Inspections, Compliance, Enforcement, and Criminal Investigations

Sanofi Pasteur 7/12/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville, MD 20852-1448

JUL 12, 2012

WARNING LETTER

CBER-12-07

UPS EXPRESS MAIL

Olivier Charmeil
Senior Vice President, Vaccines
Sanofi
World Wide Headquarters
54 rue La Boétie
Paris, France 75008

Dear Mr. Charmeil:

The Food and Drug Administration (FDA) conducted inspections of Sanofi Pasteur S.A., located at Campus Merieux, 1541 Av Marcel Merieux, Marcy l'Etoile, France, between March 19 and April 2, 2012, and Sanofi Pasteur Limited, located at 1755 Steeles Avenue West, Toronto, Ontario, Canada, between April 10 and April 25, 2012. During the inspections, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of your licensed biological drug products and intermediates. Deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210, 211, and 600-680. At the close of each inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to each facility's compliance with CGMP. Significant deviations observed during the inspections include, but were not limited to, the following:

Sanofi Pasteur Limited, Toronto, Ontario, Canada

1. You failed to establish the accuracy, sensitivity, specificity, and reproducibility of test methods employed by your firm [21 CFR 211.165(e)]. Sterility for all lots of TheraCys®, BCG Live (Intravesical) (BCG-IT) manufactured in Building **(b)(4)** since the last successful BCG Sterility Test Method Validation in 2000 cannot be assured. Revalidation of the BCG Sterility Test Method conducted from March through April 2012 failed acceptance criteria for bacteriostasis/fungistasis testing; there is no assurance that the test method is capable of detecting yeast and/or mold in the product. Further, there have been no less than 58 documented non-conformances relating to the isolation of mold within the BCG aseptic processing areas (Grade **(b)(4)** **(b)(4)** areas) of Building **(b)(4)** since August 2010.

2. You failed to assure an adequate system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)]. For example:

a. Your standard operating procedure (SOP) 1ES-114 entitled "Environmental Monitoring: Detailed Description for Building **(b)(4)**, Main Filling Areas" requires that active viable air monitoring in Grade **(b)(4)** areas be performed **(b)(4)**. Monitoring is performed at **(b)(4)** locations for approximately **(b)(4)** per location. However, filling shifts in Building **(b)(4)** are approximately **(b)(4)** in duration.

b. On April 12, 2012, filling of BCG-IT lot **(b)(4)** was observed in Room **(b)(4)** of Building **(b)(4)**. Active viable air monitoring was observed being performed approximately **(b)(4)** into the fill at **(b)(4)** locations for approximately **(b)(4)** per location. However, filling was observed to be approximately **(b)(4)** in duration.

c. Standard Work Instructions J004898 entitled "Flat Surface and Gown Monitoring Using **(b)(4)(b)(4)**" does not require monitoring of goggles worn by operators in the Grade **(b)(4)** areas, including filling operators. Goggles are not rendered sterile prior to use but instead are surface sanitized with **(b)(4)**.

3. You failed to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42(c)(10)(v)]. For example:

a. Report C017795 entitled "Year 2010 Re-Evaluation of the Approved Disinfectants/Sporicidal Agents" (effective date October 8, 2011) used bacterial and mold spores to test the effectiveness of disinfectants and sporicidal agents used at your facility, including the BCG aseptic manufacturing areas in Building **(b)(4)**. The effectiveness study is inadequate in that it did not evaluate use of the disinfectants and sporicidal agents on surfaces other than **(b)(4)**.

b. Your SOP entitled "Disinfection Program for Equipment and Manufacturing Areas in Building **(b)(4)**; BCG Department" is inadequate. Sporicidal disinfection of aseptic manufacturing areas using **(b)(4)** is only required to be performed **(b)(4)**. There have been no less than 58 documented non-conformances relating to the isolation of mold within the BCG aseptic processing areas (Grade **(b)(4)** areas) of Building **(b)(4)** since August 2010.

c. There is no documented evidence that corrective action in followup to non-conformances relating to the isolation of mold within the BCG aseptic manufacturing areas includes cleaning with a sporicidal agent.

