DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/CBER/Office of Compliance and Biologic Quality 10903 New Hampshire Avenue W071-5118 Silver Spring, MD 20993-0002, Tel 240-402-8914, Fax 301-595-1304	September 10 – October 2, 2014
	FEI NUMBER 3002875226

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thibaud Stoll, PhD. Vice President, Belgium Industrial Operations

FIRM NAME	STREET ADDRESS
GlaxoSmithKline Biologicals	Parc de la Noire Epine Ave Fleming 20
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
B-1300 Wavre, Belgium	Vaccine Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. Observation #s 1A, 9 and 10 cited during the previous inspection of 2012 on inadequate Quality Unit Oversight since 2007 to identify adverse trend of molds, investigate adverse trends, and implement corrective actions to prevent recurrences of molds in the manufacturing environment were again noted during this inspection in the firm's Rixensart and Wavre vaccines manufacturing buildings' Grades (b)(4) environmental classified areas. The firm currently has implementation corrective actions completion date of 4th Q of 2017 for the adverse molds contamination in (b)(4) of the manufacturing buildings. Specifically:

A. Although the firm stated it continues to implement corrective and preventive actions however, the adverse trends of molds present in (b)(4) Building (b)(4) that were cited during the inspection of 2012 continue. Furthermore, the control of molds adverse trends has been inadequate and the firm continues to identify molds in the Rixensart and Wavre US vaccines manufacturing facilities. Since the inspection of 2012 there have been approximately 190 mold deviations impacting (b)(4) in process/final batches of which 4 batches were rejected. For example:

i) There have been approximately 77 deviation excursions of molds in (b)(4) Building (b)(4) manufacturing building for (b)(4) HAV and IPV used in Havrix, Twinrix, Pediarix and Kinrix vaccines noted during this inspection.

B. The previous inspection of 2012 cited not less than 85 deviations of molds in Building (b)(4) areas. The current inspection noted total of approximately 113 mold excursions since the inspection of 2012. For example:

i) There have been approximately 55 deviation excursions of molds in Building (b)(4) of which 18 were deviations during the (b)(4) i.e., Cervarix, Hiberix, Menhibrix vaccines and 33 molds deviation excursions during the manufacture of the (b)(4) of Hiberix (Hib) vaccine.

ii) There has been 6 deviations excursions of molds in Building (b)(4) that houses (b)(4) Filling line: (b)(4) Filling Line #s: (b)(4) for fillings of US vaccines; 4 mold excursions in (b)(4) of i.e., Cervarix vaccine and 3 mold excursions in (b)(4) manufacture of (b)(4)

C. Since the inspection of 2012, there has been one media fill simulation failure attributed to molds: Media fill Simulation (b)(4) in vials (b)(4) Filling Line, Building (b)(4) that failed due to molds contamination. The (b)(4) Filling Line, Building (b)(4) is used for the filling of the following US drug product vaccines, i.e., Engerix-B, Havrix, Twinrix, Infanrix, Pediarix, Kinrix, Boostrix, Fluarix D-QIV and Cervarix. Per Deviation Report #200331181 dated January 07, 2014 three (3) contaminated vials were identified after the incubation period following a routine media fill simulation process performed on (b)(4) Filling Line on December 16, 2013. The contaminants were identified as spore forming fungi Aureobasidium pullulans and Rhinocladiella aurovirens.

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D. In addition, there were twenty-one (21) deviation excursions of molds identified in manufacturing personnel monitoring samples from the above noted manufacturing buildings.

E. The lack of overall investigation for the adverse trends by the Quality Unit to determine the root cause of the adverse trend of molds cited during the inspection of 2012 has not been corrected. The mold deviation excursions continue to be addressed individually as an environmental excursion.

