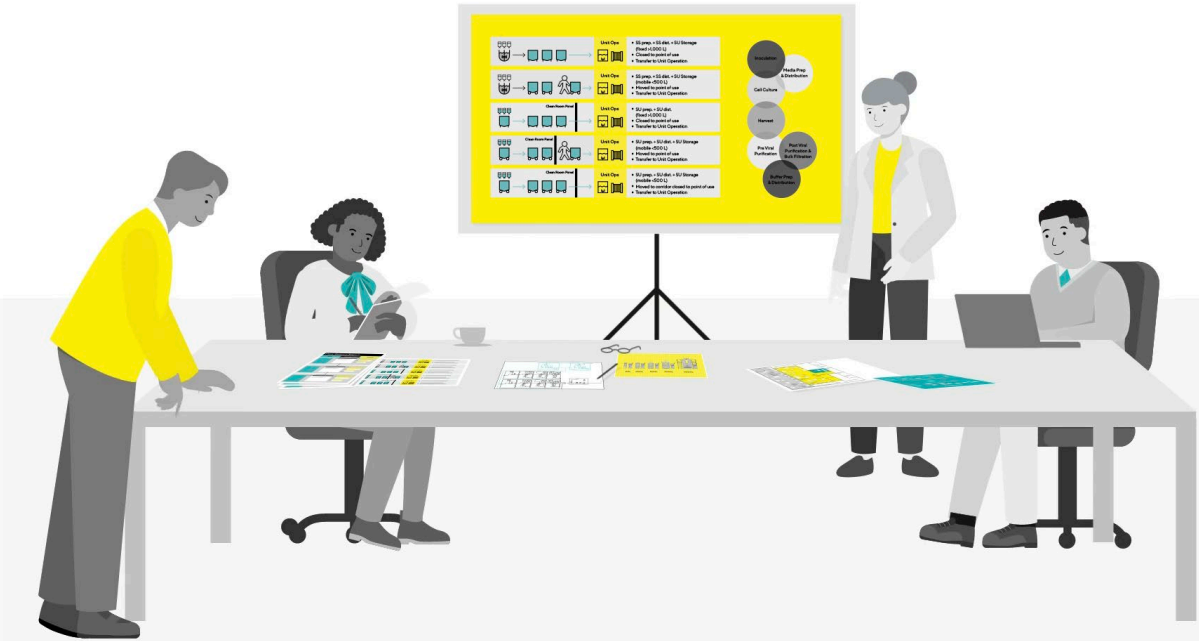


Conceptual Design

For Bioprocess Solutions

Simplifying Progress

SARTORIUS

Designing a New Manufacturing Facility for Biopharmaceuticals

The planning and designing of a new biopharmaceutical production facility is a complex process. A new facility must fulfill all regulatory requirements and the production capacity must be sufficient and flexible enough to meet ever changing demands.

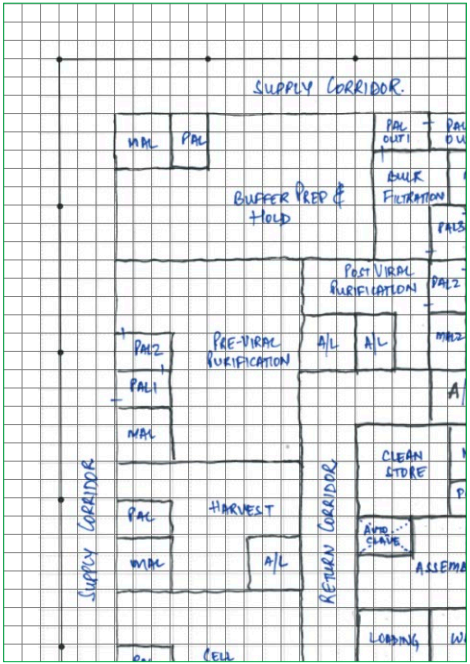
At Sartorius we have extensive experience in designing facilities that fulfill all these requirements. We can help you with the creation of a facility concept and quickly find answers to fundamental questions in order to meet demanding timelines.

Our conceptual design services deliver comprehensive process reviews, process layout studies, process scale-up designs, as well as process automation concepts.

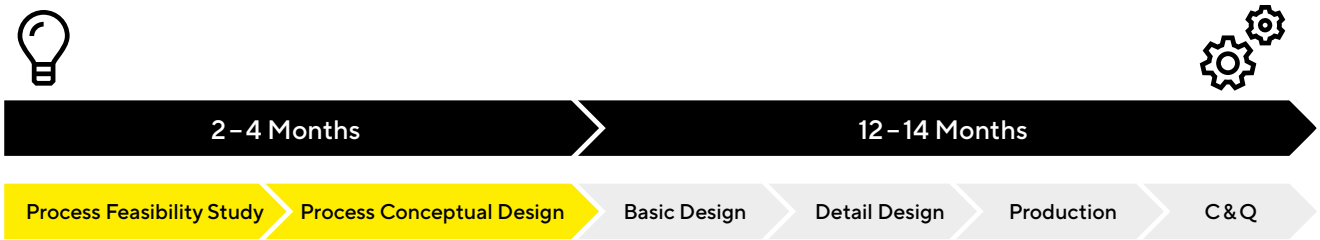
Business Drivers:
- Single or multi product facility?
- Capacity requirement?

Process Drivers:
- Campaign approach?
- Fully single-use or hybrid?

Process Drivers:
- Which room classification do need in which area?
- What kind of room segregation fits best to my needs?



