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1.0 Purpose

This SOP describes the use of crossflow filters in the production processes performed in Biopharmaceutical Development Program production areas.

2.0 Scope

This procedure applies to personnel performing operations in the Biopharmaceutical Development Program production areas.

3.0 Authority and Responsibility

3.1 The Manager, Technical Operations, Biopharmaceutical Development Program (BDP) has the authority to define this procedure.

3.2 Production personnel are responsible for training personnel on this procedure and for documenting this 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 of this procedure.

4.0 Materials and Equipment

4.1 Cross-Flow Filter Cartridge or Cassette(s) (BPR or Supervisor specified).

4.2 Filtration supply pump/skid (BPR or Supervisor specified).

4.3 Filter Cassette Holder (BPR or Supervisor specified).

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract 75N91019D00024.

4.4 Filtration supply, retentate, and permeate pressure gauges (BPR or Supervisor specified pressure ranges).

4.5 Sanitary Fittings for supply, retentate, and permeate filter connections.

4.6 Conductivity Meter.

4.7 pH Meter.

4.8 Water for Injection (WFI).

4.9 0.1 NaOH (storage solution, BDP# 46103CL or equivalent).

4.10 0.5 NaOH (cleaning solution, BDP# 46109CL or equivalent).

5.0 New Filter Setup and WFI Rinse

5.1 Obtain a BPR or Supervisor specified filter unit to be used in filtration. Assemble per the BPR, supervisor's instructions, and/or manufacturer's filter insert. Following the BPR, install a pressure gauge on the supply line, retentate line, and permeate outlet line. Install any remaining items illustrated by the BPR or as directed by the Supervisor. Label the filter with the product, BDP lot number, date, and signature.

5.1.1 If a cassette filter (Pellicon Filter Cassette or Equivalent) is to be used, follow the manufacture's filter specific torque requirements to properly assemble the filter cassette(s) in a filter holder. The filter holder used should be cleaned and released per ***SOP 14101 - Cleaning of the Millipore Pellicon 2, Millipore Pellicon 2 Mini-Holder, and/or the Pall Centrasette™ TFF Holder Hardware***.

5.2 A day prior to use, rinse the filter with WFI by feeding WFI to the inlet line via the appropriate feed pump or skid, specified by the BPR. Discharge the retentate to the biowaste.

NOTE: Supply pressure must remain below the maximum allowable pressure of the filter unit throughout all steps of this SOP. The maximum pressure is referenced in the BPR, and manufacture filter insert.

5.3 Set up to discharge the permeate to biowaste.

5.4 Remove any occlusions from the retentate line; turn on the supply pump or skid at its minimum speed and increase the speed slowly until either the pump speed or the supply pressure is within the desired range of the BPR (or Supervisor's instructions).

5.5 If the pump speed is at specification but the supply pressure has not been achieved, restrict the discharge/retentate flow until the supply pressure is within the desired range (refer to the BPR or Supervisor's instructions).

5.6 Recirculate the WFI through the filter unit for an appropriate time interval (refer to the BPR or Supervisor's instructions), then turn off the pump. Record the flush time in the BPR or Supervisor designated lab notebook.

5.7 Follow the BPR or Supervisor's instructions for storage of a WFI flushed filter or proceed to the specific section(s) of this SOP as indicated by the BPR or Supervisor's instructions.

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6.0 Stored Filter WFI Flush

6.1 Repeat Steps 5.2 - 5.6 to flush manufacturer or BPR specified storage solution from a previously cleaned and stored filter (typically 0.1N NaOH). Flushing requirements will be specified by the BPR or Supervisor's instructions.

6.2 Record the lot number that the stored filter was last used for in the BPR, or Supervisor designated lab notebook.

NOTE: Cleaned and stored filters can only be used for the same project. If a new project is initiated, Step 5.0 will have to be performed with a new filter.

6.3 Collect and submit any BPR or Supervisor specified rinse water samples per ***SOP 22002 - Request for Quality Control Testing*** and ***SOP 12169 - Rinse Water Sampling for Production Equipment*** (collection container guidance only). Use the table below for PA test specifications unless otherwise directed by the BPR or Supervisor.

Assay	Specification
TOC (SOP 22963)	≤5ppm
Conductivity (SOP 22138)	≤5µS/cm
LAL (Endotoxin, SOP 22135)	≤0.5EU/mL

6.4 Follow the BPR or Supervisor's instructions for storage of a WFI flushed filter or proceed to the specific section(s) of this SOP as indicated by the BPR or Supervisor's instructions.