2. Although the firm acknowledged in its response to the FDA-483 of 2012 that leaks in Building (b)(4) could contribute to the molds issues and indicated that it has launched a major project for the whole (b)(4) building to upgrade the water systems impacted by leaks. However leaks in Building (b)(4) and other manufacturing buildings continue. Significant leaks such as: "Area Flooding", water leaks, manufacturing process leaks and WFI leak deviations were documented during the manufactured vaccines in-process, bulk formulations and final drug products filling manufacturing areas that could allow for the growth of molds including microorganisms. Specifically, the lack of adequate corrective and preventive actions to address the continued deviations of water leaks in Building (b)(4) manufacturing areas noted as Observation #1A (ii) during the inspection of 2012 continues with approximately 212 deviations documented for area flooding and water leaks in Rixensart and Wavre US vaccines manufacturing buildings as follows:

A. There have been 16 (sixteen) "Area Flooding" and water leaks in Building (b)(4) for example:

10/2/14

i) There have been 10 areas flooding in Building (b)(4) i.e., per Deviation #200315842 dated October 14, 2013, which was caused by 300L (b)(4) water infiltration into classified area impacting 18 (b)(4) IPV (b)(4)

ii) There have been 6 Equipment leaks in Building (b)(4), i.e., Per Deviation #200289580 dated May 06, 2013 and 200371144 dated July 03, 2014 there have been two (b)(4) water leaks in Building (b)(4)

B. There have been 19 areas flooding and water leaks from equipment in Building (b)(4) used for vaccines bulk formulations and filling. For example:

i) Per 200338789 dated February 11, 2014, there was area flooding in Building (b)(4) of about 3000L of water from the cooling coil of HVAC of room (b)(4) affecting 8 rooms of Building (b)(4) This resulted in the rejection of two lots that were being processed at the time and the materials and media prepared before the flooding were discarded.

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ii) Per 200371874 dated July 04, 2014 there was water leak at (b)(4) of Building (b)(4) due to condensate drip from HVAC located above the raw material storage room along the fire detection cable. The water drip was caused by the progressive wear out of the seal of the HVAC that was installed in 2000.

iii) There were 5 areas flooding in Building (b)(4) i.e., per Deviation #200331695 dated July 2014, there was leak of (b)(4) resulting in area flooding.

C. There have been 4 (four) equipment water leaks in Building (b)(4) used in the filling of vaccines drug products. For example:

i) Per Deviation #200372710 dated July 22, 2014, there was area flooding in grade (b)(4) (b)(4) area due to rain water infiltration. This resulted in the temporary stoppage of production.

3. There were 118 manufacturing equipment and tanks' leaks during the vaccines manufacturing processes including the aseptic vaccines processing that could result in products contamination. For example:

A. There were 58 process leaks in Building (b)(4) for vaccines (b)(4) formulation and filling impacting 195 vaccine batches of which approximately 51 vaccines batches were rejected.

B. There were approximately 16 process leaks in Building (b)(4) use for final product filling impacting 38 product batches of which 5 were rejected during the filling of vaccines drug products.

C. There were approximately 7 process leaks in Building (b)(4) impacting 27 batches of which 19 were rejected during the vaccines drug products formulations.

4. The Observation #14 from the previous inspection of 2012 regarding procedures designed to prevent microbial contamination of products purporting to be sterile are not always followed that was cited, was also noted as inadequately corrected during this inspection. Furthermore, the 2012 inspection documented numerous deviations where microbial contamination was detected in aseptic manufacturing areas were also documented during the current inspection. Specifically, there have been approximately 883 action levels personnel monitoring excursions potentially impacting 604 vaccine batches, which resulted in the rejections of 25 vaccine batches. In addition, there is a lack of adequate maintenance system for equipment used to maintain aseptic conditions and prevent products contamination from the manufacturing environment and water. For example:

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A. There was a bulk media fill simulation failure due to results of personnel monitoring excursions. Per Deviation #200322563, occurrence dated of October 14, 2013 of which atypical germs were found on 3 personnel monitoring contact plates, microorganisms: Actinetobacter iwoffii, Staphylococcus aureus and Bacillus cereus were identified.

