STANDARD OPERATING PROCEDURE

Title: Procedure of Cleaning (CIP) and Sterilization (SIP) of Manufacturing and Holding Tank

SOP No.:		**Department:**	Production
		Effective Date:	
Revision No.:	00	**Revision Date:**	
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1.0 OBJECTIVE:

To lay down a procedure of cleaning (CIP) and sterilization (SIP) of manufacturing and holding tank.

2.0 SCOPE:

This SOP is applicable for procedure of cleaning (CIP) and sterilization (SIP) of manufacturing and holding tank in Three Piece line.

3.0 RESPONSIBILITY:

Operating Person – Production

4.0 ACCOUNTABILITY:

Head – Production

5.0 ABBREVIATIONS:

CIP	Clean In Place
ID	Identification
Ltd.	Limited
No.	Number
PLC	Programmable Logic Control
Pvt.	Private
QA	Quality Assurance
IPQA	In Process Quality Assurance
SIP	Sterilization in Place
SOP	Standard Operating procedure
WFI	Water for Injection
CV	Compressed valve
Ltr	Liter
Kg / cm^2	Kilogram per centimeter square
Kg	Kilogram
CM	Centimeter

6.0 PROCEDURE:

6.1 Procedure for Cleaning (CIP) of Manufacturing and Holding Tank:

The cleaning (CIP) of manufacturing and holding tank is performed by using the CIP module. Before start the CIP process check and ensure the below utility and action.

6.1.1 Ensure the availability of utility for CIP operation like Purified Water, Water for Injection, Pure Steam, Compressed Air and Electricity.

6.1.2 Open the Steam Inlet Valve and check the Pressure of Pure Steam. (It should be between 1.0 to 2.0 Kg / cm^2).

6.1.3 Open the Compressed Air Inlet Valve and check the Pressure of Compressed Air. (It should be between 4.0 to 6.0 Kg / cm^2).

6.1.4 Open compressed air Supply valve & Purified water Loop line valve main valve in Pre-rinse & Intermediate Cycle.

6.1.5 Open WFI Loop line valve in Final Rinse of the cycle.

6.1.6 Ensure all the Pneumatic valve connection and operation is OK.

6.1.7 Ensure the connection of CIP line and manufacturing/holding tank along with product line & filter housing as per requirement.

6.1.8 Ensure the printer connection & operation is OK.

6.1.9 To enter at the Operator Level, press the **"NAME"** button in the Login Menu and enter the Operator level. The following are the operator levels:

A - Operator Level

B- Supervisor Level

C - Manager Level

6.1.10 Before start each Cycle parameter should be checked by production & Verified by IPQA.

6.2 Operation of Cleaning (CIP) Process through Module:

6.2.1 Switch ON the Instrument a screen shall display as below.

6.2.2 Press on Login tab to go to the Main Menu. Enter user name & password. & tab on login icon.

6.2.3 After successfully Login press on back tab & following screen shall display.

6.2.4 The Main menu has the following options as explained below:

MODE		DESCRIPTIONS
Semi auto Mode	**:**	The auto mode button allows the operator to run the process in Semi auto mode.
Maintenance Mode	**:**	The Maintenance Mode allows operating the machine in Maintenance mode.
Login/ Log Out	**:**	To gain access to certain paramenters, login to the system with correct password. When successfully logged in, login level shall display on the screen. Allows to logout. Once desired changes are completed, it is recommended to press this key and log out so that unauthorized persons cannot change data.
P& ID	**:**	Allows Pictorial diagram of system & allow Operation of valve in Maintenance mode.

Set Parameter	**:**	Allow to set parameter on Higher Level Access. On operator Level it is not accessible.