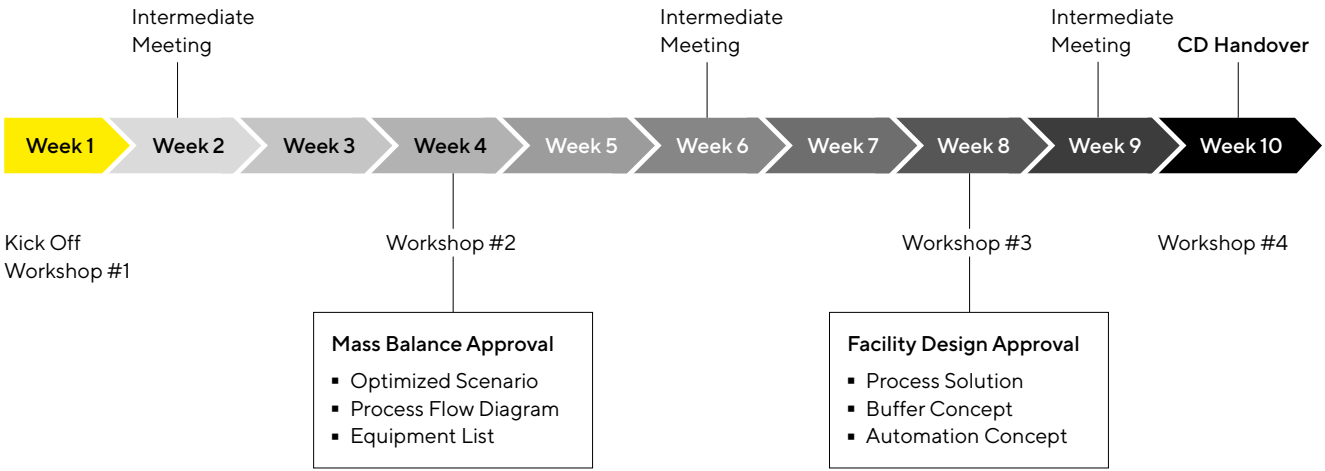
Conceptual Design



Testing of feasibility and taking key-decisions on the manufacturing strategy and design concept

- Creation of mass balances
- Process Scheduling
- Process Flow Diagram
- Media-Buffer Concept
- Equipment List
- Selection of the automation concept
- Process layout

Project Schedule | Time Schedule



Process Modelling

Based on your process information or platform based approach at different scales, we calculate the media and buffer requirements as well as the time scheduling of your processes.

By modelling different scenarios we can select the most optimal parameters for your facility.

Our experiences on different modalities (protein or viral based) with both single-use and stainless steel equipment will help you to find the best solution for all your processes.

- N-3 Shake Flask
- N-2 Rocking Motion
- N-1 Stirred Tank Reactor
- Production Bioreactor
- 2 Stage Depth Filtration
- Protein A Affinity Chromatography
- Low pH Virus Inactivation
- Cation Exchange Chromatography
- Anion Exchange Chromatography
- Virus Filtration
- Final UF | DF
- Bulk Fill and Finish

Mass Balance Review (MBR)

Process Modelling

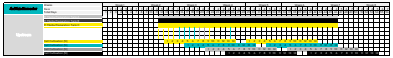
1 Description the processes that need to be modelled

Process 1

- N-3 Shake Flask
- N-2 Rocking Motion
- N-1 Stirred Tank Reactor
- Production Bioreactor
- 2 Stage Depth Filtration

3 Evaluation and optimization of the processes

5 Process and equipment scheduling based on MBR output

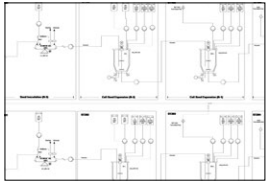


Process Modelling

2 Description of the process parameters as input for the modelling tool

	Scenario 1	Scenario 2
Binding capacity	50 g/L	50 g/L
Column height	20 cm	20 cm
Column Diameter	45 cm	60 cm
Flow rate	320 cm/h	320 cm/h
Buffers		
Equilibration	5 CV	5 CV
Post Load Wash 1	10 CV	10 CV
Elution Buffer	5 CV	5 CV
Regeneration buffer	5 CV	5 CV

4 Process flow diagram incl. equipment



6 Advanced options

- Economic Modelling

- N-3 Shake Flask
- N-2 Rocking Motion
- N-1 Stirred Tank Reactor
- Production Bioreactor
- **2 Stage Depth Filtration**
- Protein A Affinity Chromatography
- Low pH Virus Inactivation
- **Cation Exchange Chromatography**
- Anion Exchange Chromatography
- Virus Filtration
- Final UF | DF
- Bulk Fill and Finish

Evaluate the impact of different technology options on your process

- ☐ Sartoclear Dynamics
- ■ 2 Stage Depth Filtration
- ☐ Centrifugation + Depth Filtration

- ■ IEX resin (bind and elute)
- ☐ IEX resin (Flow through)
- ☐ IEX membrane (bind and elute)
- ☐ IEX membrane (flow through)

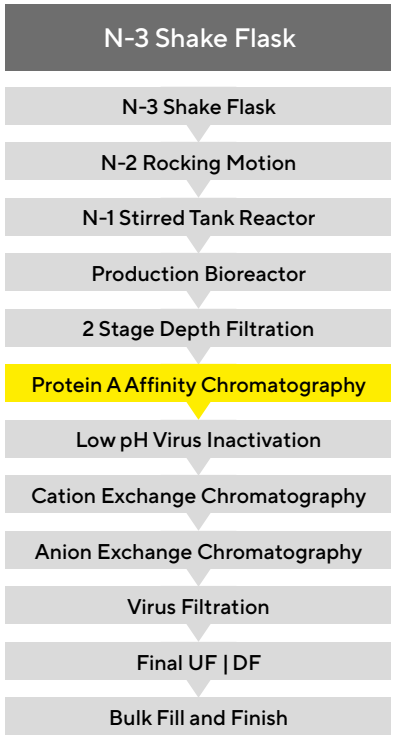
Model parameters to optimize buffer requirements and equipment sizes

	Scenario 1	Scenario 2
Binding capacity	50 g/L	50 g/L
Column height	20 cm	20 cm
Column Diameter	**45 cm**	**60 cm**
Flow rate	320 cm/h	320 cm/h

Process Description

Evaluate the impact of different technology options on your process

	Scenario 1	Scenario 2
Binding capacity	50 g/L	50 g/L
Column height	20 cm	20 cm
Column Diameter	**45 cm**	**60 cm**
Flow rate	320 cm/h	320 cm/h
Buffers		
Equilibration	5 CV	5 CV
Post Load Wash 1	5 CV	5 CV
Elution Buffer	2 CV	2 CV
Regeneration buffer	3 CV	3 CV