B. There were three sterility failures, two of which were due to equipment breakdowns during product sterility testing and the third was due to the inadequate storage of equipment. For example:

i) Per Deviation #200328274 dated November 12, 2013, during the day (b)(4) reading, one (b)(4) container and one (b)(4) container showed macroscopic signs of microbial proliferation for Rotavirus (b)(4) The root cause of the contamination was attributed to (b)(4) breakdown, which allowed for the ingress of air from the (b)(4) (b)(4)

ii) Per Deviation #200330679 dated November 26, 2013 during the day (b)(4) reading, one (b)(4) container and one (b)(4) container showed macroscopic signs of microbial proliferation for Rotavirus (b)(4) The root cause was determined to be the (b)(4) (b)(4) that came loose and was taken out of the production area for repairs. Until the part was returned, (b)(4) was used to (b)(4) (b)(4) which allowed air into (b)(4) that was not guaranteed to be air.

iii) Per Deviation 200321332 on November 11, 2013. Acellular Pertussis batch AFHABAA33 in area RX59-00-016 failed sterility test. Microorganism Stenotrophomonas maltophilia gram negative rods were identified. The root cause was attributed to the inadequate storage conditions of the diafiltration skid and cartridges during summer revamping and the use of inappropriate water quality for calibration and testing due to insufficient and clear instructions in SOPs and checklist.

5. The following observations were made in the vaccines final containers filling process:

A) On 9/18/14, during the filling of Hiberix lot (b)(4) on fill line (b)(4) a three inch piece of hair was observed inside the (b)(4)

B) The firm's validation of their (b)(4) filling process does not always reflect current practice. For example, on 9/18/14, the firm was filling Hiberix lot (b)(4) intended for the US market. The firm filled, lyophilized, and capped (b)(4) on 9/18/14, and due to an event the firm stopped the fill,

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disconnected the (b)(4) from the fill line, stored the Hiberix (b)(4) in another (b)(4) and cleaned the (b)(4). On 9/22/14, the firm set up the (b)(4) connected the Hiberix lot (b)(4) the fill line, and proceeded to fill, lyophilize, and cap (b)(4). The firm has not performed a media fill to ensure aseptic processing with the filling of this batch.

C) On 9/19/14, during the filling of (b)(4) lot (b)(4) on fill line (b)(4) rust like discoloration was observed on the stainless steel pole near the stopper bowl and there was a broken corner on the (b)(4) (b)(4). Maintenance personnel had last inspected the line between 9/6/14 and 9/7/14 and neither of these issues had been noted during their inspection. There was no documentation within the batch record concerning these two equipment issues. The filling line has been used (b)(4) different times since 9/6/14.

D) The data as recorded within the batch record may not always be accurate. For example:

i) On 9/18/14, during the filling of Hiberix lot (b)(4) on fill line (b)(4) an operator performing in-process testing of filled vials was observed multiple times incorrectly writing the time of sample pulls in the batch record. The operator wrote the sample time as 07:26 when the clock read 07:32, the operator wrote the sample time as 07:46 when the clock read 07:52, and the operator wrote the sample time as 08:06 when the clock read 08:12.

ii) On 9/19/14, during the filling of (b)(4) lot (b)(4) on fill line (b)(4) an operator performing in-process testing of filled vials was observed to write of the time of sample pulls in the batch record incorrectly. The operator wrote the sample time as 09:49 when the clock read 09:53.

E) 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, the firm has (b)(4) lyophilizers used in the production of Rotarix, Menhibrix, and Hiberix. The (b)(4) located in the Grade (b)(4) area used for the (b)(4) the lyophilizer is located (b)(4) lyophilizer and approximately (b)(4) from the (b)(4).

