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Process Example

Buffer Preparation with FlexAct® BP



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Fig. Front cover: FlexAct® BP COM

Sartorius Stedim Biotech GmbH

Technical Documentation | Technische Dokumentation
August-Spindler-Strasse 11

D-37079 Goettingen

Germany | Deutschland
Internet: www.sartorius-stedim.com
E-mail: tech.pubs@sartorius-stedim.com

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FlexAct® COM that goes beyond that which is described here, please contact us.

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Introduction

The FlexAct® BP is a standardized configurable disposable solution (CDS) dedicated to buffer preparation in biopharmaceutical processes. The FlexAct® BP addresses the entire development cycle and production capacity needs from 50 to 1,000L for buffer preparation. The integration of monitoring & control features for pH, temperature, pressure, pump speed and fluid level control is a further milestone for the implementation of process relevant single use equipment. The integrated control allows end-users to perform other tasks during the buffer preparation operation. Combined with a Flexel® for Magnetic Mixer¹⁾ and Palletank® the multifunctional Central Operating Module enables the user to install, operate and monitor a fully single use unit operation.

This document describes different models and equipment of FlexAct® COM that were available at the time of its creation. The equipment supplied with a device does not necessarily cover every possible type of equipment; some may differ from the description while others may contain additional equipment. The descriptions for the fittings can differ from the ones in the related P&I diagram and the equipment list because these documents are each adapted to the customer's specific requirements. Documentation on customer-specific designs and equipment can be separately supplied or are available on request.

Sartorius Stedim Biotech GmbH
Customer Service
August-Spindler-Strasse 11
37079 Goettingen, Germany
Phone +49.551.308.3318
Fax +49.551.308.3755
www.sartorius-stedim.com

BP	Buffer Preparation
CDS	Configurable Disposable Solution
COM	Central Operating Module
DCU	FlexAct® Sartorius Stedim Measurement and Control System
I/L	Liter
MP	Media Preparation
P&I	Diagram Piping & Instrumentation Diagram
SSB	Sartorius Stedim Biotech

¹⁾ This product uses ATMI patented Magnetic Mixer technology!

III. Definitions

FlexAct® COM

FlexAct® COM ready-to-connect system with

- Trolley,
 - DCU microbox
 - Touch-screen
 - Pump
 - Filter holder | Drip tray
 - Pump head supporting plate
- and
- PT100 temperature sensor

Setup and Equipment

Description of all component steps required to set up FlexAct® BP | components which have to be supplied by the customer.

Process Installation | Process Start

Description of all steps required to start a process. Process Capability Time at which the actual process, for example buffer preparation or virus inactivation, can be started. Process capability is reached when the initial operations are setup to completion.

IV. Operating Instructions | Intended Use

FlexAct® BP COM may only be used with equipment and under operating conditions described in the present equipment documentation. FlexAct® COM is basically a work platform. It accommodates all accessory parts necessary for transferring media within biotechnological applications.

Users must be qualified to handle the system and the process-relevant media and be aware of the hazards potentially associated with the process. Some processes may require that FlexAct® or the workplace be equipped with additional safety features or that precautions be otherwise taken to protect personnel and working environment. Additional, the operator has to follow all of the country-specific safety-laws and -rules! Safety and warning instructions given in this document only apply to the devices and supplement the rules and regulations the operator stipulates at the workplace for the respective process.

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V. Explanation of Symbols



The “Warning” symbol and this formatting indicate hazards that can be expected with a high probability and can lead to severe injuries.



The “Caution” symbol and this formatting indicate hazards that can occur and can lead to severe injuries if the notes and instructions are not observed.



This warning indicates risks that can lead to material damage.



Instructions and notes labeled with this symbol indicate steps that must be performed with particular care, or point to other especially important aspects to be observed.

▷ The box indicates other important information.

1., 2., ... Numbered paragraphs indicate steps that should be performed consecutively in the order listed.

► This symbol points to information referenced in another section.

