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 Biologics Quality 10903 New Hampshire Avenue WO71 - 5118 Silver Spring, MD 20993-0002 TEL: (240) 402-8914	July 7-19, 2016 FEI NUMBER 3003259844

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dominique D. Pintiaux, Site Manager

FIRM NAME	STREET ADDRESS
Sanofi Winthrop Industrie	1051 Boulevard Industriel
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
76580 Le Trait France	Vaccine Filler, Drug manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. The firm has repeatedly refused to provide the requested documentation for review of the CBER regulated product, (b) (4), and CDER regulated products, (b) (4) and (b) (4). The following was requested at a minimum of three times and not provided: you were asked for all planned and unplanned maintenance for the tanks and skids on (b) (4) and (b) (4), and you provided only the last two years of planned maintenance; you were asked for all maintenance on (b) (4) (b) (4) for the last two years, you provided only the planned maintenance for the last year (mechanical only); you were asked for the initial and most recent re/qualification for the sterilization of the (b) (4) tanks, and you provided the most recent re-qualification of a (b) (4) (b) (4) tank. In addition, the firm has provided incomplete documentation for review of the submitted (b) (4) Field Alerts.

2. The firm does not have a thorough understanding of the requirements for submission of (b) (4) Field Alerts. Since March 2014, the firm has submitted 58 (b) (4) Field Alerts. The majority of these Field Alerts originate as single consumer product complaints and many of the complaints have not been confirmed by the company. For example,

   A. The firm received a complaint on August 10, 2015 for a (b) (4) (b) (4) lot (b) (4), in which the (b) (4) (b) (4) failed to (b) (4) The returned complaint sample included a (b) (4) in which the (b) (4) had not been (b) (4) The QC department was able to (b) (4) the (b) (4) and successfully (b) (4) the (b) (4), the complaint was not confirmed. The initial Field Alert was submitted on December 15, 2015 and the final Field Alert was submitted on December 24, 2015.

   B. The firm received a complaint on October 16, 2015 for an (b) (4) (b) (4) lot (b) (4) for the pre- (b) (4) of the (b) (4). The returned complaint sample included a filled (b) (4) in which the (b) (4) had not been (b) (4) and the complaint was not confirmed. The unsigned draft of the initial Field Alert was dated October 21, 2015. The firm's version 2 of the Final Report included a second complaint for the same defect, for (b) (4) lot (b) (4), in which the sample was returned and the defect was confirmed. The documents for the final Field Alert were not provided.

   C. The firm received a complaint on July 3, 2014 for a (b) (4) (b) (4) lot (b) (4), in which the (b) (4) (b) (4) (cap) was difficult to remove. The complaint sample was not returned and could not be confirmed. The initial Field Alert was dated July 8, 2014. The firm's Final Report included a second complaint for the same defect, for (b) (4) lot (b) (4), in which the sample was returned but because the dose had been administered, the complaint could not be confirmed. The documents for the final Field Alert were not provided.

In addition, the initial (b) (4) Field Alerts are not always submitted within the required timeframe of 3 days from the awareness date.

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	Debra Emerson Arie C. Menachem	Debra M. Emerson, CSO Arie C. Menachem, CSO	July 19, 2016

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3. The written complaint record did not include the reason an investigation was found not to be necessary when an investigation into unexplained discrepancies was not conducted. Specifically,

   A. As part your firm's complaint investigations for (b) (4) (b) (4) you perform visual inspection of your retain samples. Your visual inspection retain samples from lot (b) (4) revealed that three of (b) (4) (b) (4) contained visual particulates. Subsequently, a visual inspection of retains from lot (b) (4) revealed visible particulates in one (b) (4). Your firm did not initiate an investigation into your inspection process to determine how these (b) (4) were released for use.

   B. Of the 452 complaints related to (b) (4) between 2015 and the present, your firm received 291 registered as " (b) (4) Difficult to (b) (4) / (b) (4) Issue"; two of these were recorded as a supplier issue while the rest did not result in a conclusive root cause. Your investigations into these complaints did not include a quantitative review of (b) (4) on the stoppers or the (b) (4); you have not determined the amount of (b) (4) required to assure adequate (b) (4) as part of your process validation.

   C. Your firm did not provide an adequate justification for the cancellation of the complaint investigation for Complaint TRA16-0663. The complaint involved the 94th complaint for (b) (4) batch (b) (4) initially coded with the failure mode " (b) (4) difficult to (b) (4)." The patient intake information included the statement: "it [i.e. the injection] took much longer for him to take that medication as compared to the first." As a result of instructions from your (b) (4) site, you cancelled this complaint. A listing of other (b) (4) complaints revealed additional complaints that in which you initiated a complaint investigation which was subsequently cancelled by the (b) (4) site.

