

Process Intensification for Large Scale Manufacturing Issues

Case Study - Innovative Technologies Applied to Human Vaccines

Vaccine Technology II
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Who we are?

What is Artelis doing (1)

- Young company, created mid 2005
- Based in Brussels, inside the R&D site of the Solvay chemical company
- 25 people, 30 by end '08, 40 by end '09
- Pilot unit:
 - 500m², with 4 CR BSL2 and BSL3 for cell and virus culture
 - 3 additional CR under construction

Who we are?

What is Artelis doing (2)

- Design, development and industrialization of:
 - Components for “technical disposables”:
 - Range of disposable mixing systems for flexible bags – Jet Drive™, transferred to ATMI Life Sciences
 - Range of stirred tank disposable bioreactors – Nucleo™, in collaboration with ATMI Life Sciences and Pierre Guérin Biolaffite
 - We are not in front of the customers, we are not suppliers

Who we are?

What is Artelis doing (3)

- Design, development and industrialization of:
 - Cell culture-based processes, for the production of viruses, viral vectors, antibodies, rec-proteins:
 - Focused on disposables
 - Focused on high cell density (HCD) processes, by cells immobilization
 - We target:
 - Human and veterinary vaccines
 - Gene therapy
 - Monoclonal antibodies
 - Cell therapy

General Background

- Share some thoughts and data on process intensification as a mean to face current challenges:
 - Need for large quantities of vaccines:
 - Influenza: move from eggs to cell culture
 - Polio: move from attenuated to inactivated vaccine
 - Large cell culture scales will be needed
 - Need for cost control & cost reduction

Outline

- Teaching - Ratan Tata (CEO, Tata Motors)
- Process intensification:
 - Costs: is the “plastic factory” a valid way for cost reduction?
 - Capacities: increasing volumetric yields
 - Is it a valid way for increasing capacities?
 - Is it a valid way for additional cost reduction?
- Teaching - Oscar Wilde (Poet, 19th century)
- Some examples – HCD achievements and targets

Teaching from R. Tata (1)

- Tata Nano launched Feb 2008 at New Delhi car show, at 2500\$
- Cheapest car in the world, the new “volks wagen”



Teaching from R. Tata (2)

- Tata Motors succeeded in developing a product:
 - Need for large quantities
 - Need for cost reduction and cost control
 - Without decreasing safety / quality

Teaching from R. Tata (3)

(Business week Feb27 2008)

- How did they do (I) ?
 - ... looking at everything from scratch:
 - “Ghandian engineering” principles: deep frugality with a willingness to challenge conventional wisdom
 - 40 patents associated with the design of Nano:
 - vs 280 patents awarded to GM each year...
 - Measuring progress solely by patents creation misses a key dimension of innovation: most valuable innovations take existing patented components and remix them in a way that more effectively serve a large number of customers

Teaching from R. Tata (4)

(Business week Feb27 2008)

- How did they do (2) ?
 - Most innovative aspect... modular design:
 - Nano is constructed of components that can be built and shipped separately to be assembled in a variety of locations
 - Nano can be sold in kits that are distributed, assembled and serviced by local entrepreneurs
 - R.Tata to *The Times*:
 - ...we will create entrepreneurs across the country who will produce the car
 - ... we will produce mass items and ship to them as kits; that's my idea of dispersing wealth

Teaching from R. Tata (5)

- Integrate the whole product chain, from early research to packaging and distribution: where is the cost?
 - Challenge current paradigms
 - Define targets and the “good enough” product
 - Avoid “innovation for innovation”, as a marcom tool
 - Main costs they identified are avoided:
 - Stocks of finished cars
 - Transport of finished cars



Process Intensification

- Costs: is the “plastic factory” a valid way for cost reduction?
- Capacities: increasing volumetric yields
 - Is it a valid way for increasing capacities?
 - Is it a valid way for timelines reduction?

