**1. Purpose** This document defines the test method for the pH measurement of intermediate, drug substance, and drug product samples at Site 3. This method conforms to USP <791> and Ph. Eur. 2.2.3.

**2. Scope** This procedure includes safety relevant to this procedure, and analyst and supervisor responsibility. The test method procedure is utilized to obtain the pH of Drug Substance and Drug Product sample material at Site 3.

**3. Definitions**

***Automatic Temperature Compensation (ATC)*:** The pH meter can be equipped with a MiniDIN connected probe or pH/ATC combination probe to measure the temperature of an analyte and automatically adjust the electrode response for the most accurate pH measurements. Alternatively, temperature can be manually entered from a calibrated thermometer into the meter for automatic compensation.

***DS*** Drug Substance

***Calibration check***A check performed prior to each use of the pH meter using a standardized buffer which is at an approximate pH of the solution being tested.

***DP*** Drug Product

***Filling Solution*** The ionic solution used to fill and store pH electrodes.

***Storage Solution*** The ionic solution used to store the pH electrodes to maintain proper working condition.

***LES*** Laboratory Execution System

**4. Materials/Equipment**

4.1 Reagents

* Standard pH Electrode Storage Solution (Orion 910001)
* pH 5.00 Standardization Buffer (certified range ± 0.01 pH units)
* pH 9.00 Standardization Buffer (certified range ± 0.01 pH units)
* pH Standardization Buffers at alternate values (certified range ± 0.01 pH units)
* Purified Water, Reagent Grade Deionized Water (Milli-Q, or equivalent)
* Sample Diluent buffer, pH 6.8

4.2 Equipment

* Flexible Arm Electrode Holder, VWR BK534476, or equivalent
* BNC Adapter, VWR BK597578E, or equivalent
* Thermo Scientific Orion Star A221 Portable pH Meter (STARA2210)
* Thermo Scientific™ Orion™ Universal Power Adapter for Star A and Legacy Star Meters (Thermo Scientific™ 1010003), or equivalent
* ROSS Ultra Semimicro Glass Electrode (ROSS 8103BNUWP)
* Thermo Scientific Orion micro ATC temperature probe with stainless steel tip (Cat #928007MD)
* Thermometer, VWR61220-416 or equivalent
* Incubator/Heat block (Fisher Scientific, Cat# 88860022, or equivalent)
* Glass Beakers, various sizes
* Lint-free wipes
* Batteries (4X AA)
* Eppendorf tubes (1.5 mL or appropriate size)

**5. Procedure**

5.1 **Calibration**

5.1.1 The pH meter must be calibrated using a two-point calibration prior to any product measurements. Calibration must bracket the intended pH range usage. The volume of the buffers used for the calibration should be equivalent to that of the sample volume to be tested.

5.1.2. The ATC probe must be calibrated and verified. All buffer solution pH measurements must be taken within the calibrated temperature range of 23-25°C. Temperatures of solutions are recorded in the appropriate location.

5.1.3. Record applicable daily calibrations and checks in LES.

5.1.4. Daily pH calibration must pass prior to execution of this method.

5.2 **Instrument instructions**

To measure pH using the Orion Star series pH meter, follow the subsequent steps:

5.2.1.1 Remove parafilm and uncover pH probe. Rinse the pH electrode and ATC probe with deionized water, blot gently with a lint-free wipe to remove excess water.

5.2.1.2 Monitor the sample temperature(s) with the ATC probe, ensuring the respective sample to be measured for pH has a stabilized temperature between 23-25°C. If an ATC probe is not available, the temperature of each applicable sample to be measured must be manually entered from a calibrated thermometer, a second analyst must verify the temperature entry.

5.2.1.3 Ensure the pH meter is in continuous read mode. If it is not in continuous, toggle to mode and settings to adjust the measurement mode.

5.2.1.4 Start the measurement and wait for the reading to stabilize.

5.2.1.5 Once the measurement is stable and the screen shows ready, record the pH and temperature of the sample, or import into LES.

5.2.1.6 Remove the probes from the sample, rinse with deionized water, blot gently with a lint-free wipe to remove excess water and place into the next sample.

5.2.1.7 Repeat steps 5.2.1.1 through 5.2.1.6 for all samples and verification buffers. When testing is complete, store the cleaned pH electrode in storage solution. Cap the tip of the cleaned ATC probe and store in air until later use. It is recommended to replace fill hole cover and wrap with parafilm to reduce evaporation.

5.3 **pH measurement of Bulk Drug Substance and Drug Product samples**

All samples will be tested in triplicate. The samples must be incubated to 23-25°C and maintained within this temperature range during pH measurement. Samples must be diluted 5:1 using Sample Diluent.

5.3.1 Pipette 3 sample aliquots of no less than 0.3 mL into three 1.5 mL Eppendorf tubes. Pipette no less than 0.3 mL of two certified buffer aliquots into separate 1.5 mL Eppendorf tubes, each having an intermediate pH for each of the two calibration curves produced during instrument calibration (e.g. verification buffer pH 5.0 to cover range pH 4-7, and verification buffer pH 8.0 to cover range pH 7-10).

5.3.2 Place samples and verification buffer tubes in a water bath, heat block, or other suitable temperature-controlled environment capable of maintaining the correct temperature range of 23-25°C. Monitor and record temperature with pH using the connected ATC probe. If an ATC probe is not available, temperature must be entered manually into the pH meter from a calibrated thermometer and a second analyst must verify the temperature entry.

5.3.4 Rinse the pH electrode and ATC probe with deionized water, blot dry and place both in the 1st verification buffer tube.

5.3.5 Once the temperature and pH value are stable, measure and record pH and temperature or import the temperature and pH value into LES.

5.3.6 Repeat steps 5.3.4 & 5.3.5 for the 2nd verification buffer ensuring the reading is within ± 0.05 pH units of the certified value within the temperature range of 23-25°C.

5.3.7 Measure each of the sample aliquots and import the temperature and pH value into LES. If LES is unavailable record the values on controlled laboratory worksheet CMP-12345. Ensure the probes are rinsed with deionized water and blot dry after each measurement/aliquot.

5.3.8 At the end of the sample analysis and after every 10 samples (30 measurements), perform checks using the two verification buffers, following steps 8.3.5 & 8.3.6.

5.3.9 The pH of the verification buffers must be within ± 0.05 units of the certified value within the temperature range of 23-25°C for all the results to be valid.

5.3.10 When testing is complete, store the cleaned electrode in storage solution. Cover the cleaned ATC probe tip with cap and store in air when not in use. It is recommended to replace fill hole cover and wrap with parafilm to reduce evaporation.

5.4.11 Report sample results per applicable product specifications.

5.4.12 In the absence of a product specification or other reporting document, report the mean pH results to 1 decimal place.

5.5 **Acceptance Criteria**

5.5.1 All verification buffer pH readings must be ± 0.05 units from the certified value within the temperature range of 23-25°C. Temperature measurements performed with pH must be within 23-25°C for samples and verification buffers.

5.5.2 Temperature measurements performed with pH must be within 23-25°C for samples and verification buffers.

5.5.3 The assay is invalid if the above criteria are not met. Should the test fail the acceptance criteria follow procedure Lab-SOP-0123.

5.5.4 If applicable, refer to the product specification for acceptance criteria of sample measurement. Should a sample fail the specification acceptance criteria, inform the Quality Control Manager or designee and follow procedure QA-SOP-019.