4. The following investigations were found inadequate:

   A. Two media fill failures occurred on fill line (b) (4), between (b) (4) and (b) (4) The same organism was isolated from both media fills, *Chaetomium subaffine*. The investigation classified the isolate as "lowest risk".

      i. As part of the investigation, the firm swabbed equipment used on the fill line which was stored in an uncontrolled area, the area where equipment was stored, and the area adjacent to the uncontrolled storage where offices were being constructed including the area (b) (4) the (b) (4) for this construction. Mold was recovered as part of the swabbing from all of these areas. No visible mold was observed in the area (b) (4) the (b) (4) or found as part of the investigation. However the Quality Manager stated that they "identified the source of the mold".

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ii. The firm brings the filling equipment in from a non-classified area for installation on the line as part of set up. There is no requirement to clean or disinfect the equipment prior to installation on the line as the site considers the fill line un-classified when not in use. As a corrective action to be able to use the fill line, the firm implemented an (b) (4) (b) (4) of the filling equipment in room (b) (4). The firm has no data to support that this (b) (4) (b) (4) cycle will decontaminate the equipment.

iii. The environmental monitoring data demonstrates that mold isolates have been recovered from the facility from January 2015 to present to include *Chaetomium* species which has been recovered 14 times.

B. Between June 2015 and September 2015, there have been 4 deviations opened for bioburden excursions (with recoveries between (b) (4) (b) (4) CFU/ (b) (4) mL) which occurred (b) (4) the (b) (4) filtration of (b) (4). The isolate for all four excursions was identified as *Bacillus pumilus* and one event includes *Bacillus cereus*. The firm concluded that the root cause of the contamination was weighing (b) (4) number 7. These (b) (4) are cleaned (b) (4) use by wiping with a (b) (4) wipe and then visual inspection of the equipment. The firm did not swab the equipment to confirm the source of the contamination. All (b) (4) batches associated with the investigations have been released.

5. Aseptic process simulations were found inadequate in that:

A. After the failure of two consecutive media fills on fill line (b) (4) between (b) (4) and (b) (4) with the same organism, *Chaetomium subaffine*, and the closure of the investigation, the firm performed a single media fill beginning on June 23, 2014. This fill line was then used to fill (b) (4) for the (b) (4) for the U.S. market.

B. (b) (4) media fill simulations, performed between June 2014 and October 2015, that are used to support the current aseptic filling processes of all U.S. fill lines at the site were reviewed. There is no reconciliation or accountability for the total number of (b) (4) added to the line, filled with media, rejected, or taken off the line as unfilled, broken, or empty (b) (4). In addition, there is not always a reason for (b) (4) being rejected off the line.

6. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established. Specifically, filling lines (b) (4) are used to fill (b) (4) (b) (4)%, (b) (4) (b) (4)%, (b) (4) and (b) (4). During production activities on 13JUL2016 we noted during our walk-through that:

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A. Tubes attached to the product and (b) (4) manifold spatially impeded first pass air from your HEPA filters prior to reaching open (b) (4) in route to filling and stoppering.

B. In Line (b) (4) a (b) (4) tube used to (b) (4) test the (b) (4), with an approximate diameter of (b) (4) was directly above open (b) (4) and impeded first pass air.

C. Zone (b) (4) of Line (b) (4) had an (b) (4) residue on the (b) (4) and (b) (4) holding the (b) (4). You could not identify the residue or indicate if particles of the residue could contaminate the (b) (4) traveling through this zone.

D. Your current Environmental Monitoring regime includes the placement of (b) (4) plates for passive air sampling of viable particles within your (b) (4). You expose these plates for (b) (4) (b) (4) on a (b) (4) basis (b) (4) setup activities), irrespective of the number of hours production occurs. You have not provided a rationale explaining why you do not monitor your filling lines throughout the filling process.

E. The firm has recovered mold isolates in (b) (4) bulk product more than 5 times since 2014 which include isolates such as *Penicillium spp* and *Cladsporium spp*. The firm did not identify the molds past the genus level. The firm does not have the ability to detect mycotoxins in the final product prior to release. All batches were released.

7. Routine calibration and inspection of electronic equipment is not performed according to a written program designed to assure proper performance. Specifically,

A. The particle counters used at your firm for assuring operations, including the filling of sterile drug product in your Class A (b) (4) are unreliable. The equipment has not been calibrated in a manner that assures that they accurately count the number of particles present during routine environmental monitoring in your (b) (4).

