

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

FDA/CBER OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY  
10903 NEW HAMPSHIRE AVENUE W071-5118  
SILVER SPRING, MD 20993-0002  
TEL: (240) 402-8914/FAX (301) 595-1304

Industry Information: [www.fda.gov/oc/industry](http://www.fda.gov/oc/industry)

DATE(S) OF INSPECTION

June 01 -11, 2014<sup>6</sup> 06/22/15

FEI NUMBER

3002806949

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

**TO: LAURA E. O'BRIEN PhD, SITE HEAD LIVERPOOL**

FIRM NAME

NOVARTIS VACCINES & DIAGNOSTICS Ltd.

STREET ADDRESS

RENAISSANCE WAY

CITY, STATE AND ZIP CODE

LIVERPOOL L24 9GR

TYPE OF ESTABLISHMENT INSPECTED

FLU VACCINE MANUFACTURER

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

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

1. The controls over the Fluvirin influenza vaccine manufacturing equipment cleaning, cleaning validation, sanitization processes and maintenance are inadequate in that ineffective cleaning and sanitization of (b)(4) (b)(4) resulted in endotoxin excursions of one (1) Fluvirin Monovalent batch with Out of Licensed Specification (OOS) and licensed in process Product Quality Specifications (PQS) out of action and alert limits test results. These endotoxin excursions have been occurring intermittently since 2012/2013 at (b)(4) manufacturing stage with 4 above alert levels; 16 alert levels during the 2013/2014 at (b)(4) and one at (b)(4) stage during the Fluvirin campaigns. However, there were 22 Fluvirin monovalent batches with endotoxin excursions during the Fluvirin 2014/2015 campaign of which six (6) out of the 22 Fluvirin monovalent batches were rejected (1 of the 6 rejected batches was rejected for breach of licensed specification) for endotoxin excursions and the remaining 16 batches were released for further manufacturing and released for distribution to the US and ROW. The most recent 2015/2016 Fluvirin monovalent batches endotoxin excursions were additional alert breaches at three (3) PQS levels within six (6) consecutive Fluvirin batches per DR 350462 dated February 06, 2015. Specifically,

A) Per (Deviation Report) DR 303003, dated (b)(4) 2014 and Technical Report #R/0354/07/14 dated August 01, 2014, during the time period of (b)(4) dates of (b)(4) 2014 to (b)(4) 2014, 22 batches with elevated levels of endotoxin with PQS alert and action levels excursions were observed at the Fluvirin manufacturing stages: (b)(4) within this period. For example:

R) (b)(4) were not adequately sanitized (b)(4) (b)(4) and inadequately validated and cleaned during the (b)(4) cleaning process. This resulted in action level breaches of bioburden proliferation in the (b)(4) (b)(4). The bioburden were intermittently introduced into (b)(4) (b)(4) which eventually contaminated the in-process Fluvirin monovalent batches and resulted in endotoxin level excursions.

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EMPLOYEE(S) SIGNATURE

*[Handwritten Signature]*

EMPLOYEE(S) NAME AND TITLE (Print or Type)

OMOTUNDE O. OSUNSANMI, CSO  
GENE ARCY, CSO

DATE ISSUED

JUNE 11, 2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER FDA/CBER OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY 10903 NEW HAMPSHIRE AVENUE W071-5118 SILVER SPRING, MD 20993-0002 TEL: (240) 402-8914/FAX (301) 595-1304 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION June 01 -11, 2015 <i>ON 6/22/15</i>
	FEI NUMBER 3002806949

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**TO: LAURA E. O'BRIEN PhD, SITE HEAD LIVERPOOL**

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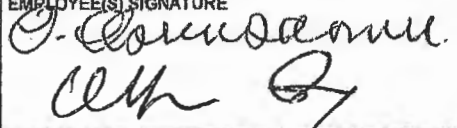
C) The instituted periodic maintenance of the (b)(4) machines is inadequate. Specifically, per Technical Report R/0354/07/14 dated August 01, 2014 after (b)(4) of (b)(4) Machine (b)(4) on (b)(4) 2014 the proliferated bioburden could have gone into the batch (b)(4) immediately after the activity on (b)(4) 2014 through (b)(4) This subsequently caused an atypical high bioburden spike which breached the specified action level. For example:

i) Per Technical Report R/0354/07/14 dated August 01, 2014 the intermittent bioburden/endotoxin contamination of (b)(4) were occurring after the contract maintenance activity of (b)(4) machines of (b)(4) (b)(4) since the 2012/2013 Fluvirin campaign.