Example: Impact of Protein A column volume

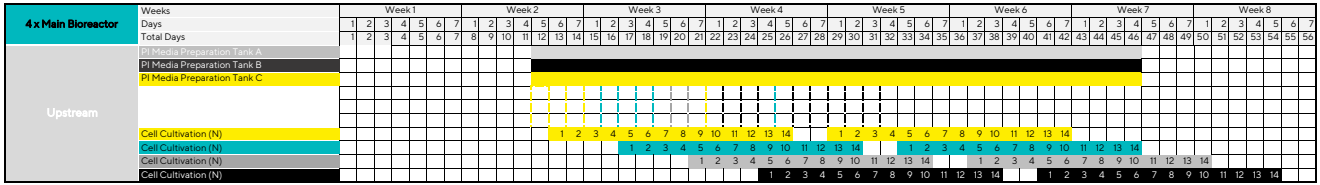
	Scenario 1	Scenario 2
Cycles per batch	8	4
Process time	13 h	7 h
Concentration out	14.6 g/L	12.9 g/L
Volume out	226	254
Buffers		
Equilibration	565	636
Post Load Wash 1	565	636
Elution Buffer	226	254
Regeneration buffer	339	382

Process Scheduling

The results from the MBR and the generated PFD can be used to create detailed scheduling in order to streamline the production process.

Reasons for process scheduling:

- Hourly based process scheduling considering 3 shifts
- Process debottlenecking
- Equipment capacity and availability evaluation
- Shared equipment strategy
- Media-Buffer preparation and holding concept



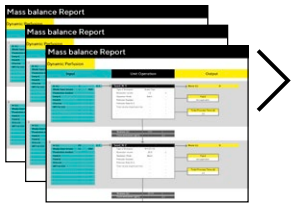
Economic Modelling

Economic modeling can help you in making better decisions for your project. Together with our partner Biosolve we can quickly evaluate the economical impact of process related factors.

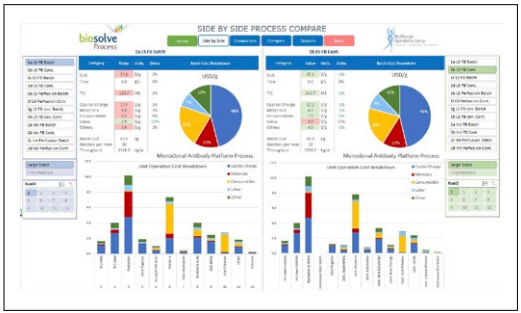
Open Questions:

- Single-use or hybrid?
- How many bioreactors?
- Fed-batch or Process Intensification?
- Single or multi-column chromatography?

Mass Balance Review (MBR)

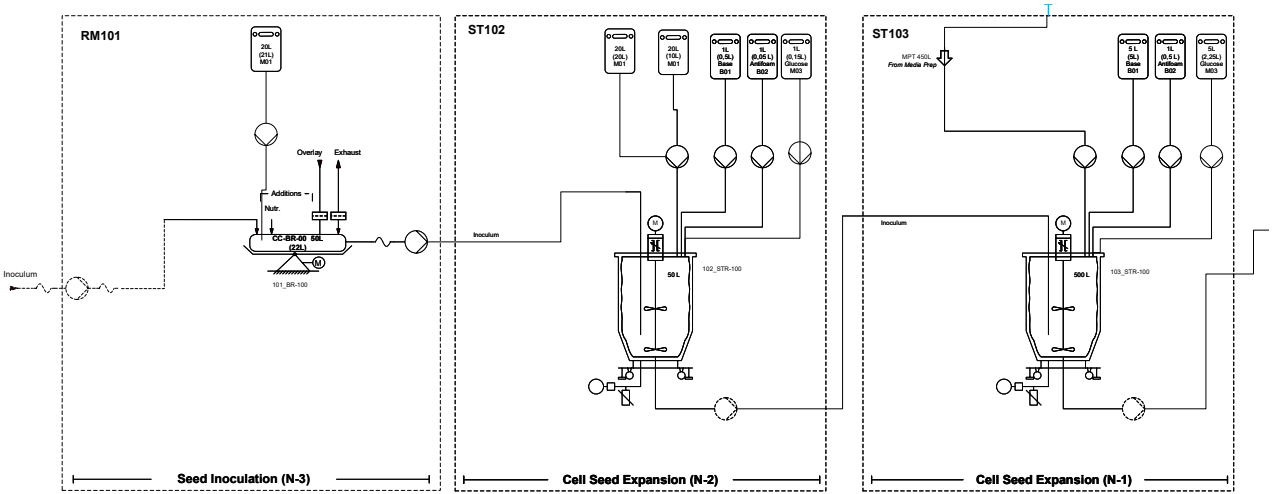


biopharm



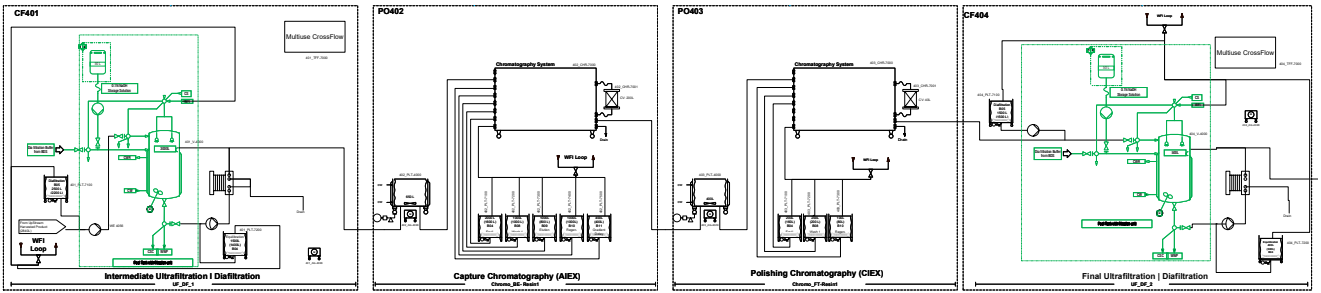
Upstream Process

(PFD). This tool provides the visualization of process relatsionships as well as the major equipment selection based on outputs of the mass balance review.



