(4)-). These personnel are trained according to SOP 1QA-117, Training Log and Lesson Plans for Quality Operations Operational Quality. The training procedure does not provide detailed instructions on how training is to be performed and criteria to be met or details of the manufacturing processes

D. Deviation 700012621was closed on 4 April 2011. -----(b)(4)---- testing was performed on 12 batches of Tetanus Toxoid -(b)(4)- and 4 batches of Tetanus Toxoid ----------(b)(4)---------- from July 2009 to November 2010 injecting -(b)(4)- of product into the animals instead of the licensed -(b)(4)- of product. The area supervisor approved the testing. This deviation was not noticed until 03 November 2010. The technicians who perform the -------(b)(4)------- Test were “grandfathered” into the new Traning Program. The instructions on how to grandfather individuals is not specifically stated in the Training SOP effective at that time. In addition, the training of individuals after a prolonged absence such as maternity leave is not consistent.

21. Deviation 700014365 was opened on 27 July 2011 due to a step in the BPR not being performed. The following deficiencies were noted from the review of this deviation:

A. Tetanus toxoid is purified by a ----------(b)(4)----------. Prior to 15 March 2004, the ----------(b)(4)---------- ----------. After 15 March 2004, the ----------(b)(4)---------- ---------- was performed by ----------(b)(4)----------. Change control (03-934) was initiated for this change. This change was classified as a minor change and was never reported to CBER.

B. Since 15 March 2004, -(b)(4)- lots of ----------(b)(4)---------- Tetanus toxoid were manufactured using an unlicensed process. Daptacel ((b)(4) lots), Adacel ((b)(4) lots), Pentacel ((b)(4) lots), Tenivac ((b)(4) lots), and DT ((b)(4) lots) were manufactured from these unapproved lots of tetanus toxoid and released to the US market.

C. A BPDR has not been filed to report the product on the market manufactured with the unapproved change in manufacture of tetanus toxoid.

D. There is no assurance of Quality oversight in the release of tetanus toxoid. Tetanus toxoid, manufactured using an unapproved change, has been released for further processing since 2004. SOPs and deviations, not representing the licensed process, were not being followed. GMP Update Training did not provide the required information for both manufacturing and quality staff to prevent this occurrence.

E. CAPA 195591 was opened as a result of this deviation to address that there was no assurance that production areas were performing the manufacturing steps as stated in their SOPs. This review did not evaluate if the SOP and BPR was compliant with the license.

F. CAPAs 195597, 195596, 196238 were opened as a result of this deviation to address that there was no assurance that Tetanus Purification staff and Senior Management realized the criticality of following GMPs and documentation. This review did not include Operation Quality who was approving the BPR and other manufacturing areas.

G. CAPAs 196241 and 196242 were opened as a result of this deviation to address that there was no assurance that there was enough trained personnel (Management) present during manufacturing. This review did not address the potential need for an increase in Quality personnel to be present during routine manufacture.

22. The following supplements that were provided to CBER did not contain the complete information to adequately address approval.

A. STN 125145/107 (+5) to include ----------(b)(4)---------- in Building -(b)(4)- was approved on 3 May 2010. This submission provides information on manufacturing that occurs in this building. This submission did not state that live IPV testing occurs on the -(b)(4)- floor.

B. STN 125147/167 to include a new ----------(b)(4)---------- Reference Standard was submitted on 24 December 2010. This submission did not provide trending data which showed the link to clinical data.

C. STN 125145/----------(b)(4)---------- ---------- ----------. Deviation 7000143365 states that the area supervisor in March 2004 directed the staff to make the change.

23. SOP 1PL-062, Procedure for Reporting Failure Investigations, states that after populating the general information about the deviation select Material/Batch Information from the Action Box to the upper right of the screen. This procedure was not followed for the Deviations 700014874 and 700015006. In addition, deviations surrounding testing of product for Sanofi Pasteur Inc. can also not be entered in this system as stated above.

24. SOP A005400 states that critical defects are defined as defects that ----------(b)(4)---------- ----------. Major defects are defined as those

that ----------(b)(4)----------. Appendix 2 states that vial cap imperfections which include incomplete crimping are classified as a -(b)(4)- defect. This type of defect may lead to safety concerns concerning sterility. SOP A004241 provides the procedures for notifying management of all significant quality and regulatory issues. This SOP does not include detailed instructions on the notification of critical complaints.