ii) (b)(4) machines maintenance schedule of (b)(4) for the (b)(4) that was implemented as corrective action to the above endotoxin contamination of the Fluvirin 2014/2015 campaign is inadequate. Photographs of (b)(4) (b)(4) that were taken by the firm's QA personnel after (b)(4) of use and maintenance performed by a contractor showed (in lesser quantity from those seen when the (b)(4) (b)(4) product residue and caustic residue build-ups on (b)(4) (b)(4) The product residues observed also have the potential for product contamination similar to those that were responsible for the contamination of 2014/2015 of (b)(4) that resulted in the in process Fluvirin monovalent batches with high endotoxin levels on some of (b)(4) (b)(4); some of which are (b)(4) (b)(4)

D) The cleaning validation of (b)(4) machines is inadequate.

i) The firm has been experiencing intermittent bioburden and endotoxin excursions at 3 manufacturing stages of the Fluvirin monovalent batches and the investigation determined that the definite root cause of the licensed OOS and in process licensed PQS endotoxin level excursions was (b)(4) that were not always effectively sanitized (b)(4) Also, that ineffective sanitization can be caused by product residue or caustic residue building up on (b)(4) (b)(4) However, there is no documentation that the adequacy of (b)(4) machines cleaning validation process was evaluated for corrective and preventive action to address bioburden and endotoxin

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excursions.

ii) (b)(4) was tested for bioburden, endotoxin, (b)(4) However, there is no documentation that swabbing of (b)(4) was conducted for the product contact surfaces and hard to clean areas of (b)(4) machine. For example:

a) There was no documentation of the swabbing of (b)(4) (b)(4) that resulted in action level breaches and bioburden proliferation. Furthermore, there was no documentation that (b)(4) by product residue or caustic residue building up on (b)(4) were swabbed during the cleaning validation.

b) Although (b)(4) in Fluvirin (b)(4) Manufacturing process was (b)(4) (b)(4) per Change Control #68435, approval date of June 25, 2010 and (b)(4) (b)(4) machine cleaning validations has been conducted after (b)(4) per the Cleaning Validation Report #CVR/0022/14 dated March 11, 2015. However, there is no specific documentation that addressed the evaluations of the adequacy of the cleaning of (b)(4) machine and/or (b)(4) of the (b)(4) machine as the result of (b)(4)

iii) The corrective actions to the endotoxin excursions of the Fluvirin monovalent batches failed to include the evaluations of the adequacies of (b)(4) cleaning and (b)(4) cleaning validations of (b)(4) (b)(4) machines in regards to the bioburden that proliferate in (b)(4) (b)(4) Although cleaning of (b)(4) machine is performed (b)(4) and the cleaning validation is performed (b)(4) however the endotoxin investigation focused mainly on corrective actions to the sanitization of (b)(4)

E) Inadequate investigation and the lack of corrective and preventive actions to prevent reoccurrences into previously intermittent endotoxin excursions at (b)(4) manufacturing step that are carried over to the licensed in process (b)(4) manufacturing stages resulted in endotoxin excursions of the above additional 22 batches of Fluvirin with licensed in-process PQS endotoxin level excursions. Specifically,

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*O. Osunsanmi*  
*Gene Arcy*

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OMOTUNDE O. OSUNSANMI, CSO  
GENE ARCY, CSO

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i) Although per DR 246600 dated August 14, 2013, several Fluvirin monovalent batches had excursion levels for endotoxin during the month of July and August 2013, i. e., A/Texas at (b)(4) had above alert limit endotoxin result of 164 EU/ml (alert limit of (b)(4) (no action level defined) also, there were (7) seven additional monovalent batches that were also investigated due to atypical results for endotoxin during this period. The investigation into the root cause of the endotoxin excursions was inconclusive and was noted to be probably due to reduced egg quality as such, no CAPA was instituted. However, the investigation conducted was inadequate to prevent the reoccurrences of the additional 22 batches noted in the above Observation #1. For example, the investigation failed to include the evaluation of the above noted inadequate (b)(4) machine sanitization, (b)(4) cleaning, cleaning validation and maintenance.