VI. Safety Instructions

Organizational measures on the part of the operator:

- ▷ The operator must point out the hazards to which personnel and the working environment may be subject during the process, must provide the suitable safety equipment, and must publish the stipulated safety requirements.
- ▷ Only operating personnel qualified to run the process may be employed for working with FlexAct® BP; they must be aware of potential hazards, and be thoroughly familiar with the handling of all devices.
- ▷ Non-authorized persons must be prohibited from working on FlexAct® BP. If hazards are associated with the process (e.g. due to process-relevant media), the workplace must be labeled with suitable danger symbols, e.g. “BIOHAZARD” and it should be possible to cordon it off or quarantine it if the circumstances require.
- ▷ The workplace must be suitable for the process, e.g. resistant to acids, bases or media and must be easy to clean, decontaminate and disinfect if contaminated.
- ▷ In general, operators must wear suitable personal protective equipment (e.g. work clothes, gloves, safety goggles as well as a facemask if appropriate).

Workplace Setup

Workplace and supply connections in the laboratory | production facility must meet the requirements stipulated in the equipment specifications. All intended equipment must be complete and free of defects and flaws.



Risk of injury if energy supply lines are inadvertently activated (e.g. power supply, water, gas inlet supplies).

Energy supply lines must be blocked or secured against inadvertent startup whenever you:

Connect or disconnect laboratory connections or connections on the production side.

Want to disassemble peripheral installations.

When transporting or moving FlexAct® BP components, be fully aware that you are moving equipment with an extremely high weight.

Ensure that all necessary measures are taken (e.g. warning information, barriers, safety gear, etc.) to prevent any danger of crushing or roll-over, and thereby the risk of injury to persons.



When assembling the PT 100 temperature sensor, make sure that the bag is filled and not to damage the sensor channel when inserting the sensor. Pierced or damaged sensor channels will make the bag unusable!

1. Ensure that all supply media on the laboratory or production sides, e.g. water, supply voltage etc., match the specifications in the "P&ID Diagram".
2. The workplace must be able to carry FlexAct® COM and BP components with all equipment and the intended peripheral devices. Observe the weight and the space requirements ► „Setup and Connection“. Use suitable transportation aids when transporting FlexAct® BP components to the place of installation and | or changing its location.
3. Secure all laboratory connections | connections on the production side carefully.

Use only the equipment provided or released for the device. Never make any technical modifications, unless Sartorius Stedim Biotech GmbH has expressly confirmed that this modification does not affect safe use.

5. Loosen | remove any transport locks.
6. Check all equipment carefully for damage. Use only flawless parts.

Getting Started

All equipment must be assembled carefully and safely.

1. Before every startup, check the assembly and connections of all equipment. Safety equipment, e.g. the overpressure | safety valves must meet the specifications and be installed.
2. Pallettanks | bags, tubing, and fittings must be leak-tight.



Persons should only stand around the equipment for carrying out necessary work. Barricade off the hazardous area and indicate this with signs!

If applicable, ensure that the respective minimum volumes as described in the ► "Operating Instructions Manual for LevMixer®" are not undershot

Observe the operating limits and optimal settings for the process. Only operate FlexAct® BP using the allowable energy supplies (power supply, water or gas supplies).



BIOHAZARD, hazards caused by media.

When working with hazardous materials, observe the pertinent safety regulations and laws!

1. Adjust the measurement and control system in strict accordance with the allowable performance data for the respective equipment ► "Operating Instructions Manual for DCU FlexAct®".
 2. Perform in-process monitoring as to whether the process parameters are achieved as expected. Take precautions to ensure that defects or disruptions cannot cause any hazards or damage.
-



After placing the tubing in the pump, always make sure to press the STOP key on the pump.

This resets the system and is indispensable for proper functioning of the pump.

Safety at the End of Process

All equipment must be assembled carefully and safely.

After concluding the process, all affected components of FlexAct® COM should be disposed of, disinfected and cleaned in accordance with their use and as prescribed by the respectively valid laws and regulations.