B. You have executed the following smoke studies for your (b) (4):

(b) (4) / Line Study № Approval Date

(b) (4)

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DURING (b) (4)

Review of these studies indicated:

- The smoke studies for (b) (4) and (b) (4) were inadequate in that they did not include dynamic filling / stoppering activities using actual (b) (4)
- Smoke studies for (b) (4) were inadequate in that their review did not allow for determination of:
  - The airflow / potential for turbulence caused by tubes directly above open (b) (4) prior to filling.
  - The influence of the (b) (4) on airflow / first pass air / turbulence above (b) (4) of open (b) (4) in the (b) (4)
- Review of the smoke studies revealed the presence of turbulence above open (b) (4) the stopper bowl and stopper (b) (4) and the (b) (4); no explanation for these issues was provided as part of your study.

C. You challenge your automated inspection equipment at the (b) (4) of (b) (4) product (b) (4); as part of this activity, you place (b) (4) with various defects to verify that your equipment can identify defective product. Your defect (b) (4) sets typically contain (b) (4) (b) (4) for each defect. Equipment that can identify at least (b) (4)% of (b) (4) containing visible particulates, glass and fibers in solution is considered acceptable. You have not determined the process capability of your equipment to evaluate if equipment consistently rejects product with defects. In addition, you do not capture data surrounding the nature or number of defects your equipment rejects. Between 2014 and the current inspection, you logged 8 deviations for fibers, particles and glass in your (b) (4) found during (b) (4) QC inspection and 24 complaints for foreign matter in solution for your products marketed in the US.

D. You "recycle" (b) (4) that your (b) (4) assembler / labeler has rejected by replacing them in the equipment after manual inspection of (b) (4) attributes; you do not capture information regarding the nature of the defects found or the number of (b) (4) recycled during packaging

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operations. "Recycled" [redacted] are not reinspected by the [redacted] electronic inspection equipment.

8. The equipment used in the manufacture, processing, and packing of [redacted], [redacted] and [redacted] is not of adequate construction and design for its intended use. For example:

A. The [redacted] inside the [redacted] of [redacted] and [redacted] are of inadequate operational design in that as the [redacted] move along the conveyor and when the [redacted] into position to [redacted] the next [redacted] the [redacted] physically goes [redacted] of the [redacted] of opened unfilled [redacted]. Specifically,

i. The [redacted] in the [redacted] of [redacted] was observed to continually pass [redacted] the [redacted] of open unfilled [redacted] in the [redacted] as it moved along the conveyor.

ii. The [redacted] in the [redacted] of [redacted] was observed to pass [redacted] the [redacted] of open unfilled [redacted] in the [redacted] as it moved along the conveyor.

In addition, the paint covering this [redacted] is worn in the joints and has evidence of peeling paint.

B. There are valves inside the filling [redacted] that contain a [redacted] painted [redacted] which was observed to be peeling. Inside [redacted] for [redacted]% there are [redacted] valves with peeling [redacted] inside [redacted] for [redacted] there are [redacted] valves with peeling [redacted] and inside [redacted] for [redacted] there are [redacted] valves with peeling [redacted]

C. The [redacted] on fill line [redacted] used for filling of [redacted]% glass [redacted], is inadequate in that the glass [redacted] travel at [redacted] the [redacted] both before and after filling and the glass [redacted] physically contact each other when they [redacted]. Specifically,

i. After the glass [redacted] are washed and sterilized, the [redacted] loads a [redacted] of [redacted] onto the [redacted] and the glass [redacted] then travel [redacted] passing by [redacted], where the [redacted] only [redacted] of the [redacted] until they [redacted] when they come in contact with each other at the [redacted] of the [redacted] where they enter the [redacted].

ii. After the [redacted] exit the [redacted] they are transported [redacted] the [redacted] approximately [redacted] and then they travel via [redacted] the [redacted] passing [redacted] units with [redacted] in which only [redacted] were observed to [redacted] the [redacted] then the [redacted] go around a [redacted] bend and [redacted] conveyor with [redacted] where [redacted] of them are [redacted] the [redacted]

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until the (b) (4) of the (b) (4) where they are placed in containers for visual inspection. There has been no evaluation for the (b) (4) of the (b) (4) as they travel (b) (4) this conveyor.

This issue was previously cited as Observation #3 on the List of Observations from the March 20 - 28, 2014 inspection.

9. Equipment and utensils are not sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,

   A. While your cleaning procedure requires a (b) (4) (b) (4) contact time between (b) (4) and (b) (4) (a (b) (4) of), your Disinfectant Efficacy Study does not contain data surrounding the required contact time between (b) (4) and (b) (4) in order to ensure a (b) (4) $\log_{10}$ kill of non spore-forming bacteria and fungi and a (b) (4) $\log_{10}$ kill of spore-forming bacteria.

   B. Your cleaning procedure requires that your sanitization solution, (b) (4) maintain a contact time of (b) (4) (b) (4) on glass and other surfaces to ensure a (b) (4) $\log_{10}$ kill of fungi and non spore-forming bacteria. You apply the (b) (4) to the surface of your equipment using a non-sterile (b) (4) wipe; we observed that the solution does not make contact with your equipment surfaces for a full (b) (4) (b) (4) due to evaporation.