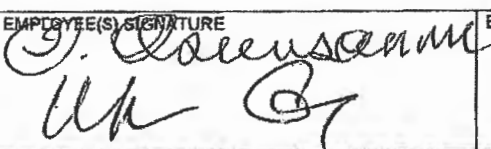
2. Objectionable conditions were noted in the manufacturing of the Fluvirin monovalent batches. For example:

A) Fluvirin batch with high bioburden levels that was above the action limit of (b)(4) at (b)(4) (b)(4) stage (b)(4) was further processed into Fluvirin monovalent batch, final batch and released for US distributions. Specifically,

i) Per DR 307187 dated June 19, 2014 Fluvirin monovalent B/Mass batch (b)(4) with bioburden result of 3,400,000cfu/ml (alert of (b)(4) /action limit of (b)(4) ) at (b)(4) stage and endotoxin result of 2100 EU/ml (alert limit of (b)(4) ) was further processed into (b)(4) Fluvirin filled batches that were released from (b)(4) to (b)(4) 2014 to US and ROW.

3. Inadequate stability study was conducted for Fluvirin A/Texas batch (b)(4) with bioburden result of 93,000cfu/ml at (b)(4) step and alert excursion result for endotoxin at (b)(4) step with result of 114EU/ml alert (b)(4) ); PQS excursion for endotoxin at (b)(4) is 71EU/ml and breach of licensed PQS endotoxin action level at (b)(4) step with result of 14EU/ml. The batch was considered as worst case for endotoxin and, as such, was placed on stability. The batch was placed on stability study per the Non Routine Fluvirin Stability Protocol for 2014/2015 Campaign on September 30, 2014. Although the batch was placed on stability due to the above licensed PQS endotoxin excursions, testing for endotoxin and sterility are (b)(4) scheduled to be conducted (b)(4) which was at the end of the batch expiration date of (b)(4)

4. Some of the 19 CAPAs that were opened as a result of the above Fluvirin monovalent batches OOS and PQS

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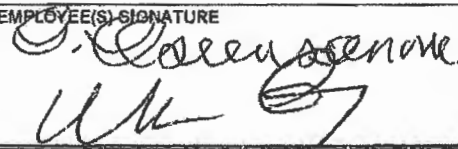
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endotoxin level excursions of 2014/2015 Fluvirin campaign at (b)(4) manufacturing stages were not closed in a timely manner to prevent reoccurrence. For example:

- A) CAPA 316201 to "Review of process monitoring protocol for Fluvirin (b)(4) with a view to include on the PQS" (Product Quality Specification) was initiated on July 31, 2014 and still opened as of June 11, 2015.
- B) CAPA 316226 for the implementation of a process for (b)(4) qualification of analysts performing endotoxin testing was initiated on July 31, 2014 and still opened as of June 11, 2015.
- C) CAPA 316214 to determine if there are any (b)(4) improvements for (b)(4) process was initiated on July 31, 2014 and was not closed until January 15, 2015.
- D) CAPA 316234 to introduce endotoxin testing (b)(4) (b)(4) was initiated on July 31, 2014 and was not closed until January 23, 2015.
- E) CAPA 316207 to update the Fluvirin (b)(4) (b)(4) was opened on July 31, 2014 and was not closed until November 21, 2014.

5. The investigation conducted into the root cause and the corrective and preventive action instituted into (b)(4) (b)(4) monovalent in process bioburden excursions per DR 327773 dated September 28, 2014 that occurred during the 2013/2014 (b)(4) campaign is inadequate. The investigation failed to include all of (b)(4) manufacturing areas that could cause the bioburden and endotoxin excursions. Specifically,

A) Per DR 327773 from the start of (b)(4) campaign of 2013/2014, high proportion of (b)(4) batches exhibited bioburden PQS breaches at 10 out of (b)(4) manufacturing stages (b)(4) that bioburden are monitored and thirty (30) batches out of total of (b)(4) monovalents manufactured during the 2013/2014 campaign had alert and action levels bioburden excursions and in some cases up to five (5) PQS bioburden action levels occurred per batch. The investigation determined the root cause to be (b)(4) (b)(4). However, the investigation and corrective action failed to evaluate (b)(4) machines (b)(4) cleaning, cleaning validation and maintenance.