4. You failed to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including validation of all aseptic processes [21 CFR 211.113(b)]. For example:

a. Your SOP 1ES-481 entitled "Personnel Conduct and Aseptic Technique for the Aseptic Processing Area – Filling and Packaging, Building **(b)(4)**" is not followed.

i. On April 11, 2012, a filling operator was observed to reach across open vials that were to be filled in order to remove downed vials from the accumulation table and stoppers that were stuck in the stopper rail. Written investigation reports document deviations for out of limit results on gowns of filling operators, including deviations #700015281 and #700013656.

ii On April 11, 2012, a filling operator was observed to place **(b)(4)**, used to remove downed vials and stoppers that were stuck in the stopper rail, onto the stainless steel base of the filling unit.

b. There are no written SOPs describing personnel conduct and aseptic technique for aseptic processing conducted in BCG areas in Building **(b)(4)**. Operations performed in these areas include filling and freeze drying.

5. You failed to establish and follow a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)]. For example:

a. Diphtheria potency, tetanus potency, and component mouse immunogenicity testing on reconstituted Pentacel® are **(b)(4)** shelf life (30 months); testing is not being performed at the 12 and 18 month time points.

b. Review of stability data indicates that the D-Antigen **(b)(4)** test is being performed on reconstituted Pentacel® as the Poliovirus potency test; this test has no approved acceptance criteria and is not a licensed test.

6. You failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, inprocess materials, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. The General Safety Test (GST) for BCG Diluent was removed from the Master Test Specification document in error. During a comparison of the Master Test Specification document against regulatory requirements in September 2010, the discrepancy in the specification for BCG Diluent was discovered. BCG Diluent, manufactured using an unapproved change, was released between 2009 and 2010.

7. You failed to inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application [21 CFR 601.12]. For example:

a. Change Control 2007-0552 describes the change in the procurement of **(b)(4)** used in the IPV safety test. Instead of **(b)(4)** shipped to your facility. This change was not reported to the Agency.

b. Change Control #2037829, created on August 13, 2010, describes the implementation of identity testing **(b)(4)** of Fluzone® and PRP-T. The additional release tests were not reported to the Agency.

c. Change Control #2038691, created on August 26, 2010, describes the extension of the expiry date of the current in-house reference **(b)(4)** vaccine (Lot **(b)(4)**) used for **(b)(4)** Testing. The change control requests extension of expiry to August 31, 2011. The extension of expiry dating on the reference used for release and stability testing was not reported to the Agency.

d. Change Control #2062497, created on July 28, 2011, describes the extension of the expiry date for the current in-house reference **(b)(4)** vaccine (Lot **(b)(4)**) used for **(b)(4)** Testing. The change control requests extension of expiry to August 1, 2012. The extension of expiry dating on the reference used for release and stability testing was not reported to the Agency.

e. Change Control #2020065, created on October 14, 2009, describes significant changes in the manufacture of IPV intermediates. Changes made to the **(b)(4)**. These changes were not reported to the Agency and were partially rescinded, with respect to **(b)(4)**, in 2011.

f. Change Control #2067746, created on October 6, 2011, describes a change to the Tetanus Toxoid manufacturing process; specifically, the implementation of a **(b)(4)**. During the investigation for Quality Notification for Deviation #700014365, it was determined that the **(b)(4)**steps had not been performed since 2004, at which time an area supervisor instructed operators to implement the **(b)(4)** process. This deviation in manufacturing was not fully evaluated until July 2011, and the change was not reported to the Agency until March 2012.

Additionally, significant deviations in the manufacture of your intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FD&C Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

ORGANIZATION AND PERSONNEL

8. Your quality control unit failed to review and approve written procedures. Standard Work Instructions (SWIs), which include detailed instructions for operators and technicians, are not required to be reviewed and approved by the quality control unit. Examples include SWI J005428 entitled "Cleaning/Disinfecting and Operational Requirements for Routine Labortory Testing in All Areas of QC Virology" and SWI J005084 entitled "Aseptic Techniques."

9. Your SOP 1QA-058 entitled "Training Log and Lesson Plans for Bulk Manufacturing, BCG Production, Building **(b)(4)**" is inadequate. Lesson Plans do not include specific details on how training is to be conducted. Review of Supplement 13 entitled "Propagation of BCG Culture Lesson Plan" revealed that instructions do not include the number of **(b)(4)** to be inoculated. Review of operator training records revealed that the number of **(b)(4)** inoculated using the Lesson Plan does not reflect the number inoculated during routine manufacturing.

