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1.0 Purpose

This procedure describes the standardization of the pH monitor of the 6 mm Chromatography Systems and the cleaning procedure for the systems.

2.0 Scope

This SOP applies to Biopharmaceutical Development Program (BDP) personnel who perform standardization and cleaning of 6 mm Chromatography Systems.

3.0 Authority and Responsibility

3.1 The Manager, Technical Operations, Purification, BDP, has the responsibility and authority to define this procedure.

3.2 Production personnel are responsible for training on this procedure and for submitting documentation of the training to Biopharmaceutical Quality Assurance (BQA).

3.3 Production personnel are responsible for the implementation of this procedure.

3.4 BQA is responsible for quality oversight and approval of this procedure.

4.0 Equipment and Materials

- WFI Quality Water.
- Cleanroom Wipes, BDP PN 20315, or BDP approved equivalent.
- Sterile 70% IPA, BDP PN 30129, or BDP approved equivalent.
- 0.5N NaOH, BDP PN 46109CL, or BDP approved equivalent.
- 20% Ethanol, BDP PN 46202CL, or BDP approved equivalent.
- pH Strips, BDP PN 20473, or BDP approved equivalent.

- PBS, BDP PN 47350, or BDP approved equivalent.
- Swabs, BDP PN 21674 or BDP approved equivalent.
- 15 mL polypropylene screw cap centrifuge tube, BDP PN 20006, or BDP approved equivalent.
- TOC vials, BDP PN 20442 or BDP approved equivalent.
- Input cleaning manifold or nerve head.
- Output cleaning manifold or nerve head.
- pH 4 buffer, BDP PN 30107, or BDP approved equivalent.
- pH 10 buffer, BDP PN 30109, or BDP approved equivalent.

5.0 Standardization of the pH Monitor(s)

5.1 Standardization of a pH Monitor

NOTE: Standardization of the pH monitor is required when the probe is changed, i.e., in the event of a probe failure or an Interproduct Parts Replacement, as designated by ***SOP 21529 - Equipment Interproduct Cleaning and Clearance****,* is to be performed**.**

NOTE: A minimum of two pH standard buffers having pH values appropriate for the specific application, i.e., they bracket the expected pH of the sample.

5.1.1 Attach new pH probe(s) to the System.

5.1.2 Turn on the System and computer, if not already on.

5.1.3 Log into the Unicorn software.

5.1.4 Go to the System control menu > system > calibrate.

5.1.5 From the pull-down menu, select the applicable pH probe.

5.1.6 For the first reference value, enter pH 4.0.

5.1.7 Rinse pH probe(s) with WFI and blot dry.

5.1.8 Place pH probe(s) in the pH 4.0 solution.

5.1.9 Click on the Read Value button.

5.1.10 Rinse pH probe(s) with WFI and blot dry.

5.1.11 For the second reference value enter 10.0.

5.1.12 Place pH probe(s) in the pH 10.0 solution.

5.1.13 Click on the Read Value button.

5.1.14 Rinse pH probe(s) with WFI and blot dry.

5.1.15 Document the standardization on Form 14109-03.

6.0 Cleaning Procedures

6.1 Using a cleanroom wipe and WFI followed by 70% IPA, wipe the exterior of the 6 mm Chromatography System. Visually inspect the 6 mm Chromatography System exterior and verify that it is clean.

6.2 Connect the system solvent lines and sample line to WFI at ambient temperature using an input cleaning manifold or nerve head.

6.3 Connect the outlet lines to an output cleaning manifold or nerve head.

6.4 Determine the appropriate cleaning required and document on Forms 14109-01, 14109-02, 14109-03, and any associated forms from ***SOP 21529 - Equipment Interproduct Cleaning and Clearance*****.** Procedures remain the same differing only in the post-cleaning sample requirements**.**

6.4.1 For in process cleaning, no PA testing is required.

6.4.2 For Interbatch cleaning, an LAL rinse sample from the flow-through line is required.

6.4.3 For post-maintenance cleaning, an LAL rinse sample of the affected pathway is required.

6.4.4 For release cleaning (interproduct), PA testing is required per ***SOP 21529 - Equipment Interproduct Cleaning and Clearance***.

6.5 Either manually, or using a pre-programed method system cleaning program, flush each of the inlet lines, sample line, outlet lines, waste line, bubble trap, and column 1 (up, down, and bypass positions) with WFI. Verify that each line is flushed at a minimum flow rate of 200 mL/min (12L/Hr) for at least 1 minute.