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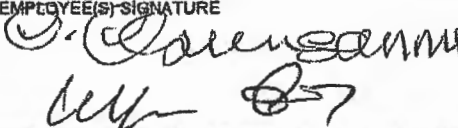
B) The firm failed to consider that although (b)(4) may be contaminated as the result of (b)(4) (b)(4) as noted by the investigation, however contamination of (b)(4) can also occur as the result of transfer of product residues from (b)(4) by (b)(4) (b)(4). For example,

i) (b)(4) are changes every (b)(4) with (b)(4) (b)(4) as one of the corrective actions to the above Fluvirin endotoxin excursions of 2013/2014. However per DR 331551 dated October 16, 2015 and Work Order # WO523873 dated October 22, 2014 the (b)(4) maintenance contractor noted after servicing of (b)(4) machine on (b)(4) (b)(4) on (b)(4) 2014 that some (b)(4) had visible (b)(4) (b)(4) residue on (b)(4) and there were some examples where (b)(4) (b)(4) appeared to have a buildup of debris. Also, that one (b)(4) had a small amount of (b)(4) on (b)(4) mostly caused by (b)(4) during processing.

6. Inadequate investigations are conducted into the Fluvirin potency assay OOE, OOT and OOS deviations test results per the SOP 208367, V 25 titled: Procedure for Investigation, Corrective Action and Follow-Up of Laboratory Results Indicating Non-Conformance. Although individual investigations are conducted into the OOS, OOE and OOT deviations, however, there has been no formal investigation opened that includes manufacturing and potency assay validation to address the OOS, OOE and OOT deviations since March 2013. Specifically,

A) Several of the Fluvirin (b)(4) filled products potency assay OOE, OOT and OOS test results deviation root causes included the documentation of the Potency Assay, titled, USA Assay Influenza Hemagglutinin Content by (b)(4) and in some cases the recommendation to (b)(4) (b)(4). However, there is no documentation that the potency assay has been evaluated or reviewed for revalidation in regards to high numbers of OOS, OOT and OOE results and was last conducted in 2001 per Document #AVR/0001/00 dated February 18, 2001 using (b)(4) (b)(4). No justification is provided.

i) There were 73 batches of Fluvirin potency assay OOT deviations for (b)(4) filled products stability OOTs.

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ii) There were 67 batches of Fluvirin potency assay OOE deviations of (b)(4) filled products OOE.

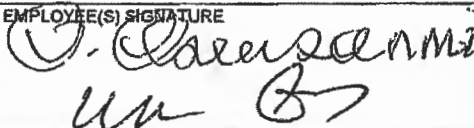
iii) There were total of 14 OOS deviations of which six (6) of the batches were for final container Fluvirin potency assay and 8 batches of (b)(4) OOS deviations

7. The list of product deviations/non-conformances provided at the start of the inspection since 2013, did not accurately reflect the actual numbers of non-conformances that have occurred in the Fluvirin (b)(4) manufacturing processes. The SOP #208630, V. 28, titled, Deviations and CAPA Management-Initiator and Owner has a schematic diagram that allows for the cancelations of multiple similar non-conformance deviations and a "Master DR" For example:

A) DR 327773 dated October 28, 2014 for (b)(4) bioburden action and alert levels was listed on the deviation list provided, however, the deviation report contained 15 bioburden excursions, which occurred on different dates and batches but were not listed on the deviation list provided during the inspection.

8. An investigation was conducted in 2013 on multiple complaints regarding LEAKING Fluvirin Multiple Use Vials (MDV) across various batches produced for the 2013/2014 campaign. Specifically, complainants alleged leaks from stoppers or crimps of the vials. For example, one such complaint (#260714) alleged, in part, that 30 MDVs leaked and that 250 to 300 patients may have received doses from such vials. A lead investigation was already opened (#257884) and attempts were made to understand the nature of the apparent leaks. A report, Investigation Report for the Over-Arching Investigation into Leaking Vials Complaints of the 2013/2014 Fluvirin campaign (R/0534/12/13) indicates, in part, that various experiments were conducted with returned complaint samples. The introduction of air into the vials from syringes was investigated and was found to be a significant contributor for the leaks. Although leaks were substantiated as a result of the experiments, your firm did NOT investigate the MINIMUM amount of air necessary to cause a leak.