10. Your SOP 1QA-117 entitled "Training Log and Lesson Plans for Quality Operations Operational Quality" is inadequate. Lesson Plans do not include specific details on how training is to be conducted. Review of Supplement 14 entitled "Executed Batch Record Review Lesson

Plan" revealed that instructions do not include details on how to perform a review for, among other elements, "completeness" or "GMP and GDP compliance."

BUILDINGS AND FACILITIES

11. Your SOP 1PL-090 entitled "Personnel, Equipment and Material Flows" is not followed. On April 13, 2012, facility personnel and an FDA investigator were allowed to enter the washing and sterilizing area of Building **(b)(4)** immediately after having been in the live virus testing area of Building **(b)(4)**. SOP 1PL-090 **(b)(4)**.

12. There is no documentation to confirm that all pressure differential alarms are promptly investigated as required by your SOP 1ES-300 entitled "Routine Monitoring of Pressure Differentials in the Manufacturing Area."

13. You failed to maintain buildings in a good state of repair. On April 18, 2012, nesting birds were observed in the intake grills for the air handling units serving Building **(b)(4).** Building **(b)(4)** currently houses **(b)(4)** on the **(b)(4)** floor, and laboratories on the **(b)(4)** floors.

PRODUCTION AND PROCESS CONTROLS

14. You failed to follow written production and process control procedures in the execution of various production and process control functions. For example:

a. Your SOP A004253 entitled "Management of Seed Lots and **(b)(4)**" is not followed. During the inspection, keys that would allow access to the locked freezers used for storage of BCG **(b)(4)** seeds were observed in an **(b)(4)** in Building **(b)(4)**.

b. Your SOP A004253 entitled "Management of Seed Lots and **(b)(4)**" is not followed. There is no documentation that verifies the inventory of seeds and cell banks is reconciled **(b)(4)** times per year, as required by the SOP. Further, the SOP is inadequate in that it does not specifically require reconciliation of Inventory Withdrawal Transaction Forms with inventory information regarding seeds and cell banks in the **(b)(4)**.

15. You failed to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material. For example:

a. Validation has not been conducted to determine the maximum **(b)(4)** for the **(b)(4)** chromatography column used for purification of Poliovirus monovalent lots.

b. Samples of **(b)(4)** lot **(b)(4)** were used in your study #SS01-006-REP (version 2.0) entitled "Robustness of the Inactivation Process in IPV Production" which was conducted to demonstrate the robustnesss of the inactivation steps in the Inactivated Polio Vaccine manufacturing process. The study did not document that testing of the **(b)(4)** sample of **(b)(4)** during routine production resulted in a positive **(b)(4)** for Poliovirus **(b)(4)**.

16. BCG-IT is a sterile product requiring aseptic processing **(b)(4)** manufacturing process. On April 11, 2012, various steps in the manufacturing process for BCG-IT were observed in Building **(b)(4)**.

MICROBIOLOGICAL CONTROL

17. You failed to validate the effectiveness of disinfectants used in Building **(b)(4)**, where live Poliovirus is grown, under actual conditions of use. Literature reviews are the only supporting documentation of the effectiveness of the **(b)(4)** disinfectants used in Building **(b)(4)** for facility and equipment cleaning.

18. Regarding the **(b)(4)** process used to decontaminate equipment in the live virus areas of Building **(b)(4)**:

a. There is no written SOP describing the **(b)(4)** process; and

b. The **(b)(4)** process has not been validated.

This equipment is sent off site for calibration and maintenance or delivered to other campus buildings for maintenance and use.

19. There are no written SOPs describing personnel conduct and aseptic technique for aseptic processing conducted in BCG areas in Building -**(b)(4)**. Operations performed in these areas include **(b)(4)**.

20. Your SOP A005256 entitled "Control of Logbooks" is not followed. The SOP states that logbooks must be reviewed in accordance with the assigned review cycle on the master list. Review of Decontamination Log Records for Building **(b)(4)** revealed that not all log records are

being reviewed; examples include Decontamination Log Record for Run **(b)(4)** dated June 10, 2011, and Decontamination Log Record for Run **(b)(4)** dated June 13, 2011.

