Observation 1:

- A vial (U/mL) has been distributed by the drug substance facility. The vial is used in the process for the drug substance manufacturing. And is used in further manufacturing that includes filling into the vials, along with the drug substance and is used in further manufacturing that includes filling into the vials, along with the drug substance.

- U/mL vial (U/mL) and (U/mL) batches of drug substance have been distributed to the United States. The distribution system is not qualified/validated nor is the product tested for quality.

Observation 2:

Aseptic behavior and monitoring is inadequate. On September 17, 2021, during the manufacturing of the drug product (batch (U/mL) on Filler (U/mL) the following items were observed:

a. The Restrictive Access Barrier (RAB) (U/mL) that were Grade B space, environmental monitoring plates, were not sanitized prior to entering Grade A space.

b. The described process in 2.a. is conducted in Grade A space during the filling operations that can be up to 100% to include RAB interventions for such operation. The design of the environmental monitoring (EM) process for the filling machine is inadequate to minimize the number of RAB interventions, which may impact product quality during the manufacturing of the drug product.
c. During the exchange of EM plates, the technician sanitized their gloves for each entry into the filler’s Grade A space, with environmental monitoring of the technician’s gloves by finger dab performed after the last entry. Personnel environmental monitoring is only representative of that last EM plate change based on the design of the activities.

Observation 3:

According to document No. v3, for drug product manufacture identification testing should be performed for each lot/shipment received, with the current procedure for frequency of test inadequate.

Observation 4:

Facilities and equipment are not adequately validated and maintained for manufacture. Specifically,

a. The product contact surface materials of construction are not validated and maintained for manufacture. Specifically, on 13 September 2021 as observed through the_____ of the discoloration (black in appearance) was observed on the sidewalls of the vessels. The firm indicated the discoloration was rouge, with the qualified state not maintained.

Furthermore, within the_____ area, was observed with a line of discoloration on the interior vessel side wall. The firm indicated that this was under investigation and the potential root cause was an obstruction.

b. Within (Grade D area) and near (Grade A air supply) for drug substance intermediate manufacture and dispensing, the wall mounted transfer lines with a covering were observed with the outer surface as dirty, uncleaned.

c. Raw materials are stored at 20 - 25°C in the Warehouse. Store pending manufacture post This area is not validated for 20 - 25°C raw material storage.
d. A floor seam was observed in a deteriorated condition.

e. A leak was observed at the equipment/fl line. The firm indicated that the leak was due to a fault with no work order in place at the time of the noted observation.

f. was observed with a leak. You indicated the source of the leak was from the respective. There was no work order in place at the time of the noted observation.

Furthermore, a leak was observed at the The firm indicated that the source of the leak was a loose with no work order in place at the time of the noted observation.

Observation 5:

Cleaning validations in support of drug substance manufacture are deficient. Specifically,

Cleaning validation excludes swab sampling of tanks, and chromatography skids. The firm indicated that testing mitigates the need for swabbing, where testing assures in support of effective cleaning. Though testing may assure adequate it should not be used as a substitute for not performing swabbing of equipment surfaces that may present an elevated challenge in removal of product residue. Furthermore, cleaning rinse samples should include bioburden and endotoxin testing to a specification where are used.

Observation 6:

Standard operating procedure is inadequate. Specifically,
According to trend reports for the drug substance used in drug substance manufacture (July 2020 - October 2020) and October 2020 - December 2020), pH was at an alert limit, generating a negative trend from approximately July 2020 to November 2020. Standard operating procedure v24, 6.12.2.e indicates if any physiochemical result exceeds the action limit for times for a sample point, an out of trend investigation will be initiated as per Handling of Out of Trend Investigations SOP. The procedure fails to elevate repeated alert level excursions that should include a trend investigation in mitigation of an aberrant condition and documentation of corrective action.