Process Intensification

- Interim conclusions:
 - Yes, a plastic factory makes sense for
 - Capital investment reduction
 - Operational costs reduction
 - Financial risk reduction
 - Significant reduction of timelines – first on the market
 - Yes, increasing volumetric yields makes sense for
 - Maximizing chances of supply large amount of doses
 - Avoiding risky investment before having clinical results



Process Intensification Plastic factory

- Case study:
 - Process
 - Cell culture at 1000L, adherent cells on μ carriers
 - Standard purification process
 - “From scratch” comparison
 - Between:
 - Stainless steel factory with classical agitated bioreactors
 - Plastic factory
 - Assuming identical output (doses per year)
 - Identical level of quality

Process Intensification Plastic factory

- Comparison based on:
 - Internal work at Artelis, especially modeling of PD timelines and costs (investment & operational)
 - Validation by external engineering professionals (Solvay)
 - Validation by external business development companies (Alcimed, Genaxion)
 - Challenged by literature ([references](#) in attachment)

Process Intensification Plastic factory

- Comparison focused on :
 - costs
 - investment
 - operational
 - timelines / speed to market / economical impact
- Additional thoughts on :
 - quality
 - risk management



Process Intensification Plastic factory

- Costs (1)
 - Avoiding CIP & SIP : total water economy was estimated at around 130m³ per batch (only \cong 10m³ needed for the process)
 - Avoiding CIP & SIP leads to :
 - Dramatic decrease in the need for cleaning and rinsing water / Dramatic downsizing of WFI loop
 - Dramatic decrease of neutralization, or other treatments of waste fluids / infrastructure

Process Intensification Plastic factory

- Costs (2)
 - Moving to a plastic factory leads to :
 - Decrease in the need for washing and autoclaving (materials and assemblies) / infrastructure
 - Significant reduction in the surface area, autoclaves, HVAC
 - Significant increase in the cost of materials / disposables

Process Intensification Plastic factory

- Costs (3)
 - Investment reduced by 60%, from €40 Million to €17 Million
 - WFI loop, power supply (WFI + decontamination)
 - HVAC, equipment
 - Surface area
 - Operational costs reduced by 30%
 - Maintenance
 - Manpower
 - QC, QA
 - Materials/disposables
 - Fluids
 - Energy consumption



Process Intensification Plastic factory

- Costs (4) :
 - In addition, 2 years in advance are highly valuable. Money-saving model gives a range from €300 million to €900 million, in the frame of this case study:
 - 2 competitors
 - Several times in advance
 - 7\$/dose
 - Different market penetration rates
 - Asymptotic 50-50 market share



Process Intensification Plastic factory

- Speed to market : time saving estimated by considering (1) :
 - Quality & compliance / process:
 - IQ/OQ/PQ
 - CIP/SIP, validation
 - Process development: avoiding CIP & SIP allows quicker turnarounds and increase “development capacity” in a given space and with given resources

Process Intensification Plastic factory

- Speed to market : time saving estimated by considering (2) :
 - Production of clinical batches under GMP conditions
 - Building, both from scratch, a plastic factory and a classical manufacturing facility
 - Everything was put on a timeline, including clinical studies

Process Intensification Plastic factory

- Speed to market : conclusion

It is reasonable to expect a 18-24 month saving when a Plastic factory is implemented, compared to a traditional “all stainless steel” factory



Process Intensification Plastic factory

- What about quality?
 - CIP & SIP often mentioned among GMP deficiencies (inadequate validation) – avoided in a plastic factory
 - Cross contamination / change-over procedures significantly reduced in a plastic factory
 - Constrains on suppliers:
 - Raw material origin and traceability
 - Sterility validation
 - CR manufacturing and assembly

Process Intensification Plastic factory

- What about risk management?
 - Financial risk: investing in large scale unit for Phase III clinical batches not requested - plastic factory allows final scale production in pilot rooms
 - Investment in manufacturing facility can be delayed as timelines are reduced for building and its validation



