1. The firm has repeatedly refused to provide the requested documentation for review of the CBER regulated product, _______ and CBER regulated products, _______ and _______. 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 _______ and _______ and you provided only the last two years of planned maintenance; you were asked for all maintenance on _______ 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 requalification for the sterilization of the _______ tanks, and you provided the most recent requalification of a _______ tank. In addition, the firm has provided incomplete documentation for review of the submitted _______ Field Alerts.

2. The firm does not have a thorough understanding of the requirements for submission of _______ Field Alerts. Since March 2014, the firm has submitted 58 _______ 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 _______ lot _______ in which the _______ failed to _______. The returned complaint sample included a _______ in which the _______ had not been _______. The QC department was able to _______ the _______ and successfully _____ the _______ 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 _______ lot _______ for the pre- _______ of the _______. The returned complaint sample included a _______ in which they _______ not _______ 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 _______ lot _______, 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 _______ lot _______ in which the _______ _______ 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 _______ lot _______ 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 _______ _______ Field Alerts are not always submitted within the required timeframe of 3 days from the awareness date.
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 (a) you perform visual inspection of your retain samples. Your visual inspection retain samples from lot (b) revealed that three of lot (c) contained visual particulates. Subsequently, a visual inspection of retain from lot (d) revealed visible particulates in one (b) Your firm did not initiate an investigation into your inspection process to determine how these (b) were released for use.

B. Of the 452 complaints related to (e) between 2015 and the present, your firm received 291 registered as "(f) Difficult to (g) ” 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 (h) on the stoppers or the (i) you have not determined the amount of (j) required to assure adequate (k) 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 (l) batch of (m) initially coded with the failure mode "(n)’. The patient intake information included the statement: “it [the injection] took much longer for him to take that medication as compared to the first.” As a result of instructions from your (o) site, you cancelled this complaint. A listing of other (p) complaints revealed additional complaints that in which you initiated a complaint investigation which was subsequently cancelled by the (q) site.

4. The following investigations were found inadequate:

A. Two media fill failures occurred on fill line (r) between [redacted] and [redacted]. The same organism was isolated from both media fills, Clavatium subaemone. 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 (s) for this construction. Mold was recovered as part of the swabbing from all of these areas. No visible mold was observed in the area (t) or found as part of the investigation. However the Quality Manager stated that they “identified the source of the mold”.

FILE NUMBER 3903289844
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Firm Name: Sanofi Winthrop Industrie
City, State and Zip Code: 76580 Le Trait France
Type of Establishment Inspected: Vaccine Filler, Drug manufacturer

TO: Dominique D. Pintiaux, Site Manager

During an inspection of your firm we observed:

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 unclassified when not in use. As a corrective action to be able to use the fill line, the firm implemented an (b)(4) of the filling equipment in room (b)(4). The firm has no data to support that this filling 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) CFU/mL) which occurred during the 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 areas are cleaned by wiping with (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) with the same organism, Chaetomium sp, 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. 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 meeting the requirements of the current good manufacturing practice for finished pharmaceuticals are not established. Specifically, filling line (b)(4) are used to fill (b)(4)%, (b)(4)%, and (b)(4)% During production activities on 13JUL2016 we noted during our walk-through that:

DATE(S) OF INSPECTION: July 7-19, 2016

FIRING NUMBER: 3003259644
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**

**Firm Name:** Sanofi Winthrop Industrie  
**Street Address:** 1051 Boulevard Industriel

**City, State and Zip Code:** 76580 Le Trait France  
**Type of Establishment Inspected:** Vaccine Filler, Drug manufacturer

**To:** Dominique D. Pintiaux, Site Manager

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**Inspection Observations:**

**A.** Tubes attached to the product and manifold spatially impeded first pass air from your HEPA filters prior to reaching open we were directly above open we and impeded first pass air.

**B.** In Line a tube used to test the with an approximate diameter of was directly above open we and impeded first pass air.

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

**D.** Your current Environmental Monitoring regime includes the placement of plates for passive air sampling of viable particles within your You expose these plates for on a basis (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 bulk product more than 5 times since 2014 which include isolates such as *Penicillium spp* and *Cladosporium 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 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.** You have executed the following smoke studies for your:

\[
\text{Line} \quad \text{Study No} \quad \text{Approval Date}
\]
Review of these studies indicated:

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

C. You challenge your automated inspection equipment at the ___, as part of this activity, you place ___ with various defects to verify that your equipment can identify defective product. Your defect ___, typically containing ___ for each defect. Equipment that can identify at least ___% of ___ 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 ___. Found during _QC inspection and 24 complaints for foreign matter in solution for your products marketed in the US.