1. Setup and Equipment

1.1 System Overview

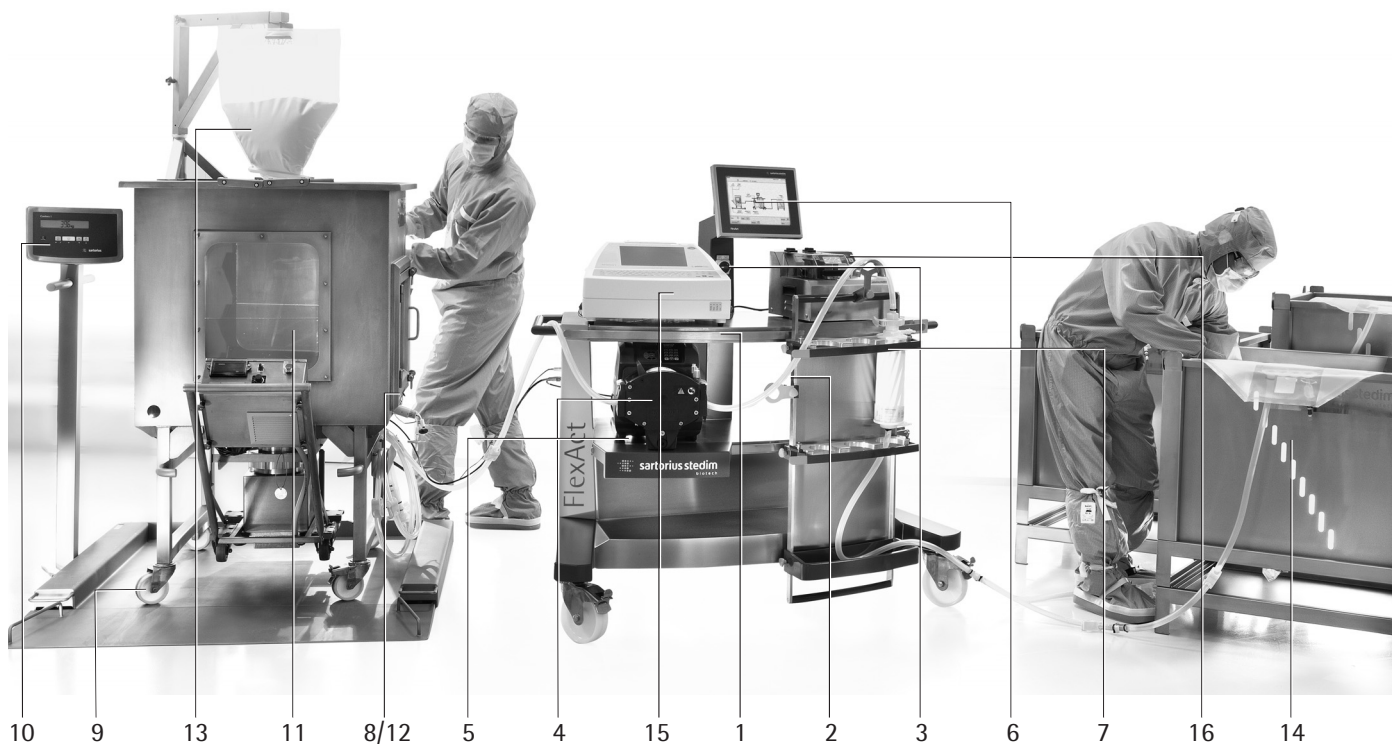


Figure 1-1: Overview FlexAct® BP COM :

Components FlexAct® COM

- (1) Central Operating Module COM
- (2) I-Dom with pressure transmitter
- (3) Main switch | Emergency-Power-Switch
- (4) Pump
- (5) Pumphead support
- (6) Touch-Panel
- (7) Filterholder MidiCaps/MaxiCaps
- (8) PT100 RTD

- (9) Floor scale
- (10) COMBICS1 indicator
(identical for BP and MP)
- (11) MagMixer® with pallet tank
(„Media Preparation“)
- (12) SU-pH sensor
- (13) Powder Bag
- (14) Pallet tank („Storage“)

Useful accessory

- (15) Sartochek®
- (16) BioWelder® | BioSealer®

1.2 Hardware

- FlexAct® BP Central Operating Module
- Magnetic Mixer Drive Unit with toolbox
- Palletank® for Magnetic Mixer with load cells (FXC114155) or Palletank® for Magnetic Mixing XC110821) on floor scale
- Palletank® for Storage
- 1 to 2 Watson-Marlow 520/R2 pumps
- Biosealer® (optional)
- Sartocheck® (optional)