Downstream Process

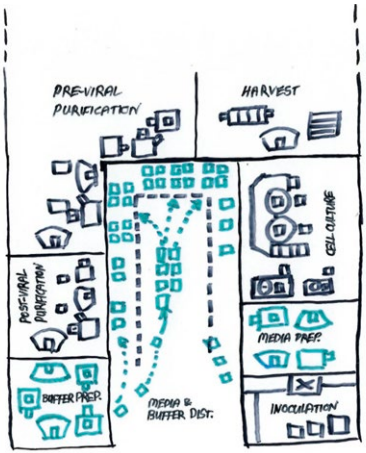
Parallel to the PFD preparation a buffer concept will be selected and visualized.



Buffer Distribution Concept

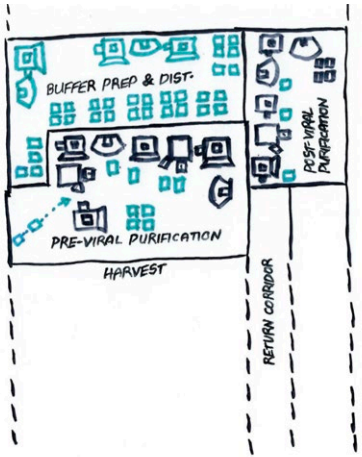
As most DSP steps require large buffer volumes, the process layout is highly impacted by the buffer preparation and distribution concept.

Single-use technology offers flexible new options for buffer concepts. Two examples can be seen on the right.



Separated preparation | ready made

- Lower room classification in distribution area
- More challenging with large buffer volumes



Combined preparation and storage

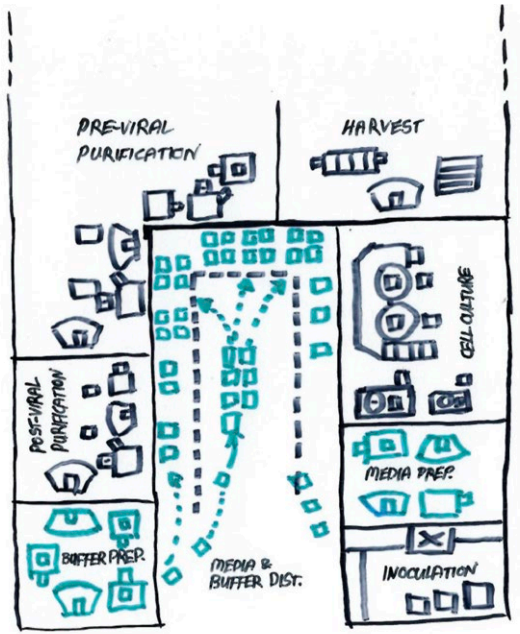
- Less trafficking
- Adjacency and wall area requirement

Example Concept 1:
Separated Preparation | Ready Made

Buffer preparation is remote from the point of use.

Advantages:
- High mobility and flexibility
- Distribution area can be reduced to CNC, leads to less operational cost
- Smaller Buffer Prep
- Less movement in Pre Viral & Post Viral area

Challenges:
- Adjacency and wall area required for previral and post viral room with distribution corridor
- Suitable only for low titer process, challenging for high titer process
- Fixed palletanks
- High trafficking

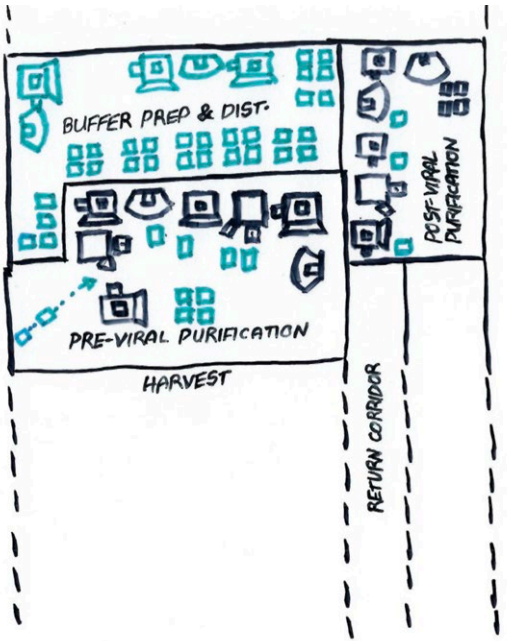


Example Concept 2: Combined Preparation and Storage

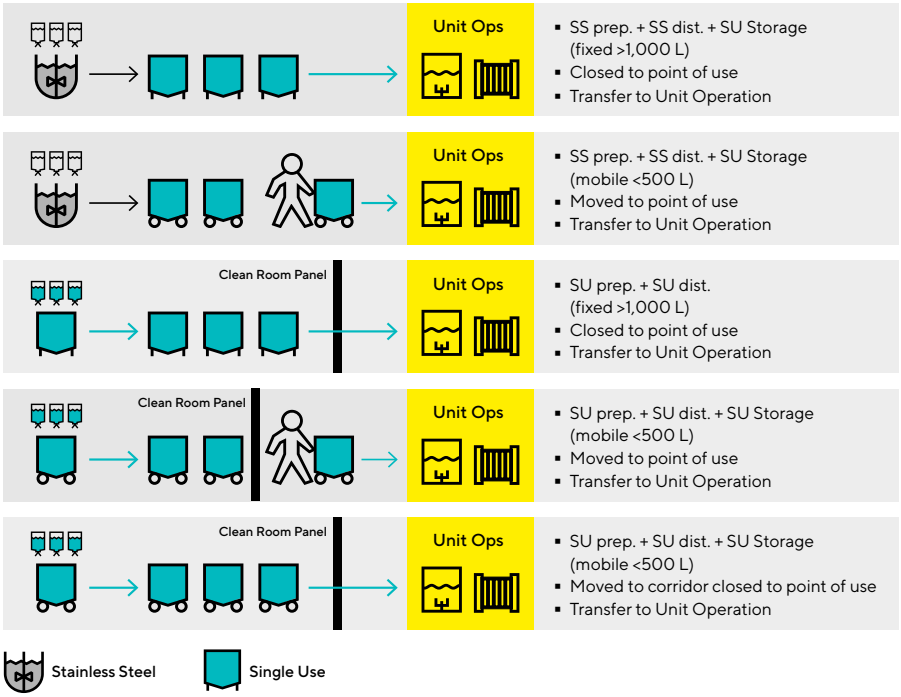
Large volume buffers are prepared and stored in proximity to the point of use.

