SOP Title:	**Operating Procedures for Automated Aseptic Filling Using the Flexicon FMB210**
SOP Number:	**15139**
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1. PURPOSE

This SOP describes standard operating procedures to be followed for using the Flexicon FMB210 for automated filling.

2. SCOPE

This procedure describes the necessary steps to follow for initial preparation, set-up and operation of the Flexicon FMB210.

3. RESPONSIBILITIES

3.1 Manufacturing Manager of Fill Finish, Biopharmaceutical Development Program (BDP)

- Defines procedure

3.2 Biopharmaceutical Manufacturing Personnel

- Performs procedure
- Trains personnel

3.3 Biopharmaceutical Quality Assurance (BQA)

- Provides quality oversight

4. MATERIALS AND REAGENTS

4.1 The use of BDP approved materials is required for CGMP processes.

Part Number	Description	BDP Approved Substitution Permitted?
10665	Steri-Perox 6%	☒ YES ☐ NO
20315	Sterile wipes	☒ YES ☐ NO
22120	Sterile SUITE-Cover	☒ YES ☐ NO
22328	Sterile alcohol wipes	☒ YES ☐ NO
22370	Sterile silicone wipes	☒ YES ☐ NO
30129	Sterile 70% Isopropyl Alcohol, IPA	☒ YES ☐ NO

4.2 Vials (3ml, 5ml, and 10ml with 13mm neck finish).

4.3 Stoppers (13mm)

4.4 Aluminum seals (13mm)

5. EQUIPMENT

5.1 Watson Marlow Flexicon FMB210 (MEF#91670)

5.2 FMB210 format parts for 3ml, 5ml, and 10ml vials with 13mm neck finish .

6. PROCEDURE

6.1 General procedures

6.1.1 Proper gowning is defined **in SOP 19406 Gowning Requirements for Personnel and Visitors: ATRF Manufacturing and Support Areas**.

6.1.2 Proper aseptic practices are described in **SOP 15137 Standard Aseptic Practices for Cleanrooms and BSC's for Production Operations**.

6.1.3 Environmental Monitoring (EM) samples to be taken as part of this procedure are defined in **SOP 22315 Environmental Monitoring in BDP GMP Areas at the ATRF.**

6.1.4 Verify the area/gowing status with BQA prior to entering the Aseptic Processing Area (APA).

6.1.5 Prior to any installation of parts, thoroughly clean and sanitize the fixed parts of the unit by wiping them with a sterile wipe moistened with Steri-Perox 6%. Work from top to bottom and back to front. It will be necessary to use the sterile SUITE-cover with reach tool to access some higher areas of the Lexan enclosure. Change the wipes frequently and wipe in a single direction, avoiding a back and forth motion. Follow the above procedure by spraying surfaces and wiping with a sterile wipe moistened with 70 % sterile IPA. Sanitize all change parts that cannot be autoclaved (see below) using a wipe wetted with Steri-Perox 6% followed by IPA. Document the cleaning in the Flexicon FMB210 logbook.

6.1.6 Spray hands with sterile IPA prior to performing any aseptic operations including assembly or interventions within the Flexicon enclosure.

6.1.7 Position sample probes for the continuous EM, (refer to section 5.10). Start continuous EM in order to capture data from the equipment assembly and set-up functions.

6.2 Installation of Change Parts

6.2.1 Assemble the appropriate change parts on a small cart/table that can be located next to the Flexicon for use during equipment setup. A complete set of change parts includes the following:

6.2.1.1 (1) Bowl for aluminum seals (autoclavable)
6.2.1.2 (1) Bowl for stoppers (autoclavable)
6.2.1.3 (1) Chute for aluminum seals (autoclavable)
6.2.1.4 (1) Chute for stoppers (autoclavable)
6.2.1.5 (1) Head for aluminum seal application (autoclavable)
6.2.1.6 (1) Head for stopper application (autoclavable)
6.2.1.7 (1) Star wheel (non-autoclavable)
6.2.1.8 (1) In-feed screw with mounting bracket (non-autoclavable)
6.2.1.9 (1) Guide rail (non-autoclavable)
6.2.1.10 (1) Ejector arm (non-autoclavable)
6.2.1.11 (1) Tool plate spacer (non-autoclavable)
6.2.1.12 (1) Bowl height spacer (non-autoclavable)
6.2.1.13 (1) Guide block for peristaltic pump (not autoclaved)

NOTE: Change parts are stamped for identification. Parts stamped with a number "1" are for 3ml vials, those stamped with a number "2" are for 5ml vials and those stamped with a number "3" are for 10ml vials.