1.3 Single use

- FlexAct® BP bag assembly 4BP110B01AB11003
 - FLEXEL® Bag for Magnetic Mixer 100L (PROBE pH)
 - FLEXEL® 3D Bioprocessing Bag for storage 100 L with Sartopore® 2 Gamma Midicap
- Transfer Set (TITRATION)

1.4 Customer supply

- pH standards (e.g. pH 4/7)
- Syringe with Luer connection (sampling, pH calibration)
- Acid / Base for pH correction
- Media powder
- WFI

2. Process Installation | Process Start

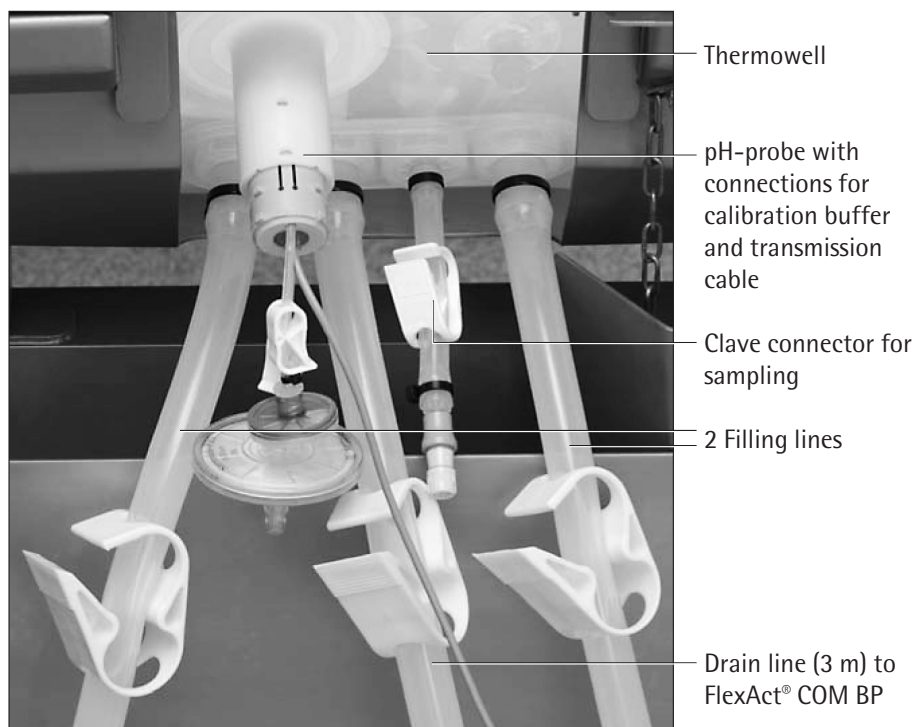
2.1 Setting up of the mixing system



2. Process Installation | Process Start

The following equipment is to be used for the process of Buffer Preparation:

1. Unpack the Flexel® Bag for Magnetic Mixer ► Manual Flexel® Bag for Magnetic Mixer.
2. Install the Flexel® Bags for Magnetic Mixer in the Palletank® for Magnetic Mixing with magnetic clamp from Magnetic Mixer drive unit toolbox ► Manual Flexel® Bag for Magnetic Mixer.
3. Connect the cable of the pH electrode to the FlexAct® COM sensor panel.
4. Connect the cable of the RTD to the FlexAct® COM sensor panel. Do not put the RTD in the thermowell of the bag.
5. Calibrate the pH electrode (use pH standards and rinse with WFI finally). Use the RTD for automatic temperature compensation during calibration ► Manual pH probe ► Manual DCU FlexAct®.
6. Connect weighing signal from the Combics weighting controller to the FlexAct® COM sensor panel.
7. Connect the WFI supply to the bag's inlet port.
8. Close the pinch clamps on the low port except the fill line. Close the clamps of both acid/base top ports.
9. Tare the load cell at the combics panel ► Magnetic Mixer Palletank® w/ load cells and Combics 1 Controller.