F) The firm uses the (b)(4) vaccine vials when performing the in-process (b)(4). It was noted that during in-process (b)(4) vials on September 18, 2014 an operator was observed to (b)(4) vials on the (b)(4) right after removing a previous sample of (b)(4) vials without allowing the (b)(4).

6. The firm's evaluation of media fill simulations used to support aseptic processing is insufficient in that atypical or objectionable organisms such as *Bacillus, Acinetobacter lwoffi, Moraxella, Roseomonas*

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gilardii, Enterococcus faecalis Shingomonas paucimobilis, and Brevibacillus choshinensis which were isolated as part of the personnel monitoring or environmental monitoring during various media fills do not require corrective and preventive actions such as a re-evaluation of the current cleaning program, gowning requalification, or the necessity to repeat the media fill.

7. Deviation 200263464 which was opened to investigate particles observed in stability samples at the (b)(4) time point for (b)(4) lots (b)(4) is incomplete in that the deviation did not contain documentation that particles were seen in one of these (b)(4) when the (b)(4) were emptied and subsequently discarded by manufacturing staff at the completion of the stability study even though employees within the manufacturing department had been involved in the stability investigation.

8. The adequacies of the vaccines process manufacturing environmental excursions in regards to the degree of microbial contaminations of personnel, air, products manufacturing contact surfaces, viable and non-viable air excursions including molds could not be adequately assess during this inspection as the result of approximately 1,190 collected environmental samples (approximately (b)(4) %) from Rixensart and Wavre manufacturing facilities that were not tested. For example, approximately 494 environmental samples collected in Building (b)(4) in Grade (b)(4) that are to be used (b)(4) of the vaccines drug product batches were not tested or the tests were invalidated due to cracked (b)(4) cracked (b)(4) and "fallen" (b)(4)

9. The following deficiencies were noted in the firm's validation:

A) The firm could not provide a scientifically sound justification for the implementation of a lag time on (b)(4) different (b)(4) autoclaves which are used to sterilize manufacturing equipment and personnel gowning components. The lag time implemented was based off the historical review of the individual cycles per individual autoclave to replace a (b)(4) that had been filled with (b)(4) water and was used as the artificial cold spot within the autoclave. The lag times incorporated into the cycles range from (b)(4) minutes.

B) There is no procedure or requirement to requalify all temperature monitored units. For example, cooler (b)(4) is approximately (b)(4) cubic meters which holds approximately (b)(4) The cooler was initially qualified in 1989. The firm performed a study in 2009 to determine the correct placement of additional monitoring probes however, there is no protocol or report for this study. There has been no re-qualification of this unit to ensure that the unit continues to operate as initially qualified or to ensure that the monitoring probes are positioned in the appropriate locations within the cooler.

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10. The controls of water system to prevent contamination are inadequate. For example:

A. There were total of 17 Water for Injection (WFI) leaks in vaccines manufacturing buildings (b)(4) (b)(4) use for vaccines (b)(4) formulation and filling. For example, there were WFI leaks from the WFI tanks, WFI Loops.

B. The water systems used in the manufacture of vaccines are inadequately maintained to prevent microbial contamination. Specifically, the controls over the manufacturing incoming water source (well), the purified water equipment used to make Water for Injection (WFI) and for the rinsing of production equipment used in the manufacture of vaccines at the Rixensart facility were observed on September 24, 2014 to be in serious need of maintenance and repairs. For example:

i) The water well which is the water source for the Purified Water and WFI Systems that was underground in a closed enclosure was noted opened and completely corroded, covered in rust and flooded by rising water from the ground. Rubber hoses were noted to be used to pump out ground water surrounding the well.

ii) The inspection of the equipment in the Building (b)(4) for the manufactured of the Purified Water from the water well used to manufacture the WFI for the production of vaccines and for the rinsing of manufacturing equipment were noted to be corroded and covered in and rust with several leaks from the following equipment: (b)(4) (b)(4) (b)(4) and leak beneath the (b)(4) for the well water (b)(4) located just outside the Building (b)(4). Two (b)(4) cubic meters of (b)(4) were noted with several streaks of brown/bronze and white markings with several water leaks on the floor from the equipment.