Process Intensification HCD cultivation

- What if:
 - Volumetric productivity increased by 25 compared to standard bioreactor with cells on μ carriers
 - Size of the bioreactor decreased by 25, with identical cell media consumption
 - Adherent cell culture implemented in a fixed-bed bioreactor:
 - Avoid implementation of L-S separation for perfusion
 - Avoid scaling up to large scales (100L would be equivalent to 2500L)

Process Intensification HCD cultivation

- Consequences
 - No need for a large scale facility:
 - For scaling-up to large scale
 - For manufacturing of Phase III efficacy batches
 - Debottlenecking for product development
 - Avoid technical difficulties related to scaling-up adherent cell culture at very large scales:
 - Maximize the probability of success



Teaching - Oscar Wilde

- Facts / rationale / perception

“Truth is rarely pure and never simple”,
The importance of being earnest, 1895, Act I



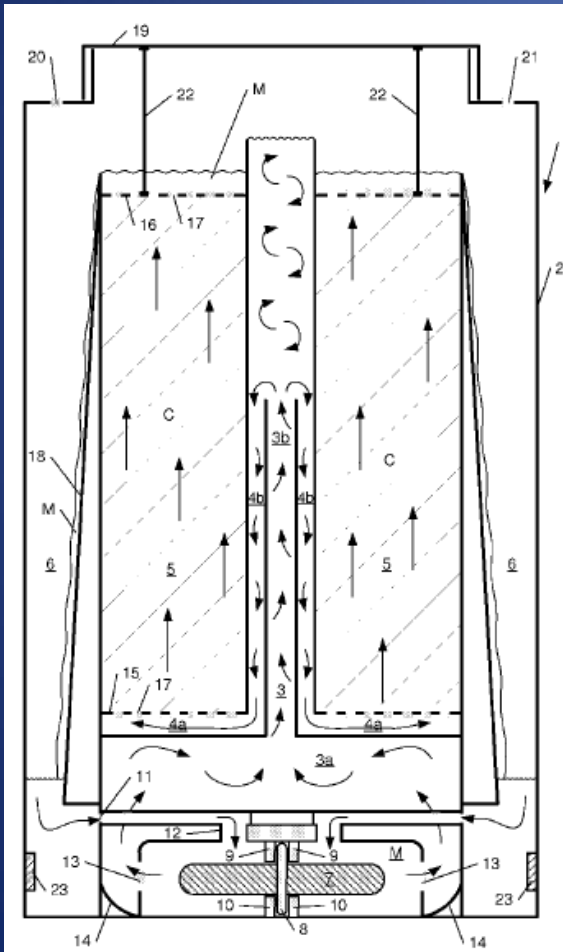
Process Intensification Volumetric Yields

High-Cell-Density disposable bioreactors:

– ARTELIS has several patents pending for a cell culture technique at high cell density (in fixed-bed bioreactors) in disposable bioreactors

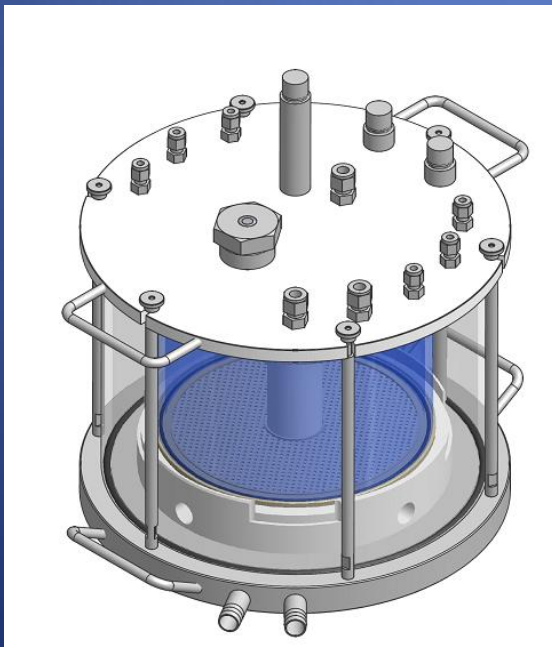
– Principle

- Fixed-bed: cells adhere to carriers
- Integrated medium circulation for oxygenation and nutrients
- Design in line with single-use bioreactor