Connections at the low port of Flexel® Bag for Magnetic Mixer (probe pH)

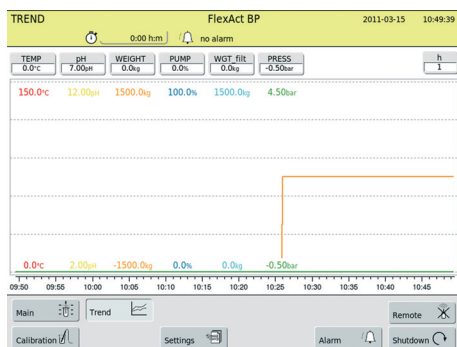
2.2 Filling of mixing bag



1. Fill the Flexel® Bag for Magnetic Mixer with WFI up to 80 to 95% of the final volume. Open the 8" top port and insert the top port into the stainless steel clamp holder. Refer to the manual of Flexel® Bag for Magnetic Mixer for the filling of the bag and the instructions for the preparing of the buffer.
2. Remove the magnetic clamp from the bag and couple the Magnetic Mixer drive unit under the Palletank® for Magnetic Mixer.



3. Insert the RTD in the thermowell
4. Insert the pH electrode inside the bag.
5. Start impeller rotation with the Magnetic Mixer Drive Unit.



6. The pH will be logged – like all other process values – automatically by the DCU of FlexAct® COM and the diagram of the progress can be viewed by pressing the TREND-button of the DCU-touchscreen.

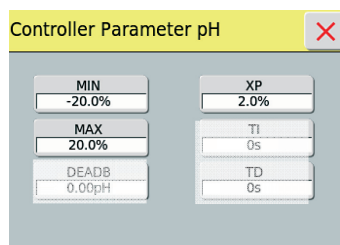
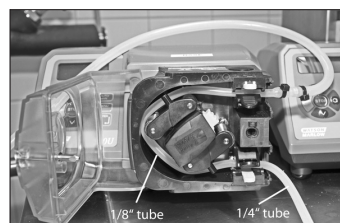


Powders can be mixed inside the same powder bag or multiple bags can be used if appropriate. It is also possible to transfer the powder in multiple steps to facilitate rehydration, dispersion and dissolution.

7. Connect the 8"/4" reducer (FMA114007) to the 4" port of the powder bag and transport the powder transfer bag to the FlexAct® COM BP system.
8. Connect the powder transfer bag onto the 4" port of the Bag for Magnetic Mixer.
9. Remove the pinch clamp from the powder Transfer Bag to transfer the powder inside the Flexel® Bags for Magnetic Mixer.
10. Mix until complete dissolution of the powders (refer to preparation instructions provided by individual buffer supplier).
11. If more than one Powder Transfer Bag is being used, add content of the other Powder Transfer Bags to the Palletank for Magnetic Mixer.
12. Keep the powder bag connected to the Bag for Magnetic Mixer and open one of the 1/4" top line for air removal during dilution.
13. Tare the Magnetic Mixer Palletank® w/ load cells and Combics Controller.
14. Add the remaining quantity of WFI to reach the final buffer volume, then close the top port.
15. Mix until complete powder dissolution (refer to preparation instructions provided by individual buffer supplier).
16. If required, remove the powder bag by opening the 4" Triclamp connection, and close the Bag for Magnetic Mixer with the 4" plug, gasket and union clamp to minimize exposure. Use a 4" plug kit (FMA114179) to close as well the powder bag.
17. Close the clamp at the fill line and disconnect the fill line from the water supply.
18. Record the final pH, temperature and weights values.
19. If required retrieve a buffer sample with the Luer syringe through the needleless sampling port.