6.2.5 Click the icon Set Parameter and set the CIP parameter as mentioned in below table.

6.2.5.1 CIP parameter for manufacturing / Holding tank capacity 300 Ltr. to 1200 Ltr.

Stage	Parameter	Range
Pre Rinse	Tank level	250.0 Ltr
	CP VFD RPM	2300 RPM
	Print Interval	0060 Second
Intermediate Rinse	Tank level	250.0 Ltr
	Temperature	080.0 °C
	CP VFD RPM	2300 RPM
	Print Interval	0060 Second
Final Rinse	Tank level	250.0 Ltr
	CP VFD RPM	2300 RPM
	Conductivity	01.20 µS/cm
	Temperature	080.0 °C
	Air Flushing Time	002 Minute
	Print Interval	60 Second

6.2.5.2 CIP parameter for Manufacturing /Holding tank capacity 50 Ltr.

Stage	Parameter	Range
Pre Rinse	Tank level	30.0 Ltr
	CP VFD RPM	1500 RPM
	Print Interval	0060 Second
Intermediate Rinse	Tank level	30 Ltr
	Temperature	080.0 °C
	CP VFD RPM	1500 RPM
	Print Interval	0060 Second
Final Rinse	Tank level	30.0 Ltr
	CP VFD RPM	1500 RPM
	Conductivity	01.20 µS/cm
	Temperature	080.0 °C
	Air Flushing Time	002 Minute
	Print Interval	0060 Second

6.2.5.3 CIP parameter for manufacturing tank capacity 10 Ltr.

Stage	Parameter	Range
Pre Rinse	Tank level	10.0 Ltr

	CP VFD RPM	1500 RPM
	Print Interval	0060 Second
Intermediate Rinse	Tank level	10 Ltr
	Temperature	080.0 °C
	CP VFD RPM	1500 RPM
	Print Interval	0060 Second
Final Rinse	Tank level	10.0 Ltr
	CP VFD RPM	1500 RPM
	Conductivity	01.20 µS/cm
	Temperature	080.0 °C
	Air Flushing Time	002 Minute
	Print Interval	0060 Second

6.2.6 After this press on back tab and select Semi auto mode following Screen will is displayed.

6.2.7 To Start CIP select Pre rinse cycle.

6.2.8 After completion of Pre rinse cycle, select Intermediate Cycle. Open the manual valve of pure steam and then pneumatic valve will be opened automatically to supply the pure steam in the jacket. The temperature of purified water will be increased upto 80°C.After this intermediate cycle will be started.

6.2.9 After Completion of Intermediate Cycle Select Final Rinse Cycle. Close the Valve of Purified Water& Open Valve of WFI& Start the cycle. Cycle will automatically Completed after The set valve of the Conductivity.

6.2.10 After Complete of Final Rinse select Air Flushing Cycle to break pressure & Remove Stem & water Droplet.

6.2.11 To Monitor CIP use P&ID diagram.

6.2.12 After Completion of CIP cycle close the valve and supply of purified water, Water for injection and pure steam.

6.2.13 If after WFI rinse the conductivity is not achieved within specified limits. Buzzer will be appear to restart the final WFI rinse cycle. Close the buzzer and final rinse cycle will restart automatically.

6.2.14 After completion of Cycle Print out shall be checked by production& verified by IPQA.

6.2.15 Attach print out in respective BMR.

6.2.16 Record the operation details in **"Machine Utilization record"** as per Format.

6.3 Procedure for Sterilization (SIP) of Manufacturing and Holding Tank:

For sterilization process inbuilt program is available in manufacturing and holding tank. Before start the SIP process check and ensure the below utility and action.

6.3.1 Ensure the availability of utilities, Pure Steam, Compressed Air and Electricity.

6.3.2 Ensure the electricity mode is selected to UPS power.

6.3.3 Open the Steam Inlet Valve and check the Pressure of Pure Steam. (It should be between 1.0 to 2.0 Kg / cm^2).

6.3.4 Open the Compressed Air Inlet Valve and check the Pressure of Compressed Air. (It should be between 4.0 to 6.0 Kg / cm^2).

6.3.5 Ensure all Pneumatic & manual diaphragm valve connected properly.

6.3.6 Connection of respective tank with product line and housing with cartridge filter as per requirement.

6.3.7 Ensure the printer connection & operation is OK.

6.4 Operation of Sterilization Process (SIP) of Manufacturing and Holding Tank (Make: Pharmatech):

6.4.1 Ensure the connection of steam line and manufacturing/holding tank along with product line & filter housing as per requirement.

