Smart Continuous GMP Manufacturing

Dirk Tillich @ BioTech 2016, Wädenswil, Switzerland
Agenda

- Intro Finesse
- BioPharma Challenges
- Perfusion Methods in Use
- Process Automation
- SmartFactory Examples
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Business Overview

**Founded By**
Dr. Barbara Paldus
Dr. Mark Selker

**Headquarters**
Santa Clara, CA, USA

**Industry**
Life Science

**Employees**
120

**Geography (2015)**
- Americas: 48%
- Europe: 21%
- Asia/ROW: 13%
- OEM: 18%

**Product Mix (2015)**
- Systems: 80%
- Service: 10%
- Sensors: 10%

**Original supplier of Single Use USP Class VI sensors**
20,000+ units shipped since 2008

**Growing Installed Base**
- 1200+ lab-scale units
- 450+ large-scale units
- 300+ cGMP
- 45+ 2000L Single-Use Bioreactors

**Normalized Growth**
2008
2015
Global Presence

Corporate Offices
- Sales
- Service
- Distributors/Reps

Finesse Solutions AG
DeltaV Software
Asia Pacific

Headquarters
The Finesse SmartFactory Platform

Silicon Valley Technology Approach:

- Use cutting edge technology
- But make it easy to use
- Universal controllers that work with all systems

- Solutions for all scales and processes
Biopharm Market Goals

- Identify promising biologics early
- Scalable manufacturing process
- Stable product / quality

High Success Rate

- Reduce ~ $1B development cost
- Reduce capital investment
- Lower operating cost

Reduced Cost

- Reduce from ~8 years to launch
- Reduce from 4-5 years to facility

Time to Market
Challenges in Bio-Processing

- Minimize downtime
- Match process steps (USP/DSP capacity)
- Smaller, multiple lines

- Use adaptable processes / technologies
- Use adaptable controls
- Modular Automation (re-configure)

- Automate where possible
- Optimize USP/DSP together
- Integrate real-time analytics
SmartFactories can enable:

- High degree of utilization due to process flexibility
- Output scale and demand match
- Multiproduct production can drive further utilization improvements
- Continuous processing can enable flexibility in capacity
Upstream Methods Over the Years

1980’s

Batch
- Low tech
- Little involvement
- Limited monitoring
- Limited process control if any

Fed Batch
- Basic operator skills
- More hands on
- Some online monitoring
- Process control and feed strategy

Present

Intensified Process
- Highly skilled
- High level of process management
- Online monitoring, & control of reactor and ancillaries
- Additional process offline monitoring; metabolics, cell density
The Drive Towards Higher Titers

- Too much development time reaching $>10$ g/L in a batch process
- Requires highly customized media
- High titer batch process may not be scalable

- Intensified processing addresses titer
Driving Cost Reductions

Multiple campaigns contribute to further cost reduction:

- Ideally > 30 batch /year
- Product titer a factor
- Limits of batch process become apparent

How do we drive below $100 / g?

Intensified processing
Matching USP/DSP Capacity

- Focus matching upstream with downstream cycle time
- Previously USP batch time was long due to titer
- Media, better cell lines, and process control helping
- Intensified processes already designed to match USP/DSP

<table>
<thead>
<tr>
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<th>Days</th>
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<tbody>
<tr>
<td>Low Titer</td>
<td>3</td>
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<tr>
<td>High Titer</td>
<td>2</td>
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<tr>
<td>Continuous</td>
<td>3</td>
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- USP
- DSP
Several different models

- High cell density fed batch
- Perfusion
- Continuous, semi-continuous

Challenges, Real or Perceived
- Labor intensive
- Batch definition
- High level of automation and monitoring
- Highly skilled

Benefits
- Smaller footprint
- Minimized capital cost
- Minimized facility cost
- Maximum facility utilization
- Low cost media
Optimizing USP Processes

Multiple reactors and higher titer creates challenges

- Process control of several lines
- Advanced feed strategies
- Increased analytics and measurements
- Additional ancillaries, pumps, valves, transmitters
- Data management, batch records
- Integrated DSP (parameter optimization)