2.3 Setting-up of automated pH-adjustment



MIN – Speed for acid pump
 MAX – Speed for base pump
 XP – Proportional share of PID controller
 DEADB, TI, TD – not required, set to 0

1. Connect the WM 520/R2 signal cable with the corresponding plug of the sensor field. If there is a pH correction with base required connect it to the base jack, for a correction with acid in the ACID-jack.
2. Select the transfer line for acid-base titration of the correct length. For Flexel Bags for Magnetic Mixer of volumes up to 200 l a 4 m is recommended, above a length of 5 m is suitable.
3. The Transfer set (Titration) consists of a tube of 1/4" and a 1/8" ID in order to realize different flow rates, necessary to adopt the system different buffers and titrations agents. See table 1 for detailed values.
4. For 1/8" install pump at position 1, for 1/4" install at position 2. Install the required part of the Transfer set (TITRATION) in the WM 520.
 ► Manual Watson-Marlow 520/R2



It is necessary to install the pump in position 2, when using the 1/4" tube.

5. The PID-controller for pH of the configuration is preconfigured with standard parameters for buffers (± 1 pH from pKa) with an Xp of 2 %. Enter the correct process parameters into the DCU screen.

Tank size	50 l	100 l	200 l	400 l	650 l	1000 l
Length of transfer set (TITRATION)	4 m	4 m	4 m	5 m	5 m	5 m
Max. pump speed 1/8"						
1 N HCl/NaOH	20 %	40 %	80 %	–	–	–
Max. pump speed 1/4"						
1 N HCl/NaOH	–	–	20 %	45 %	75 %	100 %
Max. pump speed 1/4"						
0,1 N HCl/NaOH	%	100 %	100 %	100 %	100 %	100 %

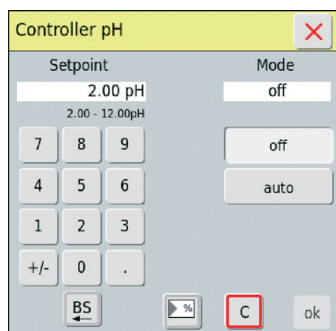
Table 1: recommended set value for Magnetic Mixer drive unit and maximum pump speed of WM 520 / recommended length of transfer set (TITRATION)

Pump speed	20%	40%	60%	80%	100%
Rpm WM 520	44	88	132	176	220
Flow rate 1/8"	80 ml/min	160 ml/min	240 ml/min	320 ml/min	400 ml/min
Flow rate 1/4"	280 ml/min	560 ml/min	840 ml/min	1120 ml/min	1400 ml/min

Table 2: flow rates for 1/4" and 1/8" tube in relation to different pump speeds

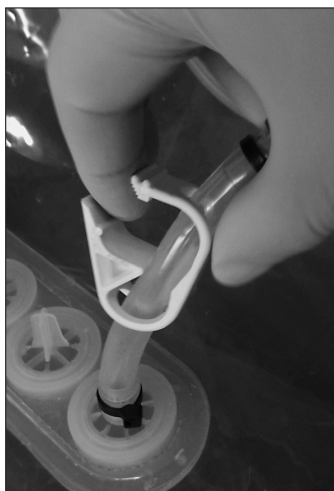
2.4. Run the automated pH adjustment process

pH
3.95 pH



1. Start the pH adjustment process by selecting the pH-controller ► Manual DCU FlexAct® COM.

2. Enter the value of the pH Set point in the box of the controller.



open top line

3. Open the clamps of the acid and base transfer line at the top port of the Flexel® for Magnetic Mixer.



Before starting the automatic dosing process open the corresponding clamps. A closed clamp can cause a crack of a tube. This will set media free and can cause serious damages to equipment and injuries to persons!

4. Put the Controller Mode "Auto".

5. If the controller mode selected to „Auto, the dosing of acid or base is running until the pH reaches the set point of the pH adjustment.