D. You “recycle ____ that your ____ assembler / labeler has rejected by replacing them in the equipment after manual inspection of ____ attributes; you do not capture information regarding the nature of the defects found or the number of ____ recycled during packaging.
operations. "Recycled" are not reinspected by the electronic inspection equipment.

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

A. The inside the and of are of inadequate operational design in that the next one move along the conveyor and when the into position to physically go of the it of open unfilled. Specifically,

i. The in the of was observed to continually pass the as it moved along the conveyor.

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

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

B. There are valves inside the filling that contain are painted which was observed to be peeling. Inside there are valves with peeling . For there are valves with peeling .

C. The on fill line is used for filling of % glass is inadequate in that the glass physically contact each other when they. Specifically,

i. After the are washed and sterilized, the loads of onto the and the glass then travel until they enter the where they come in contact with each other at the where they enter the.

ii. After the exit the are transported approximately and then they travel via which only were observed to the when the go around a

bend and they enter the
During an inspection of your firm, we observed:

- a [missing text]
- a [missing text]
- a [missing text]
- a [missing text]
- a [missing text]
- a [missing text]
- a [missing text]

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 [missing text] contact time between [missing text], your Disinfectant Efficacy Study does not contain data surrounding the required contact time between [missing text] in order to ensure a [missing text] kill of non spore-forming bacteria and fungi and a [missing text] kill of spore-forming bacteria.

B. Your cleaning procedure requires that your sanitization solution [missing text] maintain a contact time of [missing text] on glass and other surfaces to ensure a [missing text] kill of fungi and non spore-forming bacteria. You apply the [missing text] to the surface of your equipment using a non-sterile [missing text] wipe; we observed that the solution does not make contact with your equipment surfaces for a full [missing text] due to evaporation.

C. Your cleaning procedure requires that your sanitization solution [missing text] maintain a contact time of [missing text] to ensure a [missing text] kill of non spore-forming bacteria and fungi and a [missing text] kill of spore-forming bacteria for various surfaces, including [missing text]. You apply the [missing text] to the surface of your equipment using a non-sterile [missing text] wipe; we observed that the solution does not make contact with your equipment surfaces for a full [missing text] due to evaporation.

D. You use non-sterile [missing text] 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 [missing text] mL of disinfectant on [missing text] having an area of approx. [missing text] cm² (~[missing text] sq in). In production you wet non-sterile [missing text] wipes with your disinfectant solution and apply the disinfectant using these wipes.
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 A is located more than (b) feet away from the operation. The equipment probe is located more than (b) feet away from the operation.

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 [_____] and ceiling 12/19-26/15. The paint used is inadequate in that it was observed to be peeling from the side wall, a "[____]" feet from the tank used to store the [____] bulk solution.

   B. Stained and discolored HEPA filters were observed in the Class C area, storage [____].

   C. Paint was observed on the metal grid and filter of one of the HEPA units in room [____].

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

   A. The firm has [____] pressure tank used for the manufacture of drug product [____]. The site uses the same sterilization program for all the tank and considers them to be equivalent. The firm currently qualifies only the [____] tank, as it is determined to be [____]. Data to demonstrate tank equivalency and [____] of the other tank were not provided. The requalification for the sterilization of the [____] tank, which includes placing the tank with filters and tubings attached to the sterilizer, is deficient in that the sterilizer is not currently in use and was last used for production in June 2010.

   B. The shipping qualification performed for shipping tank from Le Trait, France to [____] is deficient in that:

      i. There is no data to support that the [____] locations chosen for the placement of the temperature monitoring devices inside the [____] units are positioned in the worst case locations. In addition, one of the [____] temperature monitoring devices placed in the load was lost during the study and no data was collected for that location.
ii. The study does not demonstrate worst case shipping conditions in that the load was shipped on May 23, 2013. In addition, the ambient monitor was not attached inside the refrigerated 
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) unit at the (b)(4) "a spike of 11.5°C was observed" from the 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.