21. There are no written SOPs describing the activities to be conducted by, or supervision of, employees of the outside laundry contractor. These employees have unsupervised access to non-live virus areas of Building **(b)(4)** and other buildings, including Building **(b)(4)**, Building **(b)(4)**, and Building **(b)(4)**, in order to retrieve soiled scrubs and supply clean scrubs.

LABORATORY CONTROLS

22. Your SOP A003946 entitled "Establishing Reference Vaccines for QO Testing" is not followed. SOP A003946 requires that reference vaccine be stored under controlled conditions in **(b)(4)** separate Reference Standard Storage Areas with restricted access. During the inspection, keys that would allow access to the **(b)(4)** used for storage of Tetanus Antitoxins, Diphtheria Antitoxins, and Tuberculin Standard in Building **(b)(4)** were observed in an **(b)(4)**.

BATCH PRODUCTION AND CONTROL RECORDS

23. An unapproved change was made to the Tetanus Toxoid manufacturing process; specifically, the implementation of a **(b)(4)**. During the investigation for Quality Notification for Deviation #700014365, it was determined that the **(b)(4)** steps had not been performed since 2004. This deviation in manufacturing was not fully evaluated until July 2011. Tetanus Toxoid, manufactured using an unapproved change to the manufacturing process, was released for further processing between 2004 and 2012.

FAILURE INVESTIGATIONS

24. Your investigations into the failure of a batch or any of its components are inadequate. For example:

a. Quality Notification for Deviation Investigation Report No. 700015642, which documents the failure of the test for the absence of active Poliovirus in Poliovirus **(b)(4)** lot **(b)(4)**, does not include the following:

i. An assessment of the need for precautionary decontamination of the non-live virus manufacturing areas of Buildings **(b)(4)** that potentially may have been exposed to live Poliovirus, since no definitive root cause for the failure of the test for the absence of active Poliovirus in Poliovirus **(b)(4)** lot **(b)(4)** had been identified. Only the **(b)(4)** floor laboratories of Building **(b)(4)** were decontaminated in follow-up to the failure of the test for the absence of active Poliovirus; and

ii. A thorough evaluation of Building **(b)(4)** containment issues, including effectiveness of disinfection of the facility and equipment; and numerous pressure differential alarms.

b. CAPA Action Item Form #195591 was opened as a result of an unapproved change made to the Tetanus Toxoid manufacturing process; specifically, the implementation of a **(b)(4)**. Form #195591 documents corrective action indicating that production areas will verify that mandatory steps described in the SOPs are being followed. Corrective action did not include a review to evaluate whether the applicable SOPs and BPRs were compliant with your license.

Sanofi Pasteur S.A., Marcy l'Etoile, France

1. You failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications and to extend the investigation to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. For example:

a. On February 2, 2011, deviation #246019 was opened for Conjugated Haemophilus Vaccine (lot **(b)(4)**) that was found with critical lyophilization defects **(b)(4)** that were not rejected by the semi-automated inspection process. The investigation for this deviation was incomplete as follows:

i. The investigation identified **(b)(4)** lots of product which may have been affected by the deformed **(b)(4)** that were believed to have caused the defects. However, only the lots identified as "high risk" were linked to the deviation and none of the other lots were placed on hold during this investigation.

ii. Only one of **(b)(4)** medium risk lots **(b)(4)** received any follow up.

iii. The investigation did not include a review of complaints.

b. Deviation #277463 was initiated on October 4, 2011, when Typhoid lot **(b)(4)** was Out of Specification (OOS) for polysaccharide content. The investigation was not extended to the bulk manufacturing operations after investigations into laboratory and drug product manufacturing operations were inconclusive.