iii) The inspection of Building (b)(4) for the production of the WFI from the purified water and the distributions of WFI to (b)(4) for bulk formulation and filling, disclosed the outside of the Purified Water loop tanks with several white streaks of stains as well as several equipment leaks in the area. The WFI (b)(4) were also noted with streaks of white stains and the top rims of the 2 WFI (b)(4) were partially coming off from the top of the (b)(4)

C. There have been 10 (ten) Purified Water and (b)(4) Water bioburden excursions of Too Numerous to Count (TNTC) in the Rixensart facility and 7 TNTC at the Wavre facility Purified

Water (PW) System. Although individual deviations were opened, there is no documentation that formal investigation has been opened into these TNTC bioburden occurrences.

D. There are inadequate controls and investigations to prevent microbial contamination and TOC of the Pure Steam System. Specifically, there have been nine (9) pure steam bioburden, TOC and conductivity excursions of action levels in 2014. For example:

i) There have been approximately 17 pure steam deviations of TOC, conductivity, bioburden and one mold excursion since the inspection of 2012, 13 out of the 17 were action level excursions. Five of the excursions were attributed to the maintenance of the pure steam generator wear that was cross contaminated by the industrial steam and resulted in high TOC levels; 9 were attributed to the training of the operator and the rest to unusual activity and design of the water container.

11. Employees were not adequately trained in the particular operations that they performed related to their job functions. Specifically, the current inspection noted the previous 2012 Observation #14 documenting incidences where operators were not appropriately trained on procedures, operators are not adequately following procedures and/or procedures are too difficult to follow has not been adequately corrected. There have been approximately 1,070 including 280 deviations of operators performing activities that they have not been adequately trained impacting 256 vaccines batches to have been caused by: "Process GMP Procedure not followed" and/or Insufficient and clear instructions in SOPs and Checklists" and Operator Error. For Example:

A. The dissemination of 45 liters of solution contaminated with non-inactivated polio virus that were released into the collector of the sewage treatment station from Building (b)(4) was attributed to "insufficient and clear instructions in SOP and checklist". The (b)(4) Building is mostly used for non US IPV vaccine manufacturing. However, some portion of the (b)(4) Building is also used for US vaccines manufacturing operations, For example:

i. (b)(4) Used for raw material entry for Menhibrix and HIB

ii. (b)(4) Use for raw material entrance/handling and storage room for Menhibrix and HIB production equipment for the (b)(4)

iii. (b)(4) gowning area for incoming raw materials receiving/handling.

iv. (b)(4) Corridor after material entrance to all vaccines production performed in the area.

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B. Per Deviation Report 200319034 dated November 11, 2013 on October 30, 2013 a bulk media simulation for (b)(4) was found positive. Also, on November 11, 2013 Acellular Pertussis (b)(4) failed sterility test, Methylobacterium radiotolerens a gram negative rod was identified. One of the root causes of both the media fill simulation and the sterility failures were attributed to insufficient and clear instructions in the SOPs and checklists.

C. Nineteen (19) vaccines batches were rejected due to "Process GMP-Procedure not followed", i.e., 200297382 and 200355354.

12. There is inadequate control over the firm's utility areas in that:

A) Residual liquid was observed on 9/18/14, under a heat exchanger for air handler (b)(4) in building (b)(4)

B) Growth like material was observed on 9/18/14 coming from a spout off (b)(4) for air handler (b)(4) in building (b)(4)

C) A leak was observed on 9/18/14 coming from (b)(4) in the utilities area above the (b)(4) filling line in building (b)(4)

D) There was liquid observed on 9/24/14 dripping from pipes above onto WFI and purified water lines, valves, ports, and pressure gauges in the (b)(4)

E) The technical areas of the facility is not maintained in a state of control and in that there is no current requirement for staff to use buckets or other methods to contain a leak from equipment or utility piping when it occurs and the remaining liquid is not mopped up until they have fixed the source of the leak.