6. If the set point has been reached, set the controller mode to „off".

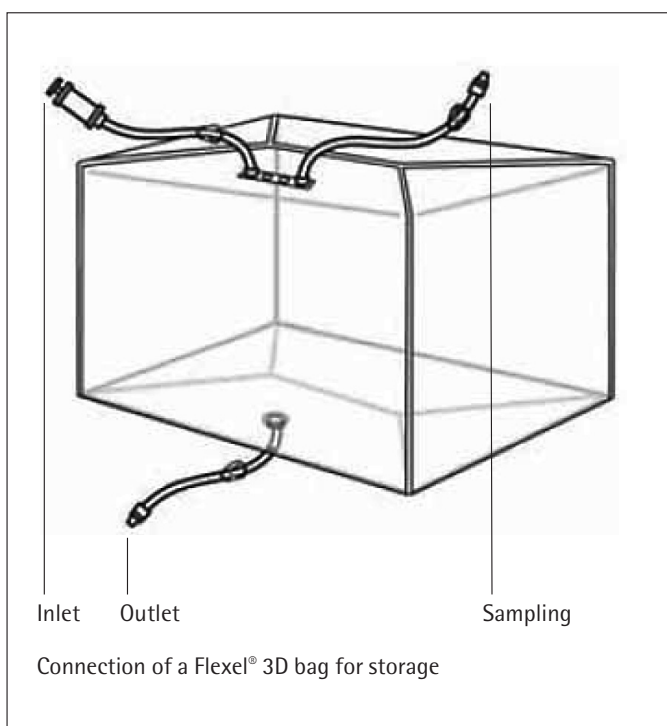


7. Close the clamp of the acid/base Transfer line!
8. Stop mixing.

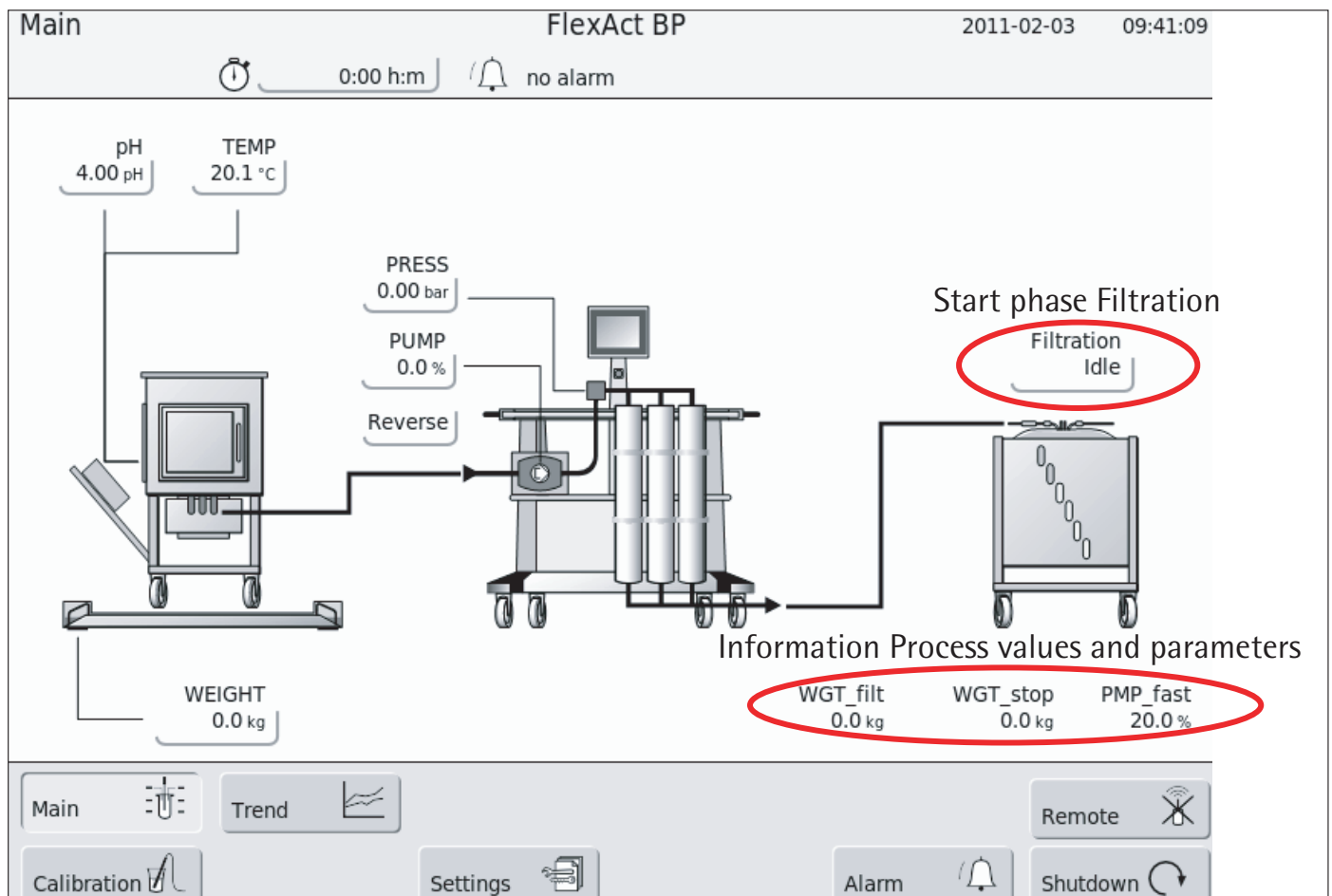


open top line

2.5. Setting up of the receiving bag and filter for filtration



2.6 Running the filtration



Screenshot of DCU touchscreen

All details of the DCU-control system are described in the operating instruction of the DCU-system ► User Manual FlexAct® BP DCU.



After the filtration step is being started a modification of the weighing signal by taring the balance or removing/adding parts of the equipment has to be strictly avoided in order to assure a correct working of the process.



1. Start the phase "Filtration" by pushing the button on the DCU-touchscreen and follow the instructions on the screen. The system will filter an adjustable volume of the buffer from the Flexel® for Magnetic Mixer via a sterile filter capsule to the receiving bag. The pump is stopped by the DCU automatically, when the adjusted volume was transferred into the receiving bag. It is not necessary to tare the balance prior filtration, because the DCU will automatically calculates the weight being filtered into the Flexel® 3D Bioprocessing Bag for Storage . At the beginning of the sequence, there is possibility to perform a pre-filling of the tubing to assure an higher accuracy of the weight filled in the Flexel® 3D Bioprocessing Bag for Storage. There is also the possibility to repeat the filtration step in order to use a manifold consisting of several bags.

2. During initial filling of the tubes, the speed of the pump can be modified by change of parameter S_Pump. Stop manually, when the liquid has reached the last Flexel® 3D Bioprocessing Bag for Storage. Open the upstream venting valve of the MidiCaps/MaxiCaps to fill MaxiCap for venting.