6.4.2 Switch **"ON"** the main switch of manufacturing/holding vessel control panel following screen will display on HMI.

6.4.3 For login press the login icon on HMI following screen will display.

6.4.4 To enter at the Supervisor Level, press the **"NAME"** button in the Login Menu and enter the Supervisor level. The following are the operation levels.

A - Operator Level
B - Supervisor Level
C - Manager Level

6.4.5 Enter the user name & Password in HMI screen the press enter one time, below display will be shown on HMI.

6.4.6 After entering the operating level & correct password following screen will display.

6.4.7 After completion of login process press home icon on HMI & following screen will display.

6.4.8 Verify the parameter of sterilization process and set range as shown below.

6.4.9 Select the SIP MODE icon from main menu following screen will display.

6.4.10 Press the Start icon from screen following display will display.

6.4.11 Start the printer for set parameter recording of sterilization. After set parameter data print out completion following screen will display.

6.4.12 Check and verify the set parameter of sterilization process as mentioned in below table.

SIP Parameter for Manufacturing and Holding tank		
Purging Time	30	Second
Sterilization Pressure	1.60	Bar
Sterilization Dead Band	00.01	Bar
Sterilization Temperature	121.4	°C
Heating ON Temperature	123.0	°C
Heating OFF Temperature	123.5	°C
Sterilization Hold Time	30	Minutes
Sterilization Fail Temperature	121.0	°C
Overshoot Temperature	130.0	°C
Cooling Temperature	100.0	°C
Print Interval	60	Second

6.4.13 After achieved the sterilization hold of vessel (121.4ºC for 30 minutes) as show following screen.

6.4.14 After completion of sterilization hold following screen will display.

6.5 Operation of Sterilization Process (SIP) of Holding Tank (Make: Bright Pharma):

6.5.1 Ensure the connection of pure steam and holding tank along with product line.

6.5.2 Switch **"ON"** the main switch of holding vessel control panel following screen will display on HMI.

6.5.3 For login press the login icon on HMI following screen will display.

6.5.4 To enter at the Supervisor Level, press the **"NAME"** button in the Login Menu and enter the Supervisor level. The following are the operation levels.

A - Operator Level
B - Supervisor Level
C - Manager Level

6.5.5 Enter the user name & Password in HMI screen the press enter one time, below display will display on HMI.

6.5.6 After entering the operating level & correct password following screen will display.

6.5.7 Select the SIP mode and below display will be appear on HMI. Enter the batch detail and press next step.

6.5.8 After this below display will be appeared on HMI.

6.5.9 Start the printer for set parameter recording of sterilization. After set parameter data print out completion following screen will display.

6.5.10 Check and verify the set parameter of sterilization process as mentioned in below table.

6.5.11 SIP Parameter for Manufacturing & Holding tank (Make: BrightPharma)

SIP Parameter for Manufacturing and Holding tank (Make: Bright Pharma)		
Heat Up Stage Pressure	1.60	Bar
Sterilization Set Temperature	123.0	°C
Sterilization Time	30	Minutes
Sterilization Stop Temperature	121.4	°C
Sterilization Reset Temperature	121.3	°C
Sterilization Overshoot Temperature	130.0	°C
Vessel air Cooling Temperature	100.0	°C
Final Vessel hold pressure	0.30	Bar
Print Interval	60	Second

6.5.12 After achieving the sterilization temperature hold the sterilization process for 30 minutes as show following screen.

6.5.13 After completion of sterilization process screen will be shown as below.

6.6 After completion of SIP cycle perform the below activity.

6.6.1 Flush the tank & product line with filtered nitrogen for at least 20 minutes.

6.6.2 Pressurize the tank with Filtered Nitrogen at pressure of 1.0 to 2.0 Bar.

6.6.3 SIP cycle the printout shall be checked by production and verified by IPQA and then attach in the respective BMR.

6.7 Operational Procedure for Bulk Solution Sterilization Process:

6.7.1 Collect the required WFI is the respective manufacturing tank and as per specified procedure mentioned in the respective BMR.