F) In the utility area below the (b)(4) filling rooms in building (b)(4) there is a tub which is approximately 2 feet by 2 feet which is used to collect liquid in the event of overpressure from the hot water circuit. On 9/18/14 there was 1-2 inches of discolored liquid inside this tub which could not drain as the drain spout is located approximately 2-3 inches up the side of the tub.

13. Disposal of product is not adequately managed. In relation to the poliovirus incident, the sponsor mentioned that the disposal of the virus was managed under "Biosafety" and ~~not~~ now disposal will be under "GMP". OTD 10/2/14

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	O. Osunsanmi Debra M. Emerson	Omotunde O. Osunsanmi, CSO Debra M. Emerson, CSO Dino A. Feigelstock, CBER	10/2/14

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/CBER/Office of Compliance and Biologic Quality 10903 New Hampshire Avenue W071-5118 Silver Spring, MD 20993-0002, Tel 240-402-8914, Fax 301-595-1304	September 10 – October 2, 2014 FEI NUMBER 3002875226

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Thibaud Stoll, PhD. Vice President, Belgium Industrial Operations

FIRM NAME	STREET ADDRESS
GlaxoSmithKline Biologicals	Parc de la Noire Epine Ave Fleming 20
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
B-1300 Wavre, Belgium	Vaccine Manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

14. The quality of the Product Quality Review (PQR) for Rotarix, Cervarix, IPV (inactivated poliovirus (b)(4) and HAVrix is deficient as follows:

A) Some of the graphs recorded in the PQR are misleading and difficult to interpret because the range of the scale used for the Y axis is considerably wider than the range of the data.
B) Some graphs are misleading because they present partial data.

C) It is difficult to interpret some of the graphs because the label of the Y axis is incorrect.

D) The language is not always totally clear, as in the case of the indicated storage condition for Rotarix, which was inadequately noted in the PQR.

15. Results are not always appropriately interpreted and followed by proper investigations, as in the case of the observed increase of (b)(4) (b)(4) (BPDR 20130411A). The result obtained (a 40x increase in the amount of (b)(4) indicates the probable (b)(4) (b)(4) in the conditions used for (b)(4) This is in disagreement with the current hypothesis of the sponsor, who hypothesizes that the presence of (b)(4) (b)(4) It seems that this fact was not noted by the sponsor, and if was, it was not investigated. In addition, the unexpected (b)(4) could represent a change in the (b)(4) system (which could potentially impact the production of poliovirus (b)(4) and was not further investigated.

16. Tests are not conducted to verify the identity and/or the quality of each component used in the manufactured vaccines. Specifically,

A. The acceptances of the process gases used in the manufacturing processes of vaccines are based on certificates of analyses received from the manufacturers. For example, there are no periodic identification tests for:

i) The (b)(4) used in the manufacturing process of Engerix-B vaccine and Cervarix vaccines during the (b)(4) process.

ii) The (b)(4) used during the manufacturing process of Rotarix vaccine (b)(4)

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iii) The (b)(4) used in the manufacture of Hiberix vaccine (b)(4) (b)(4)

B. There is no documentation that (b)(4) used in the vaccines manufacturing processes are monitored for, i.e. temperature, pressure, humidity and bioburden. In addition, there are no written procedures for the examinations, testing and monitoring of these manufacturing gas components.

17. Inadequate routine calibrations of manufacturing equipment and/or inspection according to a written program designed to assure proper performance. Specifically, there were approximately 4699 vaccines approximately (b)(4)% manufacturing equipment calibrations non conformances that include 1243expired calibration and 3456 calibration failures with notations of "Calibration and measure (b)(4) As found fail". For example:

A. There were 215 OOT calibration results impacting 86 vaccines (b)(4) C Freezers used in the storage of US vaccines (b)(4) (b)(4) For example, the equipment calibrations OOT results for the (b)(4) C US vaccine Freezer (b)(4) had OOT result of (b)(4) C, with acceptance calibration limit of (b)(4) C.