Advantages:
- Less trafficking
- Suitable for low and high titer process
- Less movement in Pre Viral and Post Viral area

Challenges:
- Adjacency and wall area required for previral and post viral room with buffer area
- Bigger space for preparation & distribution. Extra operational area required
- Fixed high volume palletanks
- Higher Grade D area leads to higher operational cost



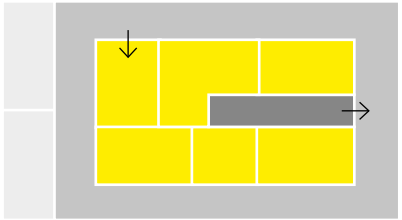
Media Buffer Concept



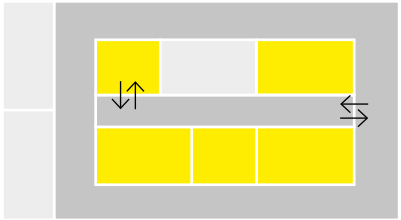
Fitting Layout Around Process Solution

Depending on the number of product, batches and flexibility requirements for the future, a process layout will be drawn. The process layout must full fill cGMP & regulatory principles and will consider personnel, material, product and waste flows. Different concepts have been generated and optimized for common single use and hybrid projects.

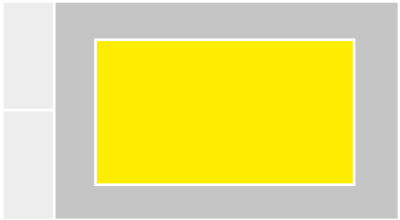
Color codes:
- Process Area
- Supply Corridor
- Support Area
- Return Corridor



Supply to Return Concept
- Unidirectional flow
- Less traffic



Mobile Buffer Concept
- Bidirectional flow
- High traffic



Futuristic Dance Floor | Ballroom Concept
- Reduce walls and airlocks
- Operational flexibility

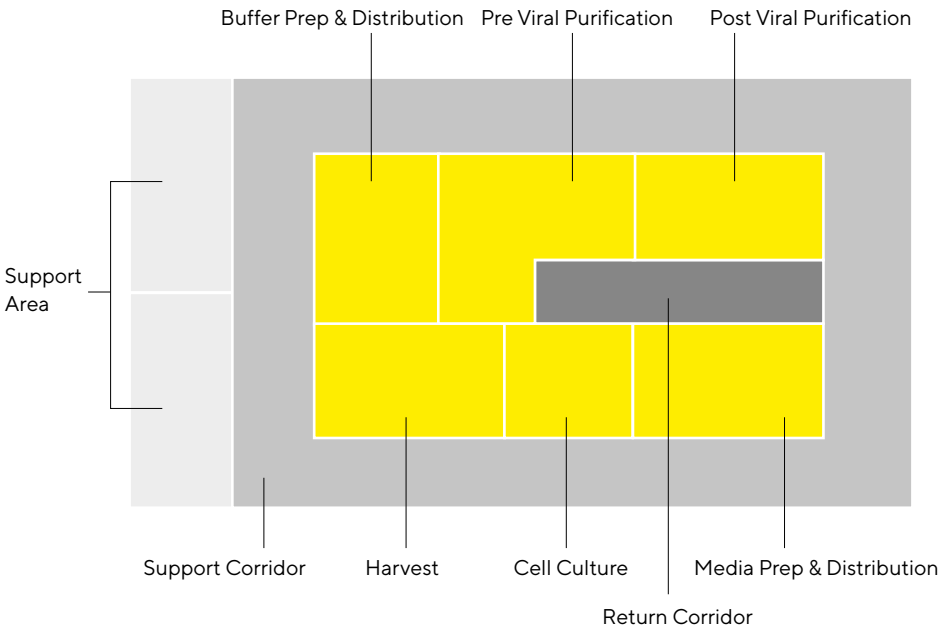
Supply to Return Concept

Characteristics of the supply to return concept:

- Unidirectional flow
- No transportation of buffers due to adjacency of buffer prep to pre and post viral purification

Guidance for 2 × 2,000 L STRs:

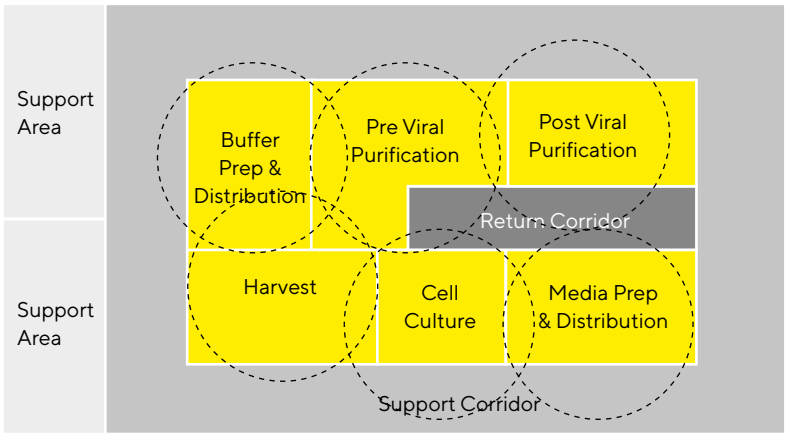
- Total process area required: 1,200 – 1,500 m²
- ISO8 | Grade C: 175 – 250 m²
- ISO9 | Grade D: 625 – 750 m²
- Grade NC | CNC: 400 – 500 m²

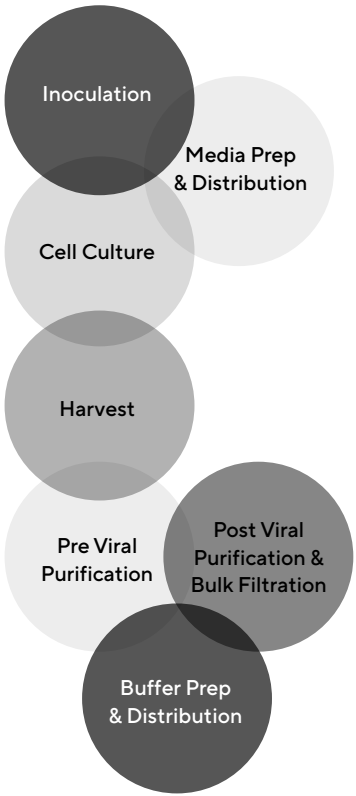


Adjacency Bubble Diagram

Adjacency of certain process areas is key for streamlined processing. Static equipment near to next process unit reduces movement of tanks and the length of tubing's.