NOTE: If using a manual flush, a suggested procedure that may be employed throughout this section is as follows for the 6 mm chromatography system. This suggested procedure may be changed to affect all pathways of the AKTA process system if applicable:

- Flush sample line S1 to waste line W1 with column down, bubble trap inline.
- Flush sample line S1 to waste line W1 with column up, bubble trap inline.
- Flush inlet line 1 to waste line W1 with column bypassed, bubble trap inline.
- Flush inlet line 2 to Outlet 1 with column bypassed, bubble trap bypassed.
- Flush inlet line 3 to Outlet 2 with column bypassed, bubble trap bypassed.
- Flush inlet line 4 to Outlet 3 with column bypassed, bubble trap bypassed.
- Flush inlet line 5 to Outlet 1 with column down, bubble trap bypassed.
- Flush inlet line 6 to Outlet 2 with column down, bubble trap bypassed.
- Flush inlet line 7 to Outlet 3 with column down, bubble trap bypassed.

6.6 Connect the system input manifold or nerve head to 0.5 N NaOH at ambient temperature.

6.7 Either manually, or using a pre-programed method system cleaning program, flush the inlet lines, sample line, outlet lines, waste line, bubble trap, and column 1 (up, down, and bypass positions) with 0.5 N NaOH. Verify that the pH of the eluate from each of these lines is greater than or equal to 13 using pH strips. If the pH does not meet specification, continue flushing until the desired pH is achieved.

6.8 Allow the Chromatography System to be exposed to 0.5 N NaOH for ≥ 60 minutes. Exposure begins when the desired pH is achieved in section 6.7.

6.9 Connect the input manifold or nerve head to WFI at ambient temperature.

6.10 Either manually, or using a pre-programed method system cleaning program, flush the inlet lines, sample line, outlet lines, waste line, bubble trap, and column 1 (up, down, and bypass positions) with WFI. Verify that the conductivity of the eluate from each of the lines is ≤ 1 mS/cm. If the conductivity does not meet the specification, continue flushing until the desired conductivity is achieved.

6.11 Disconnect the manifolds or nerve heads as necessary for sampling.

6.12 The System may be stored in WFI if the System is going to be used within 24 hours.

6.12.1 Disconnect the input manifold or nerve head from the WFI and seal the open end with a male plug.

6.12.2 Seal the open end of the output manifold or nerve head with a male plug or hemostat.

6.12.3 Label the equipment per ***SOP 14150 - Labeling of cGMP Purification Equipment for Cleaning Status***.

6.13 If storing for greater than 24 hours, connect the input manifold or nerve head to 20% Ethanol at ambient temperature.

6.13.1 Either manually, or using a pre-programed method system cleaning program, flush the inlet lines, sample line, outlet lines, waste line, bubble trap, and column 1 (up, down, and bypass positions) with 20% Ethanol through the column and the column bypass positions. Verify that each line is flushed at a minimum flow rate of 200 mL/min (12L/Hr) for at least 1 minute. Disconnect the input manifold from the 20% Ethanol and seal the open end with a male plug.

6.13.2 Disconnect the input manifold or nerve head from the 20% Ethanol and seal the open end with a male plug.

6.13.3 Seal the open end of the output manifold or nerve head with a male plug or hemostat.

6.13.4 Label the equipment per ***SOP 14150 - Labeling of cGMP Purification Equipment for Cleaning Status.***

6.14 At the start of each purification lot, all pathways of the Chromatography System will be flushed with WFI until the conductivity of the effluent from all pathways is ≤ 1 μS/cm. Document in BPR (if applicable).

6.15 Document all cleaning activities on Form 14109-02 and indicate cleaning in the system logbook Form 14109-01.

7.0 References and Related Document

7.1 **SOP 21529** *Equipment Interproduct Cleaning and Clearance*

7.2 **SOP 14150** *Labeling of cGMP Purification Equipment for Cleaning Status*

7.3 6 mm Bioprocessor Instruction Manual.

7.4 AKTA Process User Manual

7.5 **Form 14109-01** *6 mm Chromatography System Use Log*

7.6 **Form 14109-02** *Cleaning of the 6 mm Chromatography System*

7.7 **Form 14109-03** *Standardization of the 6 mm Chromatography System pH Monitor*

8.0 Change Summary