*All can be managed with the right tools*

*ULTIMATE LIMIT IS AN END-TO-END CONTINUOUS PROCESS*
Process Evolution: Batch to Conti

- Highly skilled operators
- High level of automation
- Online monitoring / control of process & ancillaries

Example 1: Continuous upstream (perfusion), batch downstream
Example 2: Batch upstream, continuous downstream
Example 3: Continuous upstream + capture, batch downstream
Example 4: Continuous upstream + downstream


- Requires more sophisticated automation and modular controllers = SMART
- Enabling technologies are needed for PAT and process integration
Problem: Islands of Automation
Why are SMART Tools required?

- Process intensification requires many considerations:

  **Process**
  - Automation of key PVs
  - Increased ancillaries
  - Complicated feed strategies
  - Equipment robustness – Sensors
  - Weight control

  **Data / Analytics**
  - Monitoring of online parameters, press, DO, pH
  - Integration of offline data
  - Significant data generation
  - Data for regulatory compliance

  **Personnel**
  - High skill level
  - More hands on
  - Tech transfer challenges
  - Familiar with the use of sensors - calibration
Smart Tools for Continuous USP

Requirements to manage a continuous strategy

• Flexible, scalable control platform
• Recipe function with cascade control
• Plug and play sensors and ancillaries
• Centralized plant management

Taking a universal approach to control:

• Control multiple bioreactors from any vendor
• Preset configurations allow for rapid change over
• Minimize training and validation
• Link to plant management system
• Move from suite to suite
**Perfusion**

- **Definition:** continuously adding nutrient solutions to a bioreactor while removing wastes from it
- **Record:** 31g/L titer
- **Benefits:**
  - Maintain optimal growth conditions for slow-growing or difficult-to-grow cell lines
  - Enable productive processing of unstable products by limiting the exposure of products to damaging proteases
  - Achieve production volumes with smaller bioreactors
  - Eliminate smaller seed bioreactors (in some cases)
  - Reduce capital costs and footprint of upstream equipment

- **Bioreactors:** many different types can be used
  - Stainless steel
  - Hollow fiber
  - Single-use (stirred tank or rocker)
Perfusion - Overview

● **History: benefits of single-use components**
  
  **Late 1980’s**: Perfusion mitigates for low titers/productivity by increasing cell concentration
  
  **2000’s**: single-use components enable perfusion by eliminating cleaning/sterilization steps, and reducing contamination risk
  
  **2010’s**: key single-use components (bags, tubing assemblies, bioreactors, mixers, centrifuges, and filter cartridges) common

● **Perfusion Rates: typically 1-3 X bioreactor volume/day**
  
  Medium perfused at dilution rates >> the cellular growth rate

● **Separation device: needed to retain cells in the bioreactor**
  
  - Cell-settlers
  
  - Centrifuge
  
  - Filters, e.g., spin, cross-flow, tangential-flow, ATF
  
  - Biosep (acoustic)
As volume changes / day or flux (continuous process) increases:

- Temperature management
- pH and lactate monitoring is critical
- Glucose monitoring required for feed strategy
- pO2, pCO2, acid / base must be maintained
Acoustic Separator: BioSep

- Popular with glass vessels up to 20L
- **Separation mechanism:** separation is performed in a resonator chamber with an acoustic field at 2.1 MHz generated by a transducer. Ultrasonic forces in the standing wave field produced will aggregate and hold the suspended cell against flow. These cells are then flushed back into the bioreactor.
  - Integration requires custom Finesse code
  - Example: 14L NBS glass or single-use vessels
    - Insight
ATF-based systems

- **ATF = ALTERNATING TANGENTIAL FLOW**
- **Separation mechanism:** action of a diaphragm moving up then down within a pump head, connected to a filter housing and attached to a standard bioreactor
- **Integration also with most Single-Use bioreactors very simple**
- **Examples: 50L to 2,000L**

