Use of bioprocess modelling tools to develop more robust, cost effective downstream processes

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Agenda

- Introduction to Biopharm Services
- Why use Process modelling?
- BioSolve Advanced Process Modelling Platform overview
- BioSolve User case study: Crucell
- Questions
BioPharm Services

The recognized leading international bioprocess consultancy
Delivering Operational Excellence

Our focus is on helping our clients achieve the goal of delivering cost effective medicines to patients through better understanding of process, product and manufacturing.
Introduction to Biopharm Services

Founded by Andrew Sinclair

Awarded MicroSmart to develop a bioprocess simulation package

Awarded a Collaborative R&D grant with Medimmune and Avecia (Fujifilm Diosynth) on novel technologies underpinning bioprocessing

BioSolve Process launched

US biodefense projects sponsored by DARPA & BARDA

UK TSB grant – software bioprocess application Extending the functionality of the BioSolve platform to recipe management and facility fit

3 software patents awarded: bioprocess simulation
Biopharmaceuticals
Today & Tomorrow

Manufacturing is a key requirement for the industrialization of the biosciences
- Insights into the cost implications of decisions made in development are critical to successful commercialization

Traditional biopharmaceuticals have been vaccines and recombinant proteins
- Flu vaccine
- Monoclonal antibodies

New products based on new science, these pose challenges in terms of industrialization and cost effectiveness
- Tissue engineering
- Cell therapies - autologous & allogeneic
- Gene therapy
- Novel vaccines
Manufacturing Costs are Important

- Manufacturing cost is single variable cost (14% of sales)
- Development costs are fixed and include losses around failed drugs (21%)

Data source: GE Healthcare webinar
Why Use Models?

- Get the big picture – what are the variables?
- Make predictions – what will happen if...
- Evaluate alternatives – which one is best?
- Communication – a simple picture or chart is better than a thousand words
- Make better business decisions

Cost breakdown by unit operation:
1000$/batch for a Mab process
Building a good cost model

- Understand the manufacturing process
  - Resource requirements
  - Timing

- Understand the cost structure
  - Fixed/variable – not always obvious
  - Beware of hidden costs
  - Activity-based costing (ABC) can help with this

- Understand where to make assumptions
  - Impossible to model all variables
  - Can introduce more error by false confidence
What is BioSolve Process?

Software that models processes from seed to vial, with BioSolve you can model processes to manufacture:
- vaccines
- peptides
- therapeutic proteins
- fill finish

Evaluate the impact of the latest technologies on a given process e.g. perfusion continuous chromo
Process Cost Model Features

Requirements

- Scalable models
  - Mass balance calculations
  - Step times
  - Equipment/consumable sizing
  - Labour requirements
  - Utility requirements

- Allow rapid evaluation
  - Solution prep methodology
  - Disposable systems
  - Mode of operation fed-batch vs. perfusion, etc.
  - Continuous operations
BioSolve Process
Configurable Process Model

Rapid process configuration
Rapid option evaluation
- Technologies
- Processes

Scalable mass balance
- Standard format
- Consumables estimates

Scalable equipment list
- Based on standard costs, sizes
- Basis for capital cost estimate

Insight into utilities, environment
- PW & WFI
- Waste streams

Capacity and capital estimates

<table>
<thead>
<tr>
<th>Process Sequence</th>
<th>Conc (g/L)</th>
<th>Vol (L)</th>
<th>Mass (g)</th>
<th>Yield (%)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 N-2 Seed</td>
<td>0.0</td>
<td>50</td>
<td>0</td>
<td>0%</td>
<td>58.0</td>
</tr>
<tr>
<td>2 N-1 Seed</td>
<td>0.0</td>
<td>500</td>
<td>0</td>
<td>0%</td>
<td>59.0</td>
</tr>
<tr>
<td>3 Production</td>
<td>5.0</td>
<td>5,000</td>
<td>25,000</td>
<td>85%</td>
<td>210.0</td>
</tr>
<tr>
<td>4 Centrifugation</td>
<td>5.0</td>
<td>4,250</td>
<td>21,250</td>
<td>85%</td>
<td>9.0</td>
</tr>
<tr>
<td>5 Depth Filtration</td>
<td>4.3</td>
<td>4,250</td>
<td>18,063</td>
<td>85%</td>
<td>9.2</td>
</tr>
<tr>
<td>6 UF/DF #1</td>
<td>40.4</td>
<td>425</td>
<td>17,159</td>
<td>95%</td>
<td>12.4</td>
</tr>
<tr>
<td>7 Protein A</td>
<td>3.1</td>
<td>4,926</td>
<td>15,443</td>
<td>90%</td>
<td>12.9</td>
</tr>
<tr>
<td>8 Virus Inactivation</td>
<td>3.0</td>
<td>5,025</td>
<td>15,135</td>
<td>98%</td>
<td>2.5</td>
</tr>
<tr>
<td>9 Capture IEX</td>
<td>7.8</td>
<td>1,847</td>
<td>14,378</td>
<td>95%</td>
<td>11.4</td>
</tr>
<tr>
<td>10 Flow Through IEX</td>
<td>7.4</td>
<td>1,847</td>
<td>13,659</td>
<td>95%</td>
<td>6.2</td>
</tr>
<tr>
<td>11 Viral Filtration</td>
<td>7.2</td>
<td>1,847</td>
<td>13,386</td>
<td>98%</td>
<td>9.3</td>
</tr>
<tr>
<td>12 UF/DF #2</td>
<td>35.5</td>
<td>369</td>
<td>13,118</td>
<td>98%</td>
<td>12.4</td>
</tr>
<tr>
<td>13 Sterile Filtration</td>
<td>34.8</td>
<td>369</td>
<td>12,856</td>
<td>98%</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Process Definition