Additionally, significant deviations in the manufacture of your intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FD&C Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

FAILURE INVESTIGATIONS

2. Investigations of process failures are incomplete and/or corrective actions are inadequate. For example:

a. Deviation #271080 was initiated for Haemophilus Conjugated Vaccine **(b)(4)** lot **(b)(4)** for exceeding the sterile filtration time limit of **(b)(4)**. Filtration of this lot took **(b)(4)**. The root cause investigation determined that the **(b)(4)** lot used for formulation of **((b)(4)** had higher values for **(b)(4)**.

i. The investigation was not extended to all manufacturing operations. The investigation was limited to activities in final formulation.

ii. Two additional Haemophilus Conjugated Vaccine **(b)(4)** lots also exceeded sterile filtration time limits (Lots **(b)(4)**). The **(b)(4)** lots used for formulation of these lots also had higher values for **(b)(4)**. An investigation has not been initiated for these additional lots and you have not determined what is causing the higher values for **(b)(4)**.

b. An investigation has not been initiated for the increasing number of **(b)(4)** events in building **(b)(4)** for Typhim production. The number of times **(b)(4)** are changed in the **(b)(4)** process has increased from **(b)(4)** in 2009 to **(b)(4)**, in some cases, in 2011.

c. Deviation # 227765 was initiated on September 14, 2010, for an adverse trend related to **(b)(4)** results at the Haemophilus **(b)(4)** step **(b)(4)** is a measurement of bacterial content. In 2009, **(b)(4)** batches were manufactured and two were OOS for **(b)(4)**; in 2010, **(b)(4)** batches were manufactured and 20 were OOS for **(b)(4)**; and in 2011, **(b)(4)** batches were manufactured and 15 were OOS for **(b)(4)**. The investigation and corrective actions are inadequate:

i. The possible relationship between the adverse **(b)(4)** trend and other issues such as pyrogen failures, filter clogging, and the OOS purity results was not investigated.

ii. Use of different **(b)(4)** lots was identified as the potential root cause; however, there was no request of the vendor to perform a formal investigation of these lots and testing on specific lots of **(b)(4)** was not initiated by Sanofi Pasteur.

iii. The 2010 manufacturing campaign ended in December 2010, but the deviation investigation was not completed until December 2, 2011.

d. There continues to be a trend in Typhoid **(b)(4)** failing pyrogen testing with no definitive root cause determined. **(b)(4)** batches failing the pyrogen test include: three of **(b)(4)** from 2008, six of **(b)(4)** from 2009 and five of **(b)(4)** for 2011.

e. The failure investigation for the Haemophilus type b **(b)(4)** failing pyrogen testing is inadequate. For example:

i. The investigation concluded that the root cause was the use of **(b)(4)** lot **(b)(4)** at the **(b)(4)** stage even though this lot was used in only four of the **(b)(4)** that failed. In addition, this lot of **(b)(4)** continued to be used in production and the investigation was not extended to the other **(b)(4)** lots used to produce **(b)(4)** with failing pyrogen tests.

ii. **(b)(4)** lots that had been used in production were not tested for impurities, including endotoxin, as part of the failure investigation. The investigation report did not provide any rationale for concluding that the implicated **(b)(4)** lot caused the

failing results.

f. Deviation # 231589 was initiated on October 11, 2010, when **(b)(4)** Haemophilus type b Polysaccharide (HIB **(b)(4)**) lot **(b)(4)** failed the **(b)(4)** pyrogen test. The report concluded "The high level of endotoxin **(b)(4)** could be at the origin of the U.S. non compliant pyrogen results." However, the lot was not further investigated to determine the reason for the high endotoxin test result.

REVIEW OF YOUR INSPECTIONAL RESPONSES

Sanofi Pasteur Limited, Toronto, Ontario, Canada

We acknowledge receipt of your written response dated May 15, 2012, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection of Sanofi Pasteur Limited, Toronto, Ontario, Canada. Corrective actions addressed in your letter may be referenced in your response to the Warning Letter. We have reviewed your May 15, 2012, response and have the following comments. The items are numbered to correspond to the observations listed on the Form FDA 483.

We acknowledge receipt of your written response dated May 15, 2012, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection of Sanofi Pasteur Limited, Toronto, Ontario, Canada. Corrective actions addressed in your letter may be referenced in your response to the Warning Letter. We have reviewed your May 15, 2012, response and have the following comments. The items are numbered to correspond to the observations listed on the Form FDA 483.