6.7.2 Add the material which bulk sterilization is to be performed.

6.7.3 Perform the mixing the material in WFI for specified time as mentioned in the BMR.

6.7.4 Check the clarity of solution and ensure that there should be no lumps in the solution.

6.7.5 Connect the pure steam with pure steam inlet in the tank jacket and drain out let with drain.

6.7.6 In the housing of exhaust vent filter there are two pneumatic valves as CV1 and CV2.In the vent pipe line there in another pneumatic valve as CV3.

6.7.7 During bulk solution sterilization pneumatic valve CV1 and CV2 are in working position and pneumatic CV3 is in nonworking position.

6.7.8 Before start the bulk sterilization process remove the pneumatic connection of CV2 as shown below.

6.7.9 Re connect the pneumatic connection of pneumatic valve CV2 at pneumatic valve CV3 position as shown in below pictorial display.

6.7.10 After this the pneumatic valve CV3 will be in working position during bulk sterilization process to remove condensate from exhaust vent filter.

6.7.11 Open the manual valve of pure steam from pendent.

6.7.12 Before start the sterilization process verify the parameter of set range and bulk solution sterilization.

6.7.12.1 Verify the set range of temperature and pressure parameter as shown below.

6.7.12.2 Verify the recipe parameter of bulk solution sterilization (Heating Mode) as per respective BMR. For example as shown below.

6.7.13 Start the process of bulk solution sterilization process through HMI.

6.7.14 After completion of process check and verify the printout of entire process and attach with respective BMR.

6.7.15 During bulk sterilization remove the air condensate by performing the manual cracking through the vent provided in the vent filter housing intermittently, if required.

6.7.16 After completion of bulk sterilization process, make the pneumatic connection at its original position.

6.7.17 During bulk sterilization process maintain the pressure of pure steam in-between 1.2 to 2.0 kg/cm^2.

6.7.18 During cooling the sterilized bulk solution first use cooling water upto achieving the temperature 90-95°C and after that use chilled water to achieve temperature below 25°C.

6.7.19 During cooling the process of sterilized bulk maintain the pressure of Cooling water and chilled water in between 2.0 to 3.0 kg/cm^2.

6.7.20 Record the temperature and pressure of cooling water and chilled water used during cooling process of sterilized bulk solution in the respective **Annexure No-I** titled as "**Recording of temperature and pressure of cooling water and chilled water during cooling of sterilized bulk solution".**

6.8 Record the Operation details as per **"Machine Utilization Record"** of SOP.

6.9 Cleaning of CIP Module:

6.9.1 Before starting cleaning of the CIP Module (Panel and SS Pipe lines) ensure that the System is cooled up to Room Temperature.

6.9.2 Before startup of cleaning, check that all the openings of the CIP System are closed.

6.9.3 Switch **"OFF"** the CIP Module before startup of Cleaning Activity.

6.9.4 Clean the external surface of the CIP System& SS Pipelines with Clean Lint Free Mopping Pad dipped in Water for Injection.

6.9.5 While Cleaning Do Not Open / Touch the Electrical Parts.

6.9.6 Dry Mop all the Electrical Parts and PLC Screen with Clean Lint Free Mopping Pad.

6.9.7 Dry the CIP System (Panel & Pipelines) with Dry & Clean Lint Free Mopping pad to ensure complete cleaning of the CIP System.

6.9.8 After Cleaning write the Status Label on the CIP System.

6.9.9 Record the Operation Details as per **"Machine Utilization Record"** of SOP.

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Recording of temperature and pressure of cooling water and chilled water during cooling of sterilized bulk solution	
Annexure-II	Load cell and Dip scale marking verification for manufacturing tank 500 Ltr	
Annexure-III	Load cell and Dip scale marking verification for manufacturing tank 1200 Ltr	
Annexure-IV	Load cell and Dip scale marking verification for manufacturing tank 300 Ltr	
Annexure-V	Load cell and Dip scale marking verification for manufacturing tank 600 Ltr	
Annexure-VI	Process flow chart of Manufacturing Line	
Annexure-VII	Product line configuration of Manufacturing Line	

ENCLOSURES: SOP Training Record.