7.0 Equilibration

7.1 On the day processing is to begin and if buffer equilibration is required per the BPR or Supervisor's instructions, obtain the specified equilibration buffer from storage.

7.2 Collect a sample of the equilibration buffer and measure the starting pH and/or conductivity values. Document these values in the BPR or per Supervisor's instructions.

7.3 Connect the equilibration buffer to the supply line of the filter to be equilibrated. Turn on the supply pump/skid and direct the permeate and discharge flow paths to the biowaste. Maintain a flowrate that does not exceed the directed filter pressure rating.

7.4 Collect a sample from the permeate flow path and measure the pH and/or conductivity as instructed per the BPR or Supervisor. Continue flushing the filter until the required pH and/or conductivity values are met. Record the final equilibrated values in the appropriate BPR or another specified document.

7.5 Upon reaching filter equilibration, turn off the pump. Re-direct all flow paths to the BPR or Supervisor specified locations for processing. Connect the process product to the filtration skid. Proceed to the specific section(s) of this SOP as indicated by the BPR or Supervisor's instructions.

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8.0 Diafiltration

8.1 Turn on the retentate recirculation pump at minimum speed and increase the speed slowly until the differential between the supply and discharge pressures is within the desired range (refer to the BPR or Supervisor's instructions).

8.2 As filtration progresses, adjustments to the retentate discharge occlusion and supply pump speed may be performed. The supply pressure must be kept below the maximum operating pressure of the filter as stated in the BPR or manufacturer's insert.

8.3 Adjust the occlusion on the permeate tubing or turn on the permeate pump as necessary to provide ≥ 1 psi permeate back pressure.

8.4 Recirculate the product solution through the filter and collect the permeate in a separate, BPR specified, container. Perform the following actions as necessary.

8.4.1 Add the diafiltration buffer to the retentate (refer to the BPR or Supervisor's instructions for buffer formulation and feeding strategy).

8.4.2 Monitor the parameters on Form 12170-01 at the appropriate intervals (refer to the BPR or Supervisor's instructions). Form 12170-01 should not be used if alternate means of data collection are available (i.e., Unicorn monitoring software or similar).

8.4.3 Continue operations until the appropriate stopping point has been reached (refer to the BPR or Supervisor's instructions).

8.5 If further processing is not required (refer to the BPR or Supervisor's instructions), empty the remaining diafiltrated product from the filter and retentate flow path back into the retentate container. Turn off all pumps. Proceed to the specific section(s) of this SOP as indicated by the BPR or Supervisor's instructions.

8.6 If directed by the BPR or Supervisor's instructions, proceed to the concentration Step 9.0.

9.0 Concentration

9.1 Turn on the retentate recirculation pump at minimum speed and increase the speed slowly until the differential between the supply and discharge pressures is within the desired range (refer to the BPR or Supervisor's instructions).

9.2 As filtration progresses, adjustments to the retentate discharge occlusion and supply pump speed may be performed. The supply pressure must be kept below the maximum operating pressure of the filter as stated in the BPR or manufacturer's insert.

9.3 Adjust the occlusion on the permeate tubing or turn on the permeate pump as necessary to provide ≥ 1 psi permeate back pressure.

9.4 Recirculate the product solution through the filter and collect the permeate in a separate, BPR specified container. Perform the following actions as necessary.

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9.4.1 Monitor the parameters on Form 12170-01 at the appropriate intervals (refer to the BPR or Supervisor's instructions). Form 12170-01 should not be used if alternate means of data collection are available (i.e., Unicorn monitoring software or similar).

9.4.2 Continue operations until the appropriate stopping point has been reached (refer to the BPR or Supervisor's instructions).

9.5 If further processing is not required (refer to the BPR or Supervisor's instructions), empty the remaining concentrated product from the filter and retentate flow path back into the retentate container. Turn off all pumps. Proceed to the specific section(s) of this SOP as indicated by the BPR or Supervisor's instructions.

9.6 If directed by the BPR or Supervisor's instructions, proceed to the diafiltration Step 8.0.

10.0 Buffer Rinsing/Storage

10.1 At the completion of concentration or diafiltration, and after all process solutions have been cleared of the filter flow path, a filter may be flushed with rinse buffer and stored at 2-8°C for later use in processing. The time interval for storage on flush buffer will be specified by the BPR or Supervisor.