LG, CruCell, Transgene, Wuxi: ATF
CruCell also PACS
Integrating Continuous Perfusion and Direct Capture

Steady state, integrated, continuous operation
High Cell Density Perfusion Technology Platform

● ATF-based perfusion culture platform
  Lab scale: 20x ATF2 and 2xATF4
  Production scale: 2xATF6 & ATF10
  Steady state culture @ >40x10^6 cells/mL for up to >100 days

● Develop platforms for both labile recombinant proteins and stable Mabs

● Large-scale cGMP manufacturing at 125-1000L scale

Lab scale ATF2 setup
Centrifuge-based Systems

● **Separation mechanism:**
Cell culture removed from the bioreactor via separation pump and delivered to centrifuge insert; pinch valves are closed. Centrifuge concentrates the cells over a set time period. Upon completion, the separation pump is turned off, and the pinch valves adjusted to that the concentrated cells are returned to the bioreactor.

● **Integrated native DeltaV custom control tower**
  – Centritech centrifuge with custom control of pinch valves
  – Integration with SUB/glass bioreactors with custom Finesse code used

● **Example: 10L glass to 50L SUB**
  – Shire
Cell Cube Systems

Single-use, scalable single-use bioreactor

Separation mechanism: cell cube vs oxygenator

1. Cells adhere to cell cube walls; cell cube surface area is scalable
2. Oxygenator provides measurement and control of process parameters
3. Recirculation Pump continuously flushes cells with new media
- Seeded 100-layer CellCube module, 384.9x10^6 cells total
- 11L of 4.32x10^5 cells/mL cell suspension harvested
  - 4.75x10^9 cells total collected
  - Average viability of 95.8%
Connecting the Islands of Automation

SmartFactory

SmartMES

Manufacturing Operations Management

EDMS  Equipment  Orders  Weighing  Training
Scalable and Harmonized Upstream

Remote Access

DeltaV Network

Plant LAN

OPC SERVER

Native control with real-time off-line analysis

DV Controller

OPC

Scales, pumps, G3Lab Universal Controller for Glass or SmartRocker, GE Wave rockers

Sartorius/Applikon Glass, Rocker, single-use bioreactors, Nova, BaychroMAT, OPC compliant units

Finesse G3Lite

Finesse G3Pro Universal controller for highest vessel flexibility as single or dual systems

Levels 1 & 2

Finesse

G3Lite

G3Pro Universal
G3Lab Universal Controller: ≤ 250L

- Glass Vessels (1-20L)
- Single-use Stirred (1-14L)
- Rockers (10-50L)
- Single-Use Bioreactors (up to 250L with VAB)
G3Pro Universal: 50L to 2,000L
Finesse TruBio® 5.0 Software

- Highly user-configurable USP SW
- Multi-feed feature is perfusion capable out-of-the-box
- Harvest feature option out-of-the-box
BaychroMAT-TruBio interface
Harmonization Downstream

Hybrid: SCADA using OPC and growing part using Finesse controller with native DeltaV

Operator Station

Professional Plus Station

Application Station and Historian

Plant LAN

DeltaV Network (Dedicated, redundant process LAN)

DV Controller

Buffer Prep

Centrifugation

Clarification

Filtration

Chromatography (Affinity/CEX/AEX)

Ultra-filtration

Virus Removal

Sterile filtration

Proprietary and Confidential @ Finesse Solutions, Inc. 2016
Flexible DeltaV code for filtration
Applications include: harvest, virus filtration/inactivation, clarification, and TFF
Flexibility allows rapid configuration for custom applications
TruChrom SW provides DeltaV control of 3\textsuperscript{rd} party skids
Both single-use and hybrid
Finesse TruChrom® 3.0 Software

- Flexible DeltaV code for Chromatography
- General functionality for AKTA-based skids
- Next generation will be fully configurable
- Flexibility allows rapid configuration for custom applications
TruBio User Interface Harmonization

**Universal laboratory controllers:**
- **Glass vessels:** Applikon, Sartorius, NBS, Finesse SmartGlass
- **Single-use vessels:** Millipore, Eppendorf, Finesse
- **Rockers:** GE/Wave, Sartorius, Finesse