B. There were 184 OOT calibration results impacting (b)(4) US vaccines incubators used for the incubations of (b)(4) and for the incubations of environmental samples for testing.

C. There were approximately 1409 expired and OOT vaccines Quality Control Laboratory equipment non conformances.

D. There were approximately 428 expired and OOT manufacturing equipment non conformances in vaccines drug products filling Building (b)(4)

18. Operations to prevent product mix-up during (b)(4) inspections of filling, labeling and packaging operations cited as Observation #1B as adverse trends of when product components from previous operations are not cleared out at the end of operations was noted again during this inspection to have been inadequately addressed through investigations and corrective actions. Specifically, although the firm in its response to the 2012 inspection promised several corrective actions which were implemented to the filling line clearance issues, however the cited issues on visual inspections of final product vials remain.

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A. There were 165 deviations initiated for line clearance excursions such as: finding product components from previous inspection not cleared out at the end of operations. Also, there 972 deviations initiated for the failure of the cleanup operations to clear out all products components at the end of the filling, labeling and packaging operations. For example:

B. The selections of finished drug products vaccine vials for the AQL inspections by the Quality Assurance (QA) Unit are not made by QA but are (b)(4) (b)(4)

19. Approximately 86 serious and unexpected vaccines adverse events were not submitted to the Agency within the required 15 days reporting period. Twenty-six (26) out of the 86 late AEs that were submitted late were submitted in 2014. Examples of AEs that were submitted late are as follows:

A. Adverse Event #B0857343A for Hepatitis B vaccine was submitted to the Agency 446 days late. The adverse event (AE) should have been submitted by March 07, 2013 but was submitted on May 27, 2014.

B. Adverse Event #B0845409A for Rotavirus vaccine was submitted to the Agency 149 days late. The AE should have been submitted on November 25, 2012, but was submitted on April 23, 2013.

C. Adverse Event #B0078433A for Rotavirus vaccine was submitted to the Agency 136 days late. The AE should have been submitted on September 02, 2012 but was submitted on January 16, 2013.

20. The following deficiencies were noted in the firm's handling of vaccine process non conformances:

A. Observation #4 of the 2012 inspection, which stated as follows: Not all events having impact or potential impact on products are handled through the deviation system and these events do not obtain the same level of assessment by QA has not been adequately corrected. Specifically, manufactured vaccines non-conformances (deviations) including non-conformances classified as Levels (b)(4) are not adequately defined in SOP 9000015857 version 05 (English version) 9000003808 version 20 (French version). Non-conformances per the SOP are defined as: An unplanned event that has been assessed as having a potential to impact material or product in terms of quality, patient safety and regulatory compliance. The definition failed to include other manufacturing events that occurred during the manufacturing processes for a total of 13,000

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manufacturing events that were not initially provided during this inspection. Furthermore, "Event" that occurred during the vaccines manufacturing process are considered and defined in the deviation SOP as "Unplanned event assessed by QA as having no GMP impact" as such, are not investigated for root cause, trending is performed and in some instances CAPAs are instituted without root cause investigations.

B. Manufacturing non conformances (deviations) are not closed in timely manner, specifically, the previous inspection 2012 documented manufacturing events are not closed in a timely manner, and manufacturing non conformances/deviations were also noted during the current inspection as not closed in timely manner.

C. The firm failed to follow SOP 9000015857, Version #05, titled: Deviation, Complaint and CAPA System Management, which requires that manufactured products non-conformance investigations be conducted and closed within (b)(4) days. For example, 57.0% and 53% of all manufacturing deviations in 2013 and 2014 (to present) respectively were not investigated and closed within (b)(4) days as required by the SOP.

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."