8.0 DISTRIBUTION:

- Controlled Copy No.01 Quality Assurance
- Controlled Copy No.02 Production
- Master Copy Quality Assurance

9.0 REFERENCES:

Equipment Manual and Qualification Report

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

Revision No.	Change Control No.	Details of Changes	Reason for Change	Effective Date	Updated By

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ANNEXURE – I
RECORDING OF TEMPERATURE AND PRESSURE OF COOLING WATER AND CHILLED WATER DURING COOLING OF STERILIZED BULK SOLUTION

Date:
Product Name:
B. No.:
B. Size:
Cooling Process started at:
Cooling Process completed at:
Frequency of Recording:20 ± 5 minutes

Time	Temperature of Bulk solution	Temperature of cooling water	Temperature of chilled water	Pressure of Cooling water / Chilled water	Checked By	Remark

ANNEXURE – II
LOAD CELL AND DIP SCALE MARKING VERIFICATION FOR MANUFACTURING TANK 500 LTR

Manufacturing tank ID No-
Dip Scale ID No-

S.No.	Load Cell Reading (Kg)	Volume Marking Level In Dip Scale (Centimeters)
1.	50	18.0
2.	100	26.0
3.	150	33.6
4.	200	42.2
5.	250	50.0
6.	300	57.6
7.	350	65.8
8.	400	73.8
9.	450	82.0
10.	500	90.0

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ANNEXURE – III
LOAD CELL AND DIP SCALE MARKING VERIFICATION FOR MANUFACTURING TANK 1200 LTR.

Manufacturing tank ID No-
Dip Scale ID No-

S.No.	Load Cell Reading (Kg)	Volume Marking Level In Dip Scale (Centimeters)
1.	50	16.4
2.	100	21.8
3.	150	26.0
4.	200	30.6
5.	250	35.0
6.	300	39.4
7.	350	44.2
8.	400	48.4
9.	450	52.8
10.	500	57.6
11.	550	61.8
12.	600	66.4
13.	650	70.8
14.	700	75.2
15.	750	79.6
16.	800	84.2
17.	850	88.6
18.	900	93.0
19.	950	97.4
20.	1000	101.8
21.	1050	106.2
22.	1100	110.8
23.	1150	115.2
24.	1200	120.0

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ANNEXURE – IV

LOAD CELL AND DIP SCALE MARKING VERIFICATION FOR MANUFACTURING TANK 300 LTR.

Manufacturing tank ID No-
Dip Scale ID No-

S.No.	Load Cell Reading (Kg)	Volume Marking Level In Dip Scale (Centimeters)
1.	50	20.8
2.	60	23.2
3.	75	26.8
4.	80	27.6
5.	100	32.8
6.	120	37.6
7.	125	38.6
8.	150	44.2
9.	160	46.6
10.	175	50.2
11.	200	56.2
12.	225	62.2
13.	250	68.0
14.	275	74.0
15.	300	79.4

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ANNEXURE – V
LOAD CELL AND DIP SCALE MARKING VERIFICATION FOR MANUFACTURING TANK 600 LTR.