**SCADA OPC overlay:**
- Controllers: Sartorius, Applikon, Eppendorf
- Analytics: Nova, Cedex, BayChromat, …
From SmartParts to SmartFactories

Vision: Facility harmonization

SmartMES
Flexible, powerful MES

SmartSystems
Universal Controllers

SmartParts
Intelligent Components

SmartTrain
Process Train and Model Assumptions
SmartMES – Scalable Options

- Right First Time
- Reduce Complexity
- Eliminate Unnecessary Work
- Embed Knowledge

- Security & Audit
- Batch Workflow / Recipe Authoring
- Procedure Workflow
- Document Management (Partial)
  - Recipes
  - Batch Records
- Federated Search
- Batch Production Records
- Order Management (Partial)
  - Scheduling and running of batch
  - Batch Workflow
    - Media Prep batch
    - Fermentation (Bioreactor)

- Manufacturing Portal (Partial)
  - Support Deployed Modules
- Process Miner
- Message Broker
- Weigh & Dispense
- Training & Development
- Equipment Tracking
- Materials Management
Finesse offers consultancy services by highly experienced seniors

Vision: Facility harmonization
- **SmartMES**: Flexible, powerful MES
- **SmartSystems**: Universal controllers
- **SmartParts**: Intelligent components
Ideally facility is designed to match pipeline:

- Upstream suites designed for scale up
- Downstream sized to prevent bottleneck
- Supporting infrastructure should be considered; warehouse, inoculum, etc…

Year 0-3
1-2x1000L

Year 4-6
3x2000L

Year 7-12
n x 2000L
SmartFactory: Example Polpharma

Polpharma – biologics facility
Gdansk, Poland (Q1 2015)

1,000L single-use train

Two bio-similar drug products
initially with four in pipe-line

Full automation upstream +
OPC integration downstream

Full validation

Used equipment purchased
wherever possible
LG Korea GMP 4k Perfusion Production

Perfusion process:
- 2x 2000L SUBs with
- Single Use Condenser
- ATF

Seed train
- 100L SUB
- 250L SUB
- 500L SUB
- 1000L SUB

2012 commissioning phase
SmartFactory Reference: Alvotech

Alvotech Production Facility
Reykjavik, Iceland (2015/2016)

6 x 2000L, 4 x 1000L,
in 2 suites, single-use/hybrid

Two bio-similar drug products
initially with further in pipe-line

Finesse’s project deliveries:
• Process Equipment
• Full automation
• Manufacturing Execution System (MES)
• Full validation
• R&D, PD lab equipment
New Wuxi Biologics GMP Production facility

Commercial Manufacturing, using Finesse’s control platform TruBio

- **Fed-batch** process has 2 trains with in total:
  - 14x 2000L Thermo SUBs,
  - 10 x SUBs as seed vessels.

- **Perfusion** processes:
  - 10x 3L glass vessels in Wuxi & Shanghai,
  - 250L SUB in Wuxi GMP manufacturing site,
  - 2x 1000L XDR, 4x seed vessels. Perfusion process is in engineering run stage (09/2016)

The new campus in Wuxi city will house the world’s largest fully disposable mammalian cell culture production plant. ... The facilities are expected to be operational by late 2016 and will support mAb, ADC and rprotein therapeutics.
Conclusions

- The current biopharma business models can be improved using continuous processing
- Paradigm is shifting from titer to process optimization and analytics (manage complexity)
- Smart Technologies exist today which can increase flexibility, decrease cost, and improve production
- Process intensification has been proven successful; Smart Systems will enable ease of use and wider deployment
Growing Installed Base
Over 1500 controllers sold in 10 years:
1000+ lab-scale units
450+ large-scale units
300+ cGMP
45+ 2000L Single-Use Bioreactors

Original supplier of USP Class VI Single Use Sensors
20’000+ sheaths shipped in bags
The proven solution in the market for BSL-3 applications
Make your process excellent.

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