Form FDA 483 Observation 1
We acknowledge receipt of your June 21, 2012, correspondence advising FDA that Sanofi Pasteur has decided to temporarily suspend manufacturing of TheraCys® (Intravesical) (BCG-IT). Your correspondence states that manufacturing has been suspended in order to renovate the Toronto BCG manufacturing facility (Building **(b)(4)**) to improve the quality of the environment within this production building. Your correspondence further states that Sanofi Pasteur is working to resolve issues encountered during recent sterility method revalidation studies in order to establish a fully validated sterility test applicable to BCG-IT

Form FDA 483 Observation 2.A
Your response states that a supplemental disinfectant efficacy study, using mold spores of in house isolates on various surfaces, will be performed and completed by **(b)(4)**. We suggest that this proposed study be conducted as soon as possible.

Form FDA 483 Observation 2.B
Your response states that the frequency of disinfecting the BCG facility with sporicidal agents will increase from a minimum of **(b)(4)** a year to **(b)(4)**; however, your response provides no rationale for this **(b)(4)** frequency. Please provide your rationale.

Form FDA 483 Observation 4.D
Your response states that you will assess the need to decontaminate scrubs, which are worn under Tyvek suits by employees who work in the live virus areas of Building **(b)(4)**, prior to pickup by the outside laundry contractor. Your assessment and revised SOP describing the procedures for the supply and retrieval of scrubs should be submitted for review.

Form FDA 483 Observation 5.C
Your response states that the use of a visitor's log book has been implemented to ensure that there is a check to determine whether personnel entering the non-live virus area in Building **(b)(4)** have been to a live virus area that day. However, your response does not adequately address how the presence of a visitor's log book will prevent personnel movement from a live virus area to a non-live virus area. Please provide additional details.

Form FDA 483 Obseravation 7
Please clarify whether the proposed study referenced in your response will include an evaluation of the effect of the **(b)(4)** chromatography step on **(b)(4)** content.

Form FDA 483 Observation 8.A
Your response states that an assessment for any potential physical means that can be implemented to further minimize operator contact with product contact components in the filling suite will be conducted and completed by **(b)(4)**. We suggest the proposed assessment be conducted in a timely manner.

Form FDA 483 Observation 8.B
Your response states that the use of disposable **(b)(4)** to manipulate vials during filling operations will be implemented by **(b)(4)**. Please provide details regarding how you will assure that **(b)(4)** are appropriately sanitized in the interim.

Form FDA 483 Observation 10.A
Your response states that the referenced change to your approved license was assessed as non-reportable. We disagree with your assessment; this change should have been submitted as a CBE-30 supplement. Since the change has already been implemented, please submit a CBE-0 supplement for this change.

Form FDA 483 Observations 10.B and 10.C
Your response states that the referenced changes to your approved license were assessed as non-reportable. We disagree with your assessment; these changes should have been submitted as prior approval supplements. Since these changes have already been implemented, please submit CBE-0 supplements for these changes.

Form FDA 483 Observation 11.B
Your response states that the referenced change to your approved license was assessed as non-reportable. We disagree with your assessment. Since the change has already been implemented, please submit a CBE-0 supplement with data supporting the suitability of the new method for procurement of **(b)(4)**.

Form FDA 483 Observation 13.A
Your response states that applicable SOPs are being updated to increase the frequency of viable **(b)(4)** monitoring to the **(b)(4)** of production operations per shift for **(b)(4)** aseptic processing areas in Building **(b)(4)**, and filling suites in Building **(b)(4)** and Building **(b)(4)**. Please provide your rationale for determining the adequacy of the revised monitoring frequency.

Form FDA 483 Observation 13.B
Your response states that a review of the EM regime for all aseptic processing Grade **(b)(4)** environments on site will be performed to determine where further monitoring enhancements are needed. Further, your response states that the review will be completed by **(b)(4)**, and enhancements will be implemented for all aseptic areas by **(b)(4)**. Please provide your justification for the proposed timeframes and details on whether you intend to implement any additional monitoring in the interim.

Form FDA 483 Observation 17.A
Your response states that possible short term alternatives or modifications to the current processing equipment are being investigated and that the assessment of potential alternatives to current container closures will be completed by **(b)(4)**. The completed assessment and proposed corrective action plan should be submitted for review.