<table>
<thead>
<tr>
<th>Product Titre</th>
<th>Capacity Utilisation</th>
<th>Production Bioreactor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00 g/L</td>
<td>80%</td>
<td>5000 L</td>
</tr>
</tbody>
</table>

Single-Use Systems

<table>
<thead>
<tr>
<th></th>
<th>MAb Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioreactors (up to 2000L)</td>
<td>No</td>
</tr>
<tr>
<td>Media Preparation (up to 2000L)</td>
<td>Yes</td>
</tr>
<tr>
<td>Buffer Preparation (up to 2000L)</td>
<td>No</td>
</tr>
</tbody>
</table>
BioSolve Process
Common Use Cases

Evaluate & screen PD options:
- Early on in PD BioSolve is used to develop robust & cost effective processes.
- Ensures consistency & reduces errors

Rapidly understand the impact of
- Scale
- facility fit
- Support business cases.

Suppliers use BioSolve Process to develop & understand the value of their technologies from the user perspective

Tech transfer groups use BioSolve Process to:
- Identify the cost effective option
- Provide a standard method for structuring process information
- Understand the cost of outsourcing

Determine capacity & expansion strategies

Optimise manufacturing
- Minimise capital
- Minimise operating cost
- Maximise asset utilisation

Support marketing in fixing pricing strategy
BioSolve Process Example Case studies

**PROMEDIOR**
Economic models guiding expression system choices in early phase clinical development

**SANOFI PASTEUR**
Developing business cases for new products & new technologies

**GE Healthcare**
Environmental life-cycle assessment of single-use versus conventional process technology for mAb production

**MedImmune and Crucell**
Process cost & facility considerations when selecting cell culture clarification technology

**UCL**
Upskilling the next generation of bioprocess engineers, linking BioSolve to USD

**Pall Corporation**
Integrating technologies in BioSolve: Pall Cadence single-pass TFF

**BD**
Total cost in use analysis of a chemically defined media supplement as compared to a legacy process using peptone supplementation
Bringing innovation to global health
Use of bioprocess analysis modeling tools to develop more robust, cost effective downstream processes

Crucell - case study

18Apr12, Prague

Magdalena Stepien, PDEng, MSc
Process Engineer
Down Stream Processing Group
Early Stage Development
Outline

- Introduction
  - Crucell overview
  - R&D pipeline
  - Importance of cost modeling to Crucell
- Case study - IgGs production
  - Assumptions
  - Process overview
  - Economic results (CAPEX, CoGs, sensitivity analysis)
  - Conclusions
- BioSolve at Crucell
# R&D pipeline

<table>
<thead>
<tr>
<th>Vaccines in development:</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>M&amp;S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow Fever (Flavimun®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aeras/own</td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GSK/own</td>
</tr>
<tr>
<td>Ebola and Marburg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
<tr>
<td>Universal influenza vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
<tr>
<td>RSV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
<tr>
<td>Cell-based Influenza seasonal (FluCell®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibodies in development:</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>M&amp;S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies antibody combination</td>
<td></td>
<td></td>
<td>Fast Track</td>
<td></td>
<td>Sanofi/own</td>
</tr>
<tr>
<td>Influenza antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>JNJ/own</td>
</tr>
<tr>
<td>Hepatitis C antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>own</td>
</tr>
</tbody>
</table>
Our vaccines
Distributed in 80+ countries

**Paediatric**
- Quinvaxem®
  Pentavalent vaccine
- Epaxal®
  Hepatitis A vaccine
- Hepavax-Gene®
  Hepatitis B vaccine
- MoRu-Viraten®
  Measles/Rubella vaccine

**Travel & Endemic**
- Epaxal®
  Hepatitis A vaccine
- Epaxal® Junior
  Hepatitis A vaccine
- Vivotif®
  Typhoid vaccine

**Respiratory**
- Inflexal® V
  Influenza vaccine

**Dukoral®**
Cholera & ETEC vaccine

*Cruccell*
Crucell Overview

Crucell is a fully integrated infectious disease vaccine and monoclonal antibodies company

– Vaccine Excellence Center within J&J

- **Global product portfolio:** 8 marketed vaccines, distributed worldwide; manufactured in Switzerland, Spain, Korea, Sweden

- **Largest independent player, major partnerships:** Sanofi Pasteur, Merck, Novartis, Pfizer, Johnson & Johnson, GSK

- **Strong innovator:** 6 unique novel vaccines and antibodies in clinical trials, leveraging broad technology base including protein production, adjuvination, formulation, oral vaccines
Why Cost Modeling?