6.2.2 Turn supply air pressure on (must be >55psi).

6.2.3 Release the trussing system by loosening the two hand levers on the back side of the tool plate and by removing the thumb screw on the hold down post on the front side of the tool plate.

NOTE: If performed during filling operations the hand levers should be manipulated from the back side of the unit to minimize having to reach over the area above the tool plate.

6.2.4 Raise the tool plate by gently lifting it up from underneath.

6.2.5 The star wheel and ejector arm are assembled simultaneously. The ejector arm is seated on a drive post and secured by a set screw while the star wheel is mounted on a drive plate utilizing two pins for alignment with two bolts to secure it in place.

6.2.6 Install the feed scroll into the drive housing by aligning the two pins on the scroll to the spaces in the drive coupling and pressing in firmly.

NOTE: It may be necessary to first remove the optical sensor from the drive housing in order to allow for proper alignment.

6.2.7 Secure the scroll to the drive housing by installing bolt through the housing into the scroll mounting bracket.

6.2.8 Assemble the scroll mounting bracket to the filler by aligning with two mounting posts and securing with bolts.

6.2.9 Install the guide rail by aligning holes in rail with three pins in filler. Firmly press downward to seat.

6.2.10 Align the seal applicator head onto the mounting pin and secure by installing and tightening bolt.

6.2.11 Install the chute for the aluminum seals by inserting the two threaded rods on the chute through the holes in the mounting brackets and secure with nuts.

6.2.12 Align the stopper applicator head onto the two mounting pins and secure with a bolt.

6.2.13 Install the stopper chute into the mounting track. Allow it to slide down until the positioning pin on the chute contacts the stop. Secure the chute to the track by tightening the two mounting bolts.

6.2.14 Place the appropriate spacer into position on the tool plate shaft and lower the tool plate until it comes in contact with the spacer. Secure the trussing system by tightening the two hand levers and the hold down post.

6.2.15 Set the outfeed guide rail width appropriate to the vial size using thumb screws.

6.2.16 Install the bowls for the aluminum seals and the stoppers onto their proper vibratory drums. Align marks on bowl with mark on drum to ensure proper positioning and secure by installing metal band at the base of each bowl and hand tightening screw adjustor.

NOTE: It may be necessary to do fine adjustments of the alignment marks once the filler has been started to assure proper movement of seals and stoppers from the bowls to the chutes.

6.2.17 Loosen the hand levers located on the mounting shafts for each of the vibratory drums. Raise the bowls up and insert the appropriate spacer on the mounting shaft. Lower the bowls until they come in contact with the spacer. Tighten the hand levers to secure in place.

6.2.18 Remove pressure plate from peristaltic pump at rear of filler.

6.2.19 Install appropriate guide block onto mounting pin on pump. Tubing block is identified by the size of the internal diameter (I.D.) of the fill tubing to be used.

6.3 Installation of Tubing Set

6.3.1 Aseptically remove inner bag containing tubing set within the curtained ISO 5 filling area.

6.3.2 Install upstream portion of “Y” section of tubing set into the guide block on pump.

6.3.3 Gently stretch tubing over rollers and place behind pin on downstream side of pump.

6.3.4 Install pressure plate onto pump and secure with two hand levers on top of pressure plate.

NOTE: It may be necessary to again stretch tubing over rollers by gently pulling on both ends. When properly installed the tubing should not move or change position in the pump during operation.

6.3.5 Mark the tubing position in the pump head as a visual indicator of tubing shift which can impact fill accuracy.

6.3.6 Feed dispensing cannula end of tubing set underneath the conveyor belt toward the cannula holder located above the star wheel at the front of the filler.

6.3.7 Aseptically connect the upstream side of the tubing set to the feed vessel. All connection(s) must be made within the curtained ISO 5 filling area.

6.3.8 Place an empty sterile vial into the star wheel at the filling position.

6.3.9 Feed the filling cannula up through the open space at the cannula holder.

6.3.10 Aseptically remove the Tyvek covering over the cannula and without touching the filling nozzle mount it in the holder.

6.3.11 Adjust the position of the holder and the cannula within the holder so that the filling nozzle is centered over the vial and approximately 1/8” overtop the neck of the vial. Secure holder and filling nozzle by hand tightening thumb screws.

6.4 Handling of Stoppers and Aluminum Seals

6.4.1 Aseptically remove inner bag of sterilized stoppers/seals within the curtained ISO 5 filling area.

6.4.2 Open the bag and gently pour the stoppers/seals into the appropriate bowl (stoppers into bowl on right, seals into bowl on left). Avoid shaking the bag over top of the bowls in order to avoid generating particles.