9. A review of 20 complaints related to leaking vials was done, which revealed that three of these complaints involved using ONLY Adverse Event (AE) intake forms (Appendix to Work Instruction 255237-4.0) to capture initial complainant information. In capturing information from complainants about product technical complaints,

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another form is routinely used along with specific questions (separate questionnaire) related to the type of complaint (MSOP 260809-07). The complaint form and associated questionnaires appear to require MORE information about product related issues than does the AE intake form. Specifically, on occasion, a complainant may mistakenly call the Medical Communication Center (MCC, AE intake center) with only a technical product complaint with no associated AE's. An AE intake form would still be generated to document the information and eventually is routed to PTC management (Pharmaceutical Technical Complaint), even though no AE occurred. Pharmaceutical Technical Complaint (PTC) management used ONLY the AE forms to capture initial complaint information pertaining to leaking vials:

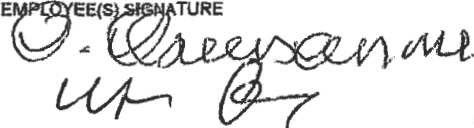
A) 260714—complainant alleged, in part, that 30 Multi-Dose Vials (MDVs) leaked and that 250 to 300 patients may have received doses from such vials.

B) 260720—complainant alleged, in part, that the rubber stoppers of 6 vials did not appear to be seated flat to create a complete seal, and one such vial appeared to have been used on up to 10 patients.

10. In addition to the above, an AE form was generated regarding a "mixed complaint" (both an AE and product complaint) as received by the MCC (Medical Communications Center for receipt of AEs), the event was evaluated by the PV CPO, and the form was routed to the PTC management Team (Pharmaceutical Technical Complaint) to address the product technical complaint aspect. The PV CPO forwarded the AE form. However, the PTC investigation used only the AE form and NOT the complaint intake form (MSOP 260809-07) and associated questions (separate questionnaire), for example:

(i) #256426—complainant alleged, in part, vaccine leaking from multi-dose vials (MDV), specifically from the metal area and leaking from around the stopper; and 2.5 vials were used from the same lot and 60 people received Fluvirin from the affected vials.

11. The current complaint system could still allow for AE forms to be used instead of PTC complaint forms, although, as indicated by employee (b)(6) this is a rare occurrence. The above processes are guided by SOPs, such as SOP 260809-08, Handling of Pharmaceutical Technical Complaints (PTC), which states: "If the PTC description is lacking detail, QA has to make efforts to obtain such details." However, this SOP does NOT address

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER  
FDA/CBER OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY  
10903 NEW HAMPSHIRE AVENUE W071-5118  
SILVER SPRING, MD 20993-0002  
TEL: (240) 402-8914/FAX (301) 595-1304  
Industry Information: [www.fda.gov/oc/industry](http://www.fda.gov/oc/industry)

DATE(S) OF INSPECTION  
June 01 -11, 2015 *06/11/15*

FEI NUMBER  
3002806949

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED  
**TO: LAURA E. O'BRIEN PhD, SITE HEAD LIVERPOOL**

FIRM NAME  
NOVARTIS VACCINES & DIAGNOSTICS Ltd.

STREET ADDRESS  
RENAISSANCE WAY

CITY, STATE AND ZIP CODE  
LIVERPOOL L24 9GR

TYPE OF ESTABLISHMENT INSPECTED  
FLU VACCINE MANUFACTURER

the gap in information between the AE and complaint forms.



SEE  
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OF THIS  
PAGE

EMPLOYEE(S) SIGNATURE  
*O. Osunsanmi*  
*Gene Arcy*

EMPLOYEE(S) NAME AND TITLE (*Print or Type*)  
OMOTUNDE O. OSUNSANMI, CSO  
GENE ARCY, CSO

DATE ISSUED  
JUNE 11, 2015