Form FDA 483 Observation 19.A
Please provide details regarding how you determined that the integrity of the BCG **(b)(4)** seed was maintained while stored in locations generally accessible by employee ID cards.

Form FDA 483 Observation 20.A
Your response states that Training Lesson Plan Number 86BCG-2000 within your SOP 1QA-058 will be updated to include the quantity of **(b)(4)** required for a new trainee to inoculate during Phase III of training. Please provide details regarding how you will assess and update, as necessary, all lesson plans used at your facility for operator training and how you will assure that lesson plans are representative of routine production steps.

Form FDA 483 Observation 20.D
Your response did not explain the process and rationale for "grandfathering" operators in lieu of completing and documenting formal training. Please explain and provide your rationale.

Form FDA 483 Observation 21.B
Your response did not address the rationale for your failure to submit a Biological Product Deviation Report following your investigation for the distributed product lots manufactured using an unapproved processing step.

Form FDA 483 21.D
Your response does not address the lack of comprehensive review by the quality control unit that allowed release for further manufacture of Tetanus Toxoid manufactured using an unapproved process.

FDA 483 Observation 22.A
Your response states that it was not deemed necessary to explicitly describe the live IPV testing which occurs in the QC testing areas on the **(b)(4)** floor of Building **(b)(4)** in the supplement for STN 125145/107 which was submitted to the Agency in November 2008. We disagree with your assessment and reiterate that this important information should have been included in your submission.

We also acknowledge receipt of your first quarterly status report dated June 29, 2012. Comments on your status report will be provided to you in a separate correspondence.

Sanofi Pasteur S.A., Marcy l'Etoile, France

We acknowledge receipt of your written responses dated April 23, 2012, May 15, 2012, June 15, 2012, and June 25, 2012, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection of Sanofi Pasteur S.A., Marcy l'Etoile, France. Corrective actions addressed in your letters may be referenced in your response to the Warning Letter. We have reviewed your responses and have the following comments. The items are numbered to correspond to the observations listed on the Form FDA 483.

Form FDA 483 Observation 1.B.(1)
We acknowledge your commitment to prepare the two reports mentioned in your response. Please submit a copy of your short term assessment of operating conditions for the filtration of high **(b)(4)** by **(b)(4)** (Bullet 2) as well as a copy of the report summarizing the project to improve the Hib **(b)(4)** process and final **(b)(4)** filtration conditions by **(b)(4)** (Bullet 3) as indicated in your response.

Form FDA 483 Observation 10
We acknowledge your commitment to implement an **(b)(4)** for U.S. and non-U.S. Human Diploid Cell Rabies Vaccine HDCV batches. Please contact the Office of Vaccine Research and Review (OVRR) at (301) 827-8757 to discuss the progress you have made and your plans moving forward.

The deficiencies described in the Form FDA 483 issued at the close of each inspection referenced above and this letter are an indication of your quality control units not fulfilling their responsibility to assure the identity, strength, quality, and purity of your licensed biological drug products and intermediates. FDA expects Sanofi to undertake a comprehensive and global assessment of all of its manufacturing operations to ensure that all products conform to FDA requirements. Please describe in detail how Sanofi will attain CGMP compliance with regard to the above observations. Please include in that description how you will use all relevant information to conduct thorough investigations to ensure that adequate steps are taken to evaluate whether deviations impact product and to implement effective corrective and preventive actions.

Neither this letter, nor the observations listed on each Form FDA 483 presented at the conclusion of the inspections, are intended to be an all-inclusive list of deviations that may exist at your facilities. We remind you that it is the responsibility of Sanofi World Wide Headquarters to ensure that your establishments are in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological products so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions may include license suspension and/or revocation.

To facilitate your remediation efforts, we request a meeting with you and other senior management at Sanofi to further discuss the issues cited in this letter and your proposed responses to address them.

Given the potential contributions of safe, pure, and potent vaccines to the public health, we encourage frequent interactions between your technical staff and FDA in an effort to help Sanofi move forward with corrective actions as rapidly as possible.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been

achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448. To schedule a meeting at your earliest convenience, please contact Anna M. Flynn, Consumer Safety Officer, in the Division of Case Management at (301) 827-6201.

Sincerely,

/S/

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: G. Eileen Macallum, D.V.M.
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