6.4.3 Do not allow any packaging or any part of the operator to pass over the adjacent bowl.

6.4.4 Remove any defective or jammed stoppers or seals using sterilized forceps and discard.

6.4.5 If stoppers or seals become jammed in the chute or application head it may be necessary to partially disassemble those parts in order to correct the problem. The exact manipulation(s) required will depend on the nature and severity of the jam. Strict adherence to standard aseptic practice must be followed to avoid contamination of the aseptic filling environment.

6.5 Handling of Vials

6.5.1 Unwrap aluminum foil from sterilized pan of vials within the curtained ISO 5 filling area.

6.5.2 Place tray of vials on infeed conveyor belt with open end of bottom tray facing the infeed scroll.

6.5.3 Remove lid.

6.5.4 Place edge of sterilized vial pusher tool between pan bottom and inner ring and pull pan bottom away while simultaneously using the pusher to hold the inner ring containing the vials on the conveyor belt.

6.5.5 Gently grab and remove inner ring to minimize knocking vials over.

6.5.6 Sterile weight check vials can be added to the vials on the conveyor belt using sterile forceps.

6.5.7 Vials that fall over on the infeed conveyor or become jammed in the infeed scroll can either be removed with sterilized forceps or tongs and discarded or stood back up on the conveyor belt.

NOTE: The forceps or tongs should only touch the outside surfaces of the vial. Never insert the forceps into the mouth of the vial. Avoid reaching over open vials as much as possible when performing these procedures.

6.6 Handling of Tools

6.6.1 Sterilized tools such as the vial pusher and forceps can be used for the duration of a filling run provided that there is no potential that they have become contaminated in any way. If the tool is dropped, makes contact with non-target surfaces, or not stored properly during periods of non-use it should be replaced.

6.6.2 The vial pusher can be stored when not being used in its original sterile package on a table within the curtained ISO 5 filling area.

6.6.3 A minimum of two forceps should be available (one for the front and back half of the filler). They should be hung within the Lexan walls of the Flexicon, above the height of the tool plate so that they are in the "clean" area of the Flexicon.

6.6.4 Repair tools (wrenches etc.) should be stored in a designated cabinet within the curtained ISO 5 filling area. They must be sanitized with Steri-Perox 6% or 70% IPA immediately prior to use.

6.7 Handling Spills and Glass Breakage on the fill line

6.7.1 For spills the Flexicon must be disassembled sufficiently to be able to absorb the spill with wipes. All surfaces and parts affected must be wiped off with 70% IPA prior to reassembly. Discard any un-stoppered vials that may have gotten spilled material splashed into them and record the numbers of vials as appropriate in the batch production record.

6.7.2 For a broken glass vial the Flexicon must be disassembled sufficiently to be able to remove and wipe up all broken glass fragments (including spilled liquid if applicable). All surfaces and parts affected must be wiped off with 70% IPA prior to reassembly. Vials that were crimped prior to the occurrence of the breakage are acceptable. Clearing the line back to the infeed screw of vials and discarding them is sufficient in most cases. If it is suspected that debris from the broken vial is more widespread consult with the area supervisor and remove and discard additional empty glassware as needed. Record numbers of discards as appropriate in the batch production record. Visually inspect the filling nozzle to be sure that no glass fragments have been lodged on it. If may be necessary to gently wipe the filling nozzle with a new sterile wipe or replace the tubing set. Consult supervisor in this case.

6.8 Programming, refer to SOP **15155 Operation of the WM Flexicon FMB210**

6.8.1 Turn on power to control panel. The standby touch screen will appear on PLC. Operators must login to access the programs and controls.

6.8.2 Open air pressure valve at regulator (minimum 55psi). Press <Air On>.

6.8.3 Press <Operation>. Verify that the active program # matches that specified in the MPR.

6.8.4 Check settings against MPR and change if necessary. Refer to **SOP15155 Operation of the WM Flexicon FMB210** for programming instructions.

6.8.5 Press <Dis> on the MC12P keypad.

6.9 Pre-Operation Testing and Calibration

6.9.1 Place a minimum of 100 sterile empty vials on the infeed conveyor.

6.9.2 Press <Vial>, <Insert>, <Cap>, and <Start> on the PLC.

6.9.3 Allow 25 vials to run through machine and collect on the outfeed table.

6.9.4 Inspect for acceptable crimping of seals. If adjustments to the seals are necessary, record the changes in the batch record.