10.2 As directed by the BPR or Supervisor's instructions, perform buffer rinsing of the used process filter. Verify all pumps are off.

10.3 Set up to divert the retentate discharge and permeate flow paths to the biowaste. Attach a container of the BPR or Supervisor specified flush buffer to the supply flow path.

10.4 Turn on the pump/skid at minimum speed and increase the speed slowly to begin the flush process. Air will be discharged from the retentate and permeate flow paths during this process.

10.5 Pump the rinse buffer through the filter for an appropriate interval (refer to the BPR or Supervisor's instructions), then turn off the recirculation pump.

10.6 Label and store the buffer flushed filter as directed by the BPR or Supervisor.

11.0 Sanitization/Storage

11.1 Prepare cleaning and storage solutions as specified by the filter manufacturer. Consult the BPR or Supervisor's instructions for the amount and type of solution to be prepared. Process filters may be sanitized and stored with the required storage solution for later use. Properly stored filters may only be used for the same product/project as directed by the Supervisor.

11.2 Dispense the cleaning solution to a BPR recirculation container. Connect the required cleaning solution to the supply flow path of the process filter. Set to discharge both the permeate and retentate flow paths to the supply container.

11.3 Turn on the recirculation pump at minimum speed and increase the speed slowly until the supply pressure is below the maximum filter operating pressure and below overall system operating pressure.

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NOTE: It is recommended that the filter supply pressure be 5-10 psi below the maximum filter operating pressure. In some cases, based on the material of construction and prior use, it is acceptable to clean the filter at a pressure below 5-10 psi of maximum when the retentate and permeate occlusion, combined with a constant supply flowrate, cannot be safely operated without compromising the structure of the filter. In this case scenario, the filter should be cleaned at a pressure that ensures sufficient flow can be achieved from the permeate and retentate without unsafe pressure readings.

11.4 Recirculate the solution through the filter unit for 15-30 minutes, or as otherwise specified by the BPR, manufacturer, or Supervisor.

11.5 At the end of the recirculation period, direct the retentate and permeate flow paths to the biowaste until the recirculation tank and filter flow path is empty.

11.6 Rinse the recirculation container, flow paths, pump, and filter unit as directed by the BPR or Supervisor.

11.7 Repeat Steps 11.1 to 11.6 if multiple cleaning solutions are required by the BPR, manufacturer, or Supervisor.

11.8 After the completion of sanitization, set up to feed the storage solution through the filter unit, and discharge both the permeate and retentate back to the feed container.

11.9 Turn on the recirculation pump at minimum speed and increase the speed slowly until the supply pressure is 5-10 psi below the maximum operating pressure.

11.10 Recirculate the solution through the filter unit for 5-30 minutes or as otherwise specified by the BPR, manufacturer, or Supervisor.

11.11 At the end of the recirculation period, turn off the recirculation pump. Cap, plug, or otherwise seal off ports on the filter unit so that the storage solution cannot escape. Label the unit with the type of storage solution, lot number, project number, initials and date.

11.12 Disconnect and clean each piece of equipment used in this procedure per the appropriate procedures (refer to the BPR or Supervisor's instructions).

11.13 Dispose of and/or decontaminate all waste generated using the appropriate procedure (refer to the BPR or Supervisor's instructions).

12.0 Documentation

12.1 Document this procedure on the Filtration Log, Form 12170-01, and process-specific Batch Records for a given process.

12.2 Cleaning of reusable filters is documented in the process specific BPR or Supervisor designated lab notebook.

12.3 **SOP 12169** *Rinse Water Sampling for Production Equipment*

12.4 **SOP 14101** *Cleaning of the Millipore Pellicon 2, Millipore Pellicon 2 Mini-Holder, and/or the Pall CentrasetteTM TFF Holder Hardware*

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12.5 **SOP 22002** *Request for Quality Control Testing*

12.6 **SOP 22135** *Endotoxin Determination by Kinetic Chromogenic Testing Using Charles River LAL System*

12.7 **SOP 22138** *Operation of the Orion Conductivity Meters, Model 150 and 150 USP and Performance of Conductivity Determinations by Current USP <645>*

12.8 **SOP 22963** *Operation of Shimadzu TOC Analyzer*

13.0 Change Summary

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