Manufacturing tank ID No-
Dip Scale ID No-

S.No.	Load Cell Reading (Kg)	Volume Marking Level In Dip Scale (Centimeters)
1.	50	18.0
2.	100	25.8
3.	120	29.0
4.	150	33.8
5.	200	41.8
6.	240	48.0
7.	250	49.6
8.	300	57.6
9.	320	60.8
10.	350	65.8
11.	365	68.2
12.	400	73.8
13.	450	81.8
14.	500	89.8
15.	550	97.8
16.	600	100.6

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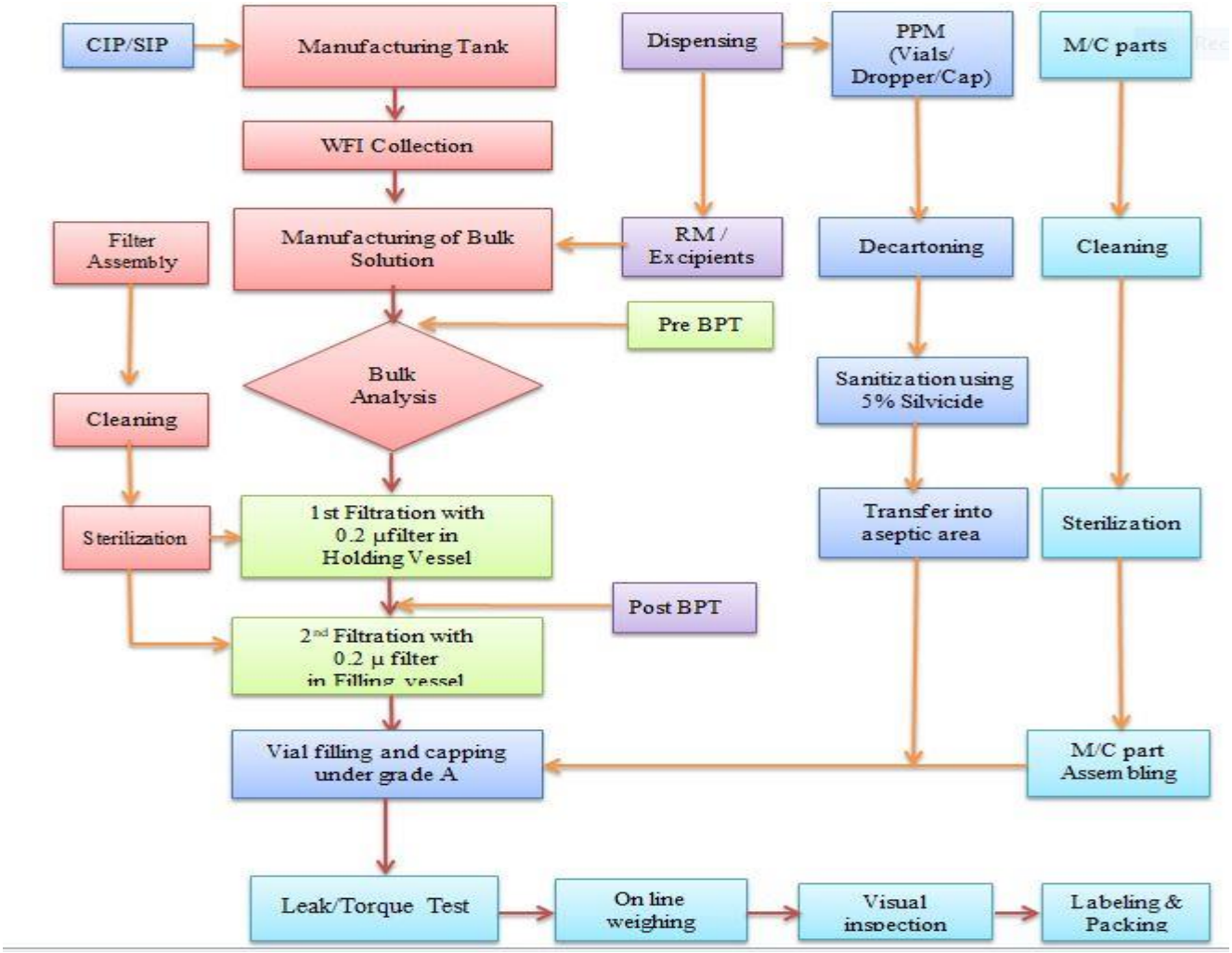
ANNEXURE – VI
PROCESS FLOW CHART OF MANUFACTURING LINE



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ANNEXURE – VII
PRODUCT LINE CONFIGURATION OF MANUFACTURING