Conceptual Design
For Bioprocess Solutions
Introduction

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.
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
- Equipment List
- Selection of the automation concept
- Process layout
Project Schedule | Time Schedule

Level A time schedule based on Deliverables | Activities

**Week 1**
- Kick Off
- Workshop #1

**Week 2**
- Intermediate Meeting

**Week 3**
- Workshop #2

**Week 4**
- Intermediate Meeting

**Week 5**
- Workshop #3

**Week 6**
- Intermediate Meeting

**Week 7**
- Workshop #4

**Week 8**
- CD Handover

**Mass Balance Approval**
- Optimized Scenario
- Process Flow Diagram
- Equipment List

**Facility Design Approval**
- Process Solution
- Buffer Concept
- Automation Concept
Process Modelling

Based on your process information 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 with both single-use and stainless steel equipment will help you to find the best solution for all your processes.
Mass Balance Review

Process Modelling

1. Description of the processes that need to be modelled

<table>
<thead>
<tr>
<th>Process 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-3 Shake Flask</td>
</tr>
<tr>
<td>N-2 Rocking Motion</td>
</tr>
<tr>
<td>N-1 Stirred Tank Reactor</td>
</tr>
<tr>
<td>Production Bioreactor</td>
</tr>
<tr>
<td>2 Stage Depth Filtration</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding capacity</td>
<td>50 g/L</td>
</tr>
<tr>
<td>Column height</td>
<td>20 cm</td>
</tr>
<tr>
<td>Column Diameter</td>
<td>45 cm</td>
</tr>
<tr>
<td>Flow rate</td>
<td>320 cm/h</td>
</tr>
<tr>
<td>Buffers</td>
<td></td>
</tr>
<tr>
<td>Equilibration</td>
<td>5 CV</td>
</tr>
<tr>
<td>Post Load Wash 1</td>
<td>10 CV</td>
</tr>
<tr>
<td>Elution Buffer</td>
<td>5 CV</td>
</tr>
<tr>
<td>Regeneration buffer</td>
<td>5 CV</td>
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</tbody>
</table>

3. Evaluation and optimization of the processes

4. Process flow diagram incl. equipment

5. Process and equipment scheduling based on MBR output

6. Advanced options
   - Economic Modelling
   - Detailed Scheduling
Evaluate the impact of different technology options on your process

Model parameters to optimize buffer requirements and equipment sizes

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<td>60 cm</td>
</tr>
<tr>
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<td>320 cm/h</td>
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</tr>
</tbody>
</table>

Process Description

- 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 Membrane Adsorber
- Nano Filtration
- Final UF | DF
- Bulk Fill and Finish

Introduction

Standard

CD Package

PROCESS SUCCESS
Evaluate the impact of changing parameters on important factors such buffer demands and equipment scheduling.

### Process 1

- **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 Membrane Adsorber**
- **Nano Filtration**
- **Final UF | DF**
- **Bulk Fill and Finish**

#### Scenario 1 vs Scenario 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Post Load Wash 1</td>
<td>5 CV</td>
<td>5 CV</td>
</tr>
<tr>
<td>Elution Buffer</td>
<td>2 CV</td>
<td>2 CV</td>
</tr>
<tr>
<td>Regeneration buffer</td>
<td>3 CV</td>
<td>3 CV</td>
</tr>
<tr>
<td>Cycles per Batch</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Process time</td>
<td>13 h</td>
<td>7 h</td>
</tr>
<tr>
<td>Concentration Out</td>
<td>14.6 g/L</td>
<td>12.9 g/L</td>
</tr>
<tr>
<td>Volume Out</td>
<td>226</td>
<td>254</td>
</tr>
</tbody>
</table>

**Buffers**

| Equilibration      | 565        | 636        |
| Wash 1             | 565        | 636        |
| Elution Buffer     | 226        | 254        |
| Regeneration buffer| 339        | 382        |

Example: Impact of Protein A column volume
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 & holding concept

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**Mass Balance Review**

### Process Scheduling

<table>
<thead>
<tr>
<th>Schedule on a Daily Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermone T</strong></td>
</tr>
<tr>
<td>Timeslot</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

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### Media Prep

- Media Mix 10 L
- Media Mix 100 L
- Media Mix 1000 L
- Media Mix 10 L
- Media Mix 100 L
- Media Mix 1000 L
- Media Mix 10 L
- Media Mix 100 L
- Media Mix 1000 L

### Upstream

- Media Bank
- Raw Material Bank
- Dependant on PFD

### Buffer Prep

- Buffer Mix 200 L
- Buffer Mix 2000 L
- Buffer Mix 20000 L
- Buffer Mix 200 L
- Buffer Mix 2000 L
- Buffer Mix 20000 L
- Buffer Mix 200 L
- Buffer Mix 2000 L
- Buffer Mix 20000 L

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### Media Bank

- Media bank
- Raw material bank
- Production bank

### Process Flow Diagram

- Inoculation + Cell culture + harvest
- Inoculation + Seed Propagation + Cell Culture + Harvest

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**Introduction**

**Mass Balance Review**

**Process Flow Diagram**

**Process Layout**

**Automation**

**Standard CD Package**
Advanced Process Scheduling

On request the advanced Process scheduling with Schedule Pro* can be added to the basic package.

- Process debottlenecking
- Shift modelling capabilities e.g. 2 shifts, Handles plant down-time, weekend and holiday schedules
- Multi-product campaign scheduling
- Cost engineering, optimization of media-buffer preparation and holds
- Labor, room, facility occupancy capabilities

* Schedule Pro is licensed from Intelligen Inc.
Economic Modeling

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?
Process Flow Diagram

(PFD). This tool provides the visualization of process relationships as well as the major equipment selection based on outputs of the mass balance review.
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 & wall area requirement
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 & 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
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 & high titer process
- Less movement in Pre Viral & Post Viral area

**Challenges:**
- Adjacency & 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
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.

**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 $2 \times 2000$ L STRs:

- Total process area required: $1200 – 1500$ m$^2$
- ISO8 | Grade C: $175 – 250$ m$^2$
- ISO9 | Grade D: $625 – 750$ m$^2$
- Grade NC | CNC: $400 – 500$ m$^2$
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 I

- Uni-directional flow in process areas
- Bi-directional flow for media & buffer areas with support areas
Process Layout Concept I

- **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 I

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

The automation of your processes and the integration into existing networks is a key factor for a successful operation.

Unit operations such as bioreactors and DSP equipment can be implemented at different levels providing you different levels of control and flexibility.

Depending on the kind of project we can either offer proprietary solutions or partner with all major industrial players such as Siemens (PCS7) and Emerson (DeltaV).

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.

- **Stand Alone Package Units**
  - Individual local control
  - Data transfer via OPC

- **Package-Units with Server | Client SCADA System**
  - Remote control of group
  - Central Unit Reports

- **Package-Units integrated into a Distributed Control System**
  - 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

DCS with Package Unit integration

- Central process Historian
- Central batch reporting
- Central recipe system

STR

TFF

FA

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
At Sartorius we have extensive experience in designing facilities for biopharmaceuticals. Our processes involve single-use and stainless steel media and buffer requirements. We calculate the media and buffer requirements as well as the time scheduling of processes to streamline the production. Economic modeling is applied in manufacturing facilities. At Sartorius we guide you to higher grades of automation and integration into cGMP & regulatory principles. Depending on the kind of project we can either offer proprietary or consultative solutions, from basic to advanced options, including proprietary server-based solutions.

For more Information: RFQSystems@Sartorius.com