Process Intensification Volumetric Yields

- Scales (prototypes) available today:
 - 5mL, 100mL, 500mL & 5L of fixed bed
 - 5L: controlled HCD (biomass probe, 2 DO probes, 1 pH probe, temp probe, feed in, perfusate)



Process Intensification

Volumetric Yields

- Feasibility – biological models
 - [MDBK cells](#) / Bovine Herpes Virus
 - Mab expression in [CHO](#) clone from Selexis
 - [Summary](#)
- Additional experience and validation with:
 - Vero cells (with and without serum) with 3 human viruses
 - MDCK cells
 - CEF

Process Intensification

Volumetric Yields

- MDBK – BHV model (I):
 - Screening of cell culture conditions at very small scale (5mL of fixed bed):
 - Screening parameters:
 - Cell density at seeding
 - TOI, MOI, media renewal, harvest time
 - Up to 15 cultures in parallel
 - Predictive of pilot scale experiments
 - Cell densities up to 40 – 60 M cells/mL
 - Viral production per cell similar to stationary cultures

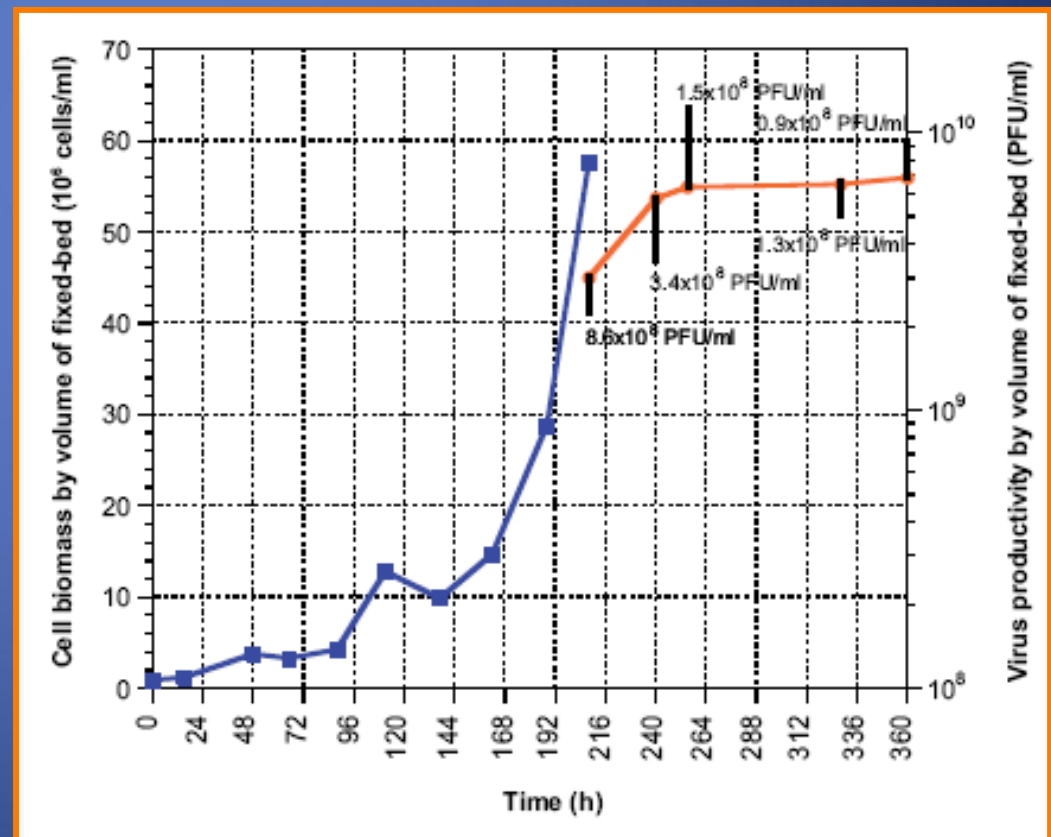
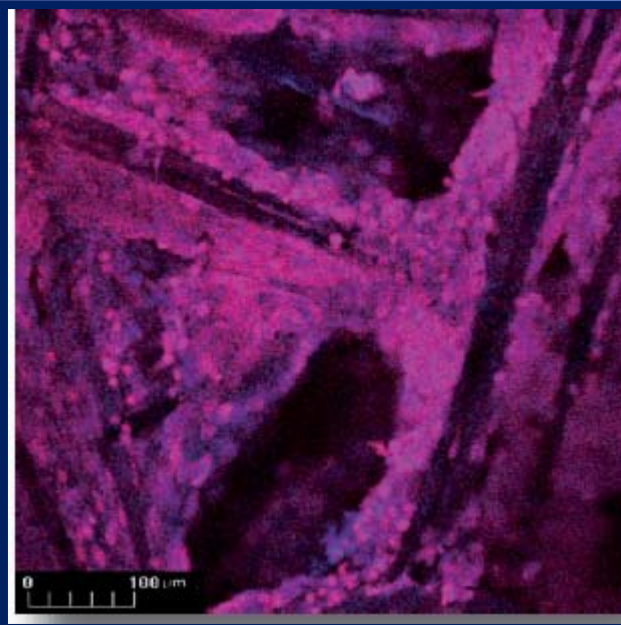
Process Intensification