3. During filtration the speed of the WM 720 pump can be set up to 100%. In case the unit will shut down due to inlet pressure alarm, please start the process with a reduced pumpspeed.
4. If needed The Flexel® Bag for Magnetic Mixer can be lifted at the end of the drainage for a full buffer recovery and to minimize air pumping upstream to the filter.
5. The filtration process stops automatically, when the „filtered weight“ was filtered into the Flexel® 3D Bioprocessing Bags for Storage
6. After the process is finished, retrieve filtered buffer samples using the sampling line (needleless sampling port with Luer syringe).

3. Ending the Process



Be aware, that the filter capsule can be pressurized! If so media will be set free and can cause serious damages to equipment and injuries to persons.



Be aware, that the tube of the Transfer Set (TITRATION) can contain acid/base! Make sure, that all acid/bases will be collected safe and properly!

1. Close the clamps of the Flexel® for Magnetic Mixer drain line.
2. Open the upstream drain valve of the filter capsule to release pressure from the capsule.
3. Disconnect the TC connection at the filter inlet and install the blind cap to prevent draining liquid.
4. Disconnect the SU-pressure sensor and remove the transfer tube from the WM 720.
5. Seal the TPE tubing line between the filter outlet and Flexel® 3D Bioprocessing Bag for Storage with a BioSealer® ► Manual BioSealer® | Alternatively close the clamp of the TPE tubing line.
6. Cut the seal | Alternatively cut the TPE tubing line between the filter and the clamp.
7. Apply a post filtration integrity test, if required, ► Manual Sartopore® 2 y-Capsules | MaxiCaps®.
8. Discard the Flexel® for Magnetic Mixer.
9. Transfer the filled buffer bag(s) to its further use.

Sartorius Stedim Biotech GmbH
August-Spindler-Str. 11
37079 Goettingen, Germany

Phone +49.551.308.0
Fax +49.551.308.32 89
www.sartorius-stedim.com

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