25. Deviation 700012133 was opened on 08 September 2010 for the incorrect specifications for BCG Diluent. The General Safety Test (GST) was removed from the master specification list even though this was a licensed test requirement for release to the US. BCG Diluent (24 lots) was released to the US market without the performance of GST. Quality oversight was not adequate in review of a change to the BCG Diluent Specification which was mistakenly removed from the General Safety Test without Agency approval. As a result, 24 lots of BCG Diluent were released to t he U.S. market with no GST which is required in the license.

26. Deviation 700015401 was opened on 08 December 2011 for a ------(b)(4)------ contamination during fermentation of Tetanus Toxoid lot -(b)(4)-. Once the contamination in the -----(b)(4)----- was observed, the operators --(b)(4)-- the ----------(b)(4)---------- is not approved in their written procedures. The Batch Records used for this unapproved step in the process were not controlled. The operators printed out an uncontrolled batch record for recording of these additional steps. The deviation does not address the use of uncontrolled batch records.

27. CAPA PR# 202664 which was created to address repeated bioburden excursions during the manufacturing of Fimbria (Component of Pertusis) (----------(b)(4)----------) was not approved until April 13, 2012; over 4 months since the trend was identified

28. The following facility maintenance issues were observed:

A. Nesting birds in the intake grills for the air handling units serving Building -(b)(4)-

B. Rusted electrical conduit near Water for Injection (WFI) production Still -(b)(4)- located in Building -(b)(4)-

C. A leak on a condenser of WFI Still -(b)(4)-

D. Water marked boxes containing HEPA filters located in the Building --(b)(4)-- Floor HVAC area. There are no written procedures instructing Maintenance Services personnel as to how to inspect the acceptability of HEPA filters prior to installation.

29. There is a lack of assurance that logbooks, temperature charts, and autoclave printout information is reviewed by management. For example:

A. There is no SOP that requires review of any autoclave log books, including but not limited to, logbooks that document dates, load contents, and autoclave run numbers for autoclaves used to sterilize production equipment and autoclaves to decontaminate live virus and bacteria. SOP A005256, Control of Logbooks is the SOP that deals with management of logbooks used throughout the firm, including autoclave logbooks. The SOP ambiguous regarding review of logbooks by management in that the SOP only states that a -(b)(4)- review cycle for review of log books is recommended. Further, review of both sterilizing and decontamination autoclave charts revealed that charts are not always documented as having been reviewed.

30. Strict control is not exercised over final product labels. Final product labels are stored in locked cages in Room -(b)(4)- of the Building ---(b)(4)---. The key to these cages was observed stored unlocked in an open working area of Building -(b)(4)-. All personnel who have access to Building -(b)(4)- and Room -(b)(4)- therefore have access to the labels. Of the approximately -(b)(4)- personnel who have access to both Building -(b)(4)- and Room -(b)(4)- only approximately -(b)(4)- require access to the finished product labels. US products including ImmuCyst, Pentacel, Daptacel, Tubersol, Adacel, and Tenivac are labeled at this site.

31. No routine testing (including identity testing) is performed on each lot of -(b)(4)- that is used as a component (----------(b)(4)----------) in ImmuCyst (BCG-IT).

32. Building -(b)(4)- houses the Live Virus Testing Laboratory on the -(b)(4)- floor and the Non-live Virus Testing Laboratory on the -(b)(4)- floor. The virus laboratories are pressurized to control possible cross contamination and to protect product test samples. There is no SOP in Building -(b)(4)- laboratories that instruct analysts as to what course of action to take when the pressure in the rooms is out of limit. Further, there are no periodic reviews of the differential pressure printouts to determine if the pressure is within range. Instances have occurred where the differential pressure was out of limit but it was not discovered until the firm had a failure of a polio safety test, reviewed the pressure differential print outs and deemed that the pressure failure may have been contributed to the failure of the safety test.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE	/s/	Paula A. Trost, Investigator Mihaly S. Ligmond, Investigator	**April 25, 2012**

Tina Roecklein, CSO
Ronald E. Lundquist, Research Chemist

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