Fitting the facility around the equipment rather than the equipment around the facility

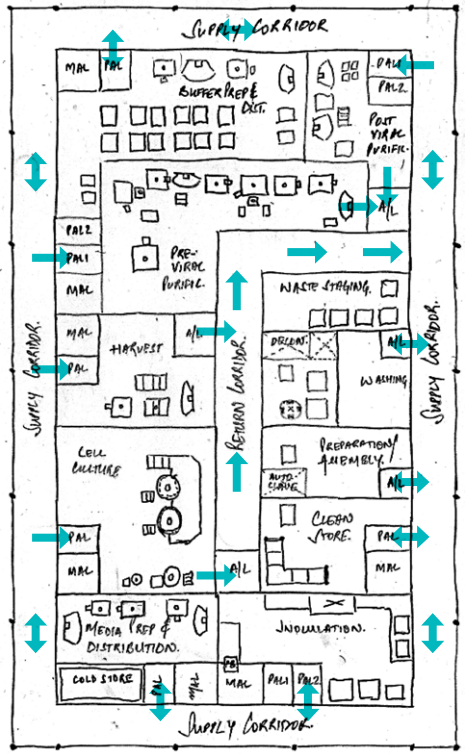




Process Layout Concept 1

→ Personnal Flow

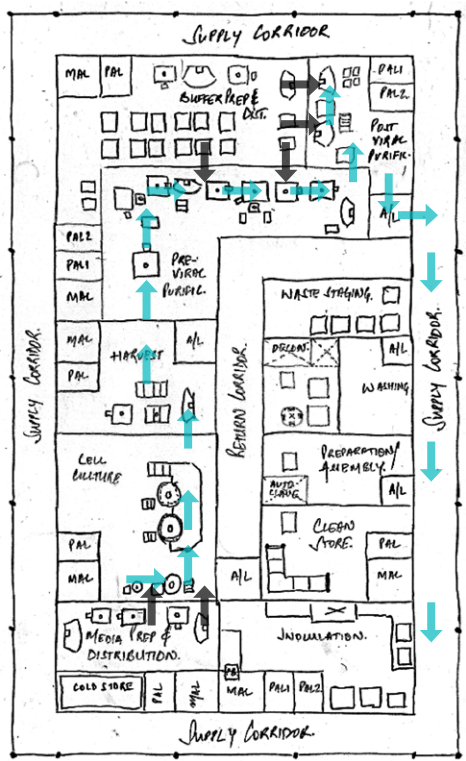
- Uni-directional flow in process areas
- Bi-directional flow for media & buffer areas with support areas



Process Layout Concept 1

Product Flow
Media-Buffer Flow

- Product streams incl. media and buffer transfer
- Product flow from one room to another via wall penetrations
- Planned room adjacency

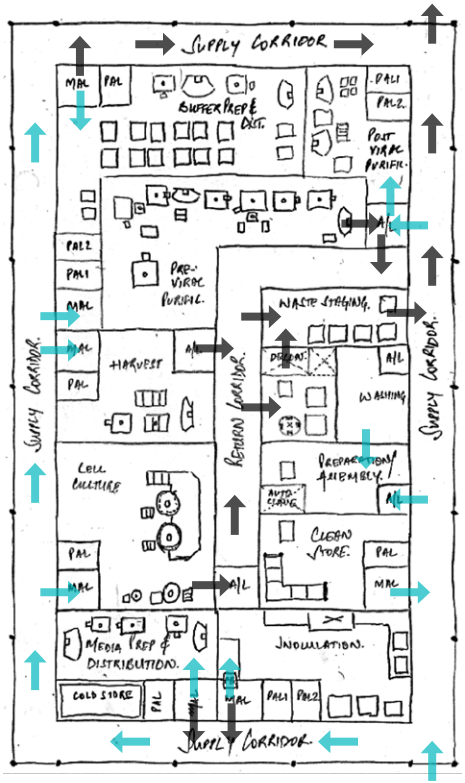


Process Layout Concept 1

Material Flow
Waste Flow

Material Flow
- Uni-directional flow in critical environments
- Risk Based Approach
- Temporal Segregation, Procedural Control

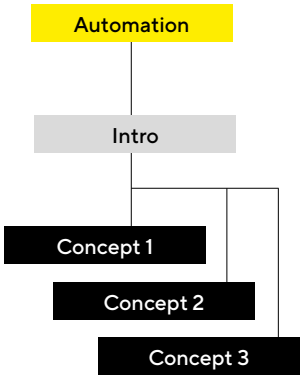
Waste Flow
- Uni-directional flow
- Decontamination of GMO soiled solid & liquid waste
- Risk Based Approach
- Temporal Segregation, Procedural Control



Introduction

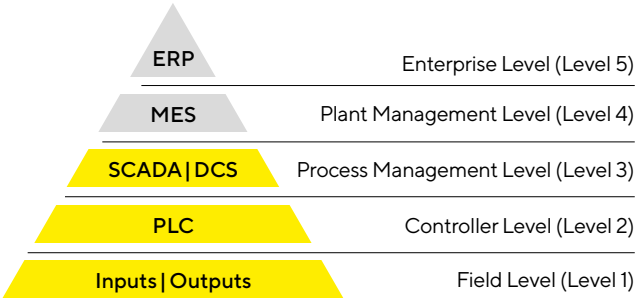
Besides equipment, automation and integration into ac ontrol infrastructure are fundamental to a successful project execution. The goal is flexibility in automation.

Sartorius single-use equipment can easily be integrated into a distributed control system (DCS), respectively into a manufacturing execution system (MES). This open system architecture covering the entire production process ensures an efficient interaction of all automation components. This is supported by consistent data management, global standard compliancy and uniform software interfaces.