6.9.5 Repeat Steps 6.9.2 thru 6.9.4 with another 25 vials. If no changes are made, repeat steps 6.9.2 thru 6.9.4 with the remaining 50 vials.

6.9.6 Open clamp on the feed vessel and expel as much air from the line as possible back into the feed vessel.

6.9.7 Press <Adjust>, then <Fill>.

6.9.8 Position a sterile empty vial under the filling nozzle.

6.9.9 With a second operator watching the empty vial so that it does not overfill press <Prime 1>. Release <Prime 1> when instructed to do so. Repeat as necessary until all air is removed. Alternatively, the filling cannula can be positioned over a PETG bottle located on the infeed conveyor to perform the priming function.

6.9.10 Weigh and record the tare weight of several sterile, empty vials. Place one “weight check” vial on the infeed conveyor.

6.9.11 Press <Operation>, <Fill>, and <Start> (<Insert> and <Cap> do not need to be active).

6.9.12 Press <Stop> as each weight check vial exits the dispensing position.

6.9.13 Remove vial and check for fill accuracy against MPR.

6.9.14 If outside of specification adjust as follows. On the MC12P keyboard press <Calib>, <Ent>. Enter the weight as determined above then press <Ent>. Repeat this process until an acceptable fill volume is obtained.

6.9.15 Repeat to confirm fill accuracy with two more weight checks. Repeat step 6.9.9 if necessary. If within specification proceed to product fill.

6.9.16 Stop the EM monitoring and remove the TSA plate. The data collected to this point should be designated as “Set-Up” EM and will be reported as such on the EM paperwork. Continuous EM monitoring will begin again at the start of the filling operation and will be designated as “Filling” EM and will be reported as such on the EM paperwork.

6.10 Environmental Monitoring (specific to the Flexicon)

6.10.1 Continuous monitoring of both non-viable and viable particles is required at a location as close as possible to the filling nozzle. The chosen locations reflect this requirement and if closer, either would not be able to be secured or would be at risk of getting caught in moving parts. The location chosen also has good adjacency to the empty loaded vials.

6.10.2 Both non-viable and viable units are positioned just outside of the Flexicon enclosure to the immediate left of the infeed conveyor. Extensions for both units are used to bring the sampling probes in under the infeed conveyor and up to vial neck height near the filling nozzle. The non-viable counter uses a flexible hose that is wiped down with 70% IPA immediately prior to being positioned. The viable counter uses a stainless-steel section of pipe with a short (less than 6”) piece of attached flexible silicone tubing; the stainless steel and attached tubing is sterilized in an autoclave as an assembly.

6.10.3 If needed, secure sampling probes in proper position using autoclaved cable ties.

6.10.4 Other specifics related to Environmental Monitoring for aseptic filling operations are defined in **SOP 22315 Environmental Monitoring in BDP GMP Areas in the ATRF.**

6.11 Post Operation Activities

6.11.1 For filling operations perform EM as specified in **SOP 22315 Environmental Monitoring in BDP GMP Areas in the ATRF**.

NOTE: Personnel monitoring is performed on all operators working within the curtained ISO 5 filling area.

6.11.2 Turn off and remove all continuous monitoring EM equipment from the Flexicon.

6.11.3 Remove all unused vials, stoppers, and seals from the machine and discard.

6.11.4 Clamp off feed vessel fluid path and remove tubing set and discard.

6.11.5 Remove autoclavable change parts and return to component prep.

6.11.6 Clean Flexicon FMB210 surfaces with 70% IPA. Note in logbook.

6.11.7 Turn off air supply valve. Bleed air from system by opening air filter vent valve.

6.11.8 Turn off power to control panel

7. DOCUMENTATION AND RECORDS

7.1 Record use and cleaning of Flexicon FMB210 in logbook. It is suggested to capture the process lot number, vial size, and number of fill cycles in the log entry. This data is useful for maintenance and tracking purposes.

7.2 Competency training records should be completed and/or updated for all operators as per **SOP 15140 Training Requirements for Operators Involved in Automated Aseptic Filling Operations**.

8. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
15137	Standard Aseptic Practices for Cleanrooms and BSC's for Production Operations
15140	Training Requirements for Operators Involved in Automated Aseptic Filling Operations

Document Number	Title
15155	Operation of the WM Flexicon FMB210
19406	Gowning Requirements for Personnel and Visitors: ATRF Manufacturing and Support Areas
22315	Environmental Monitoring in BDP GMP Areas at the ATRF