   C. Your cleaning procedure requires that your sanitization solution, (b) (4) maintain a contact time of (b) (4) (b) (4) to ensure a (b) (4) $\log_{10}$ kill of non spore-forming bacteria and fungi and a (b) (4) $\log_{10}$ kill of spore-forming bacteria for various surfaces, including (b) (4). You apply the (b) (4) to the surface of your equipment using a non-sterile (b) (4) wipe; we observed that the solution does not make contact with your equipment surfaces for a full (b) (4) (b) (4) due to evaporation.

   D. You use non-sterile (b) (4) wipes during cleaning activities together with various sterile disinfectants; you have not considered the potential for introducing additional bioburden into your equipment through the use of these wipes.

   E. Your method of disinfectant application does not mimic the method you used during your disinfectant efficacy study; you applied (b) (4) mL of disinfectant on (b) (4) having an area of approx. (b) (4) cm^2 (~(b) (4) sq in). In production you wet non-sterile (b) (4) wipes with your disinfectant solution and apply the disinfectant using these wipes.

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10. The firm does not have scientific rationale or justification for the placement of their non-viable particle monitors. For example, the non-viable particle probe in fill line (b) (4) is located more than (b) (4) the height of the sterile (b) (4) at the (b) (4) in the (b) (4) side of the (b) (4) away from (b) (4) operations. The non-viable particle probe in fill line (b) (4) and (b) (4) is located more than (b) (4) away from the oper (b) (4) in the (b) (4)

11. The controlled areas within the manufacturing department are not maintained in a state of control. For example:

    A. The firm painted the compound room walls (b) (4) and ceiling 12/19-26/15. The paint used is inadequate in that it was observed to be peeling from the side wall, a (b) (4) feet from the tank used to (b) (4) the (b) (4) bulk solution.

    B. Stained and discolored HEPA filters were observed in the Class C area, storage (b) (4).

    C. Paint was observed on the metal grid and filter of one of the HEPA units in room (b) (4).

12. The following qualification/requalification studies were found deficient:

A. The firm has (b) (4) (b) (4) tanks used for the manufacture of drug product (b) (4) The site uses the same sterilization program for all (b) (4) sized tanks and considers them to be equivalent. The firm currently qualifies only the (b) (4) tank (b) (4) as it determined to be (b) (4) Data to demonstrate tank equivalency and (b) (4) of the (b) (4) tank were not provided. The (b) (4) qualification for the sterilization of the (b) (4) tanks, which includes placing (b) (4) (b) (4) tanks with filters and tubings attached to various (b) (4) into a (b) (4) sterilizer, is deficient in that the firm could not provide scientific rationale for the placement of the biological indicators and (b) (4) In addition, the firm is performing requalification on a (b) (4) tank (b) (4) which is not currently in use and was last used for production in June 2010.

B. The Shipping Qualification performed for shipping (b) (4) in the (b) (4) from Le Trait, France to (b) (4) is deficient in that:

    i. There is no data to support that the (b) (4) locations chosen for the placement of the (b) (4) temperature monitoring devices inside the (b) (4) unit are positioned in the worst case locations. In addition, one of the (b) (4) (b) (4) temperature monitoring devices placed in the load was lost during the study and no data was collected for that location.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Debra M. Emerson Arie C. Menachem	Debra M. Emerson, CSO Arie C. Menachem, CSO	July 19, 2016

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue WO71 - 5118 Silver Spring, MD 20993-0002 TEL: (240) 402-8914	July 7-19, 2016 FEI NUMBER 3003259844

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Dominique D. Pintiaux, Site Manager

FIRM NAME	STREET ADDRESS
Sanofi Winthrop Industrie	1051 Boulevard Industriel
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
76580 Le Trait France	Vaccine Filler, Drug manufacturer

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ii. The study does not demonstrate worst case shipping conditions in that it the load was shipped on May 23, 2013. In addition, the ambient (b) (4) monitor was not attached inside the refrigerated (b) (4) or (b) (4) of the (b) (4) unit as required in the protocol.

iii. The acceptance criteria stated that the temperature during the cold chain shipment be within 2-8 C. During the transfer of the pallets from the (b) (4) unit to the refrigerated (b) (4) at the (b) (4) "a spike of 11.5 C was observed" from the (b) (4) at the (b) (4) pallet.

The report was approved by Quality on July 3, 2013.

13. Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. Specifically, you have not validated the (b) (4) CoA for the (b) (4) used during the manufacture and fill of (b) (4); while you have an open change control from 2015 to address this deficiency, to date you have not initiated the validation of the CoA.