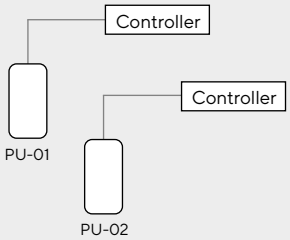
In addition to the openness of an integrated system architecture, this holistic automation approach paves the way for intelligent bioprocessing by means of Multivariate Data Analytics (MVDA) and real-time data acquisition and monitoring of your bioprocesses.

Our automation expertise covers the full spectrum from basic stand alone units, to fully integrated systems, into DCS networks.

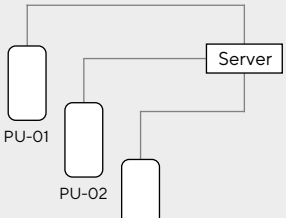


Automation Concepts Overview

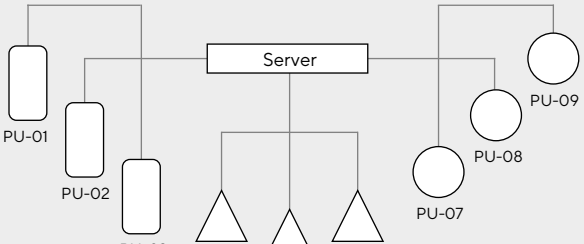
In general there are 3 different automation concepts that can be applied in manufacturing facilities. At Sartorius we guide you to the best approach for your unique situation.



- Individual local control
- Data transfer via OPC



- Remote control of group
- Central Unit Reports



- Plant wide process visualization with batch and recipe control
- Plug-and-Play capabilities

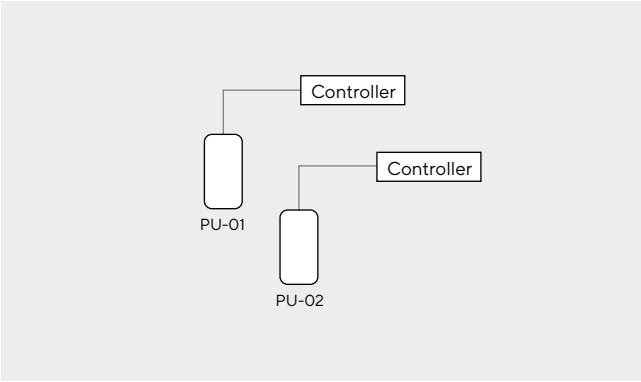
Stand Alone Package Units

All control, reporting, recipe and unit operations are localized into one system called the “package-unit”. This includes all parameter settings for unit-based control loops as well as recipes.

Acquired measurement data can be transferred to a higher level via OPC connectivity.

The autonomous process units, require individual maintenance and 21 CFR 11 reports are only possible per individual unit.

This basic approach is an ideal solution for a process with a limited set of parameters.



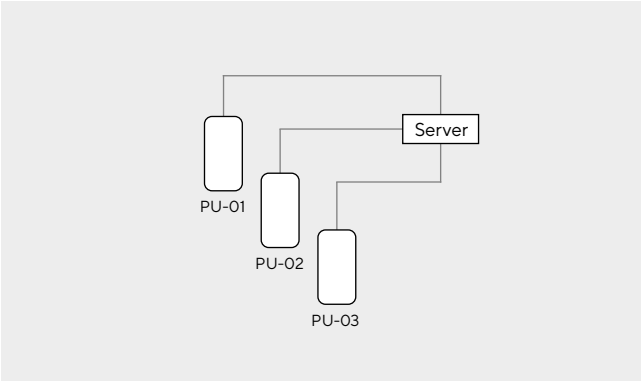
Package-Units with Server | Client SCADA System

A group of unit operations or clients (e.g. all bioreactors) is connected to a server with all control functionalities installed on it (SCADA). Control loops and recipes are used for this group only.

Additional unit operation groups may use another server system or use local package unit functionalities.

Measurement data from all individual systems can be transferred to one server which enables centralized data handling.

This classical approach has lower investment costs and is often used in pilot plants and small facilities.

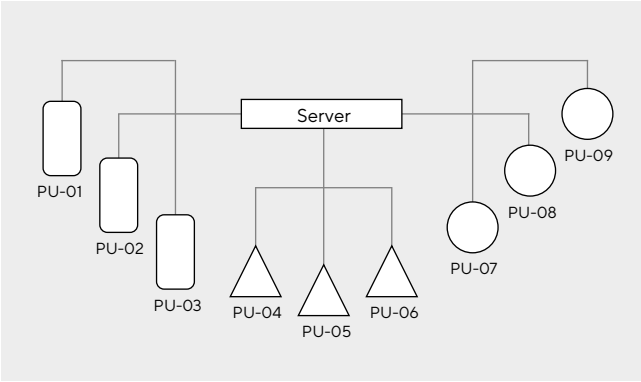


Package-Units Integrated into a Distributed Control System

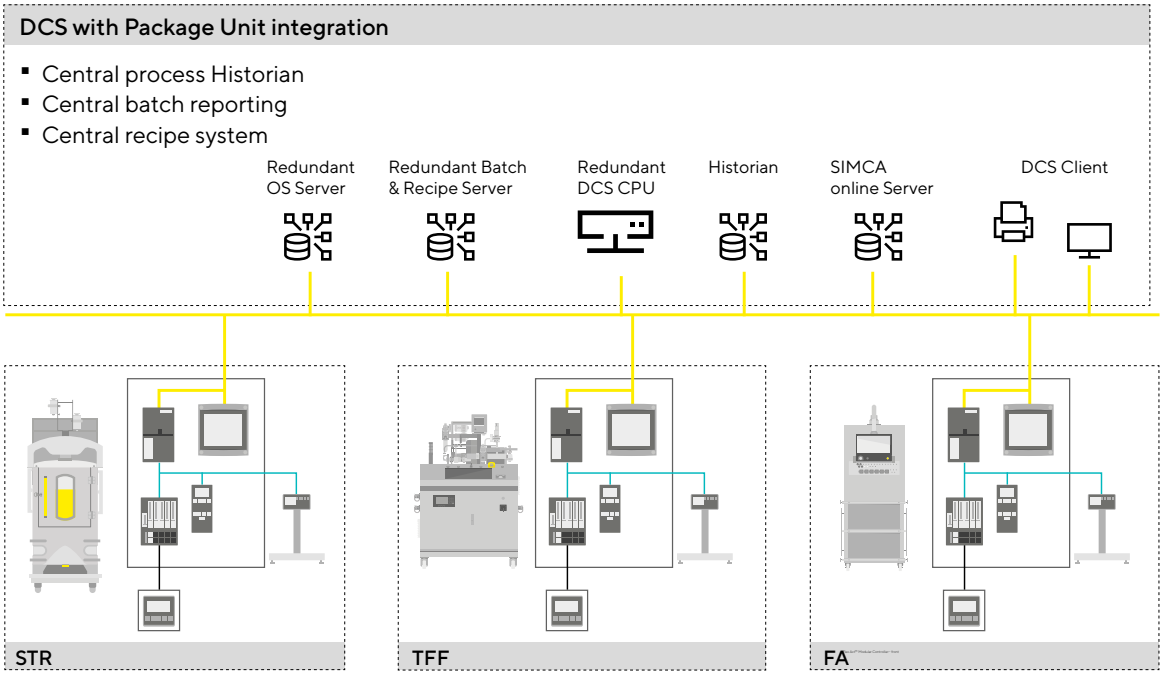
All control and data acquisition functionalities are integrated top to bottom. Parameter settings, recipes, as well as batch management control loops are distributed on a plan-wide level.