• To understand manufacturing costs early on in development
  --> especially important for:
  • High dose products (e.g. IgGs)
  • Low income products (e.g. TB, HIV, malaria)

• To avoid significant business losses
  (e.g. investment in a new production facility
  where big volumes need to be processed)
Case Study (1)
Assumptions

- Production of IgGs
- Complete disposable facility
- New facility is built
- Target manufacturing scale - 1 000 kg IgGs per year
- Upstream process: fed-batch
- Downstream process:
  - 3 column chromatography steps (Protein A, CEX, AEX)
  - x 100 resin re-use
- Media & buffer prep.: on-site
Fed Batch (FB) USP

**INPUT:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-culture duration (I+II)</td>
<td>24 days</td>
</tr>
<tr>
<td>Production duration</td>
<td>14 days</td>
</tr>
<tr>
<td>Titer</td>
<td>4 g/L</td>
</tr>
<tr>
<td>Target annual throughput</td>
<td>1000 kg IgGs</td>
</tr>
<tr>
<td>Bioreactor’s harvest</td>
<td>1 per batch</td>
</tr>
</tbody>
</table>

**OUTPUT:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Bioreactors</td>
<td>9 x 2000L</td>
</tr>
<tr>
<td>Cycle duration</td>
<td>1.6 days</td>
</tr>
</tbody>
</table>
Case-study (3)
Process overview - DSP

**INPUT:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSP recovery</td>
<td>70%</td>
</tr>
<tr>
<td>Resin re-use</td>
<td>x100</td>
</tr>
<tr>
<td>No. of DSP trains</td>
<td>1</td>
</tr>
</tbody>
</table>

**OUTPUT:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch size</td>
<td>5.6 kg</td>
</tr>
<tr>
<td>Resin re-use</td>
<td>x100</td>
</tr>
<tr>
<td>No. of batches per year</td>
<td>179</td>
</tr>
<tr>
<td>Annual throughput</td>
<td>1002 kg IgGs</td>
</tr>
</tbody>
</table>
Case-study (4)
Results - CAPEX

- Construction of a new facility
- Disposable consumables are used

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchased Equipment (PE)</td>
<td>19 mln US $</td>
</tr>
<tr>
<td>Cost of Works (CoW)</td>
<td>44 mln US$</td>
</tr>
<tr>
<td>Other Capital (OC)</td>
<td>22 mln US $</td>
</tr>
<tr>
<td>CAPEX</td>
<td>85 mln US$</td>
</tr>
</tbody>
</table>

Conclusions:
- 22% CAPEX --> equipment
- 80% equipment costs --> USP section
Case-study (5)
Results - CoGs

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Cost (US$/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capital charge</td>
<td>18</td>
</tr>
<tr>
<td>Materials</td>
<td>15</td>
</tr>
<tr>
<td>Consumables</td>
<td>31</td>
</tr>
<tr>
<td>Labour</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>78</td>
</tr>
</tbody>
</table>

Breakdown of Consumables

- Filters: 52%
- Bags: 29%
- Resins: 19%
Case-study (6)
Results CoGs

USP : Recovery : DSP cost ratio
Case-study (7)
CoGs breakdown per unit operation

1nd: Capital charge:
9 x 2000L Bioreactors

2nd: Protein A step
--> resin cost
Sensitivity analysis
Impact of titer

Conclusions
• Increasing production scale with process intensification results in higher COG savings, comparing to increasing the number of bioreactors.
PD targets - An intensified Upstream and Downstream process
Scenario Analysis in BioSolve
Non-intensified vs. Intensified process

Scenario 1 - Fed-batch process

Scenario 2 - XD™ Process
BioSolve at Crucell

- In-house training provided by BioPharm Services
- In-house workshop - validation of the model
- Process analysis expanded to vaccine processes, at early stage development
- BioSolve embedded in Crucell organization:
  - Collaboration of BioSolve users with Business Management and Engineering teams
  - Team of BioSolve power users formed
Cost analysis:

- Gives a complete forecast of manufacturing cost
- Allows to pro-actively focus on process cost bottlenecks
- Is especially important for the processes where reduction of production costs is the driver
Combating infectious diseases

by bringing innovation to global health