Implementing a single control platform across all plant applications provides a number of advantages, including more synchronized processes, increased reliability, reduced maintenance efforts and seamless transfer of real-time data for improved decision-making and increased manufacturing flexibility.

Distributed control systems are to those seeking a state of the art automation system driven by the process state.



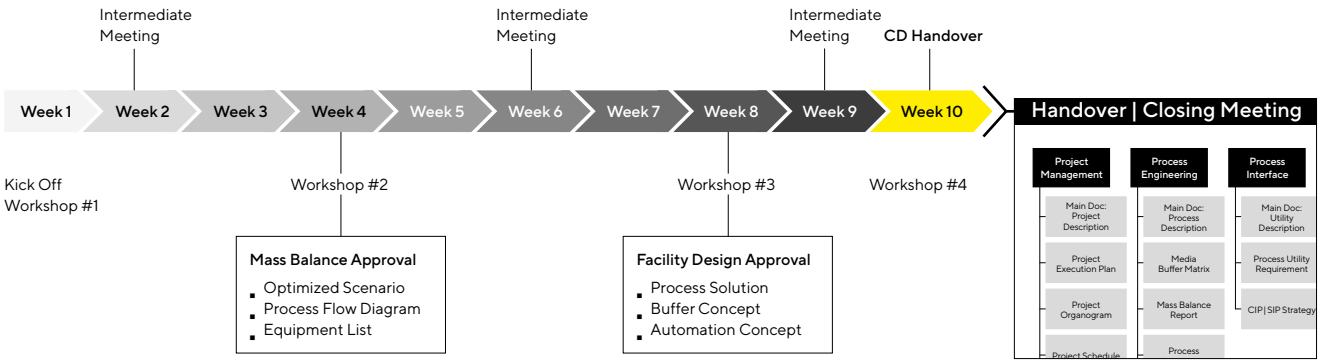
Example of a DCS Network



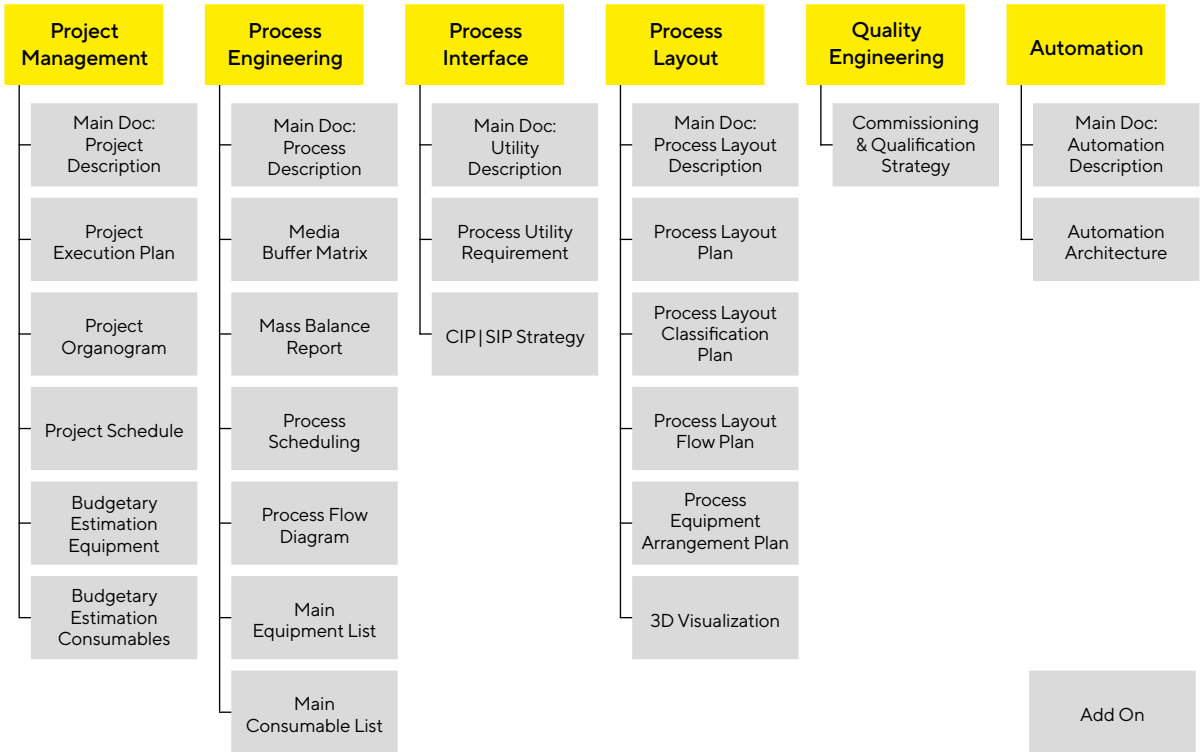
Project Schedule | Time Schedule

A concept design study from Sartorius will provide insight to your process and new production facility within 8 weeks time.

At the end of the study a handover package will be generated containing all information needed for a smooth project execution.



Standard CD Package



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