Volumetric Yields

- MDBK – BHV model (2):
 - Implementation of better culture conditions at pilot scale of 500mL:
 - 60×10^6 cells/mL
 - Similar cell densities vs to small scale
 - Similar viral specific productivity

Process Intensification Volumetric Yields

- MDBK – BHV model (3):
 - Culture at pilot scale of 500mL:



Process Intensification

Volumetric Yields

- MDBK – BHV model (4):
 - Comparison with 10L culture with Cytodex1 (6g/L)
 - Viral titer:
 - 1×10^8 pfu/mL in classical culture
 - 2×10^9 pfu/mL_{fixed bed} in fixed bed
 - Volume reduction: 20



Process Intensification

Volumetric Yields

- Mab in CHO model (I):
 - Same methodology:
 - Screening of cell culture conditions at 5mL of fixed bed
 - Implement best conditions at 500mL of fixed bed
 - Compare to fed-batch process in 100L bioreactor
 - Both are 10 days processes
 - No savings of cell culture medium

Process Intensification Volumetric Yields

- Mab in CHO model (2):
 - Results:
 - 250×10^6 cells/mL_{fixed bed} in fixed bed
 - 5×10^6 cells/mL in fed-batch agitated culture
 - 20g/L in fixed bed (2g/L/day)
 - 250mg/L in fed-batch
 - Volume reduction: 80



Process Intensification Volumetric Yields

- Summary

Biological model	Cell densities reached by volume of fixed-bed	Cell Factories or Roller Bottle number equivalent to a 25L fixed-bed	Standard stirred tank reactor volume equivalent to a 25L fixed-bed
MDBK/BHV	60x10 ⁶ Cell/ml	250 CF40 or 7300 RB	500L
CHO/MAb	250x10 ⁶ Cell/ml	N.A.	2000L

Process Intensification Volumetric Yields

- Objectives:
 - Scale-up fixed bed bioreactor to 100L
 - Implement customized process control unit
 - Reach a consistent 25x volume reduction for viral processes, compared to reference production on Cytodex (human and some vet vaccines)
 - Reach a consistent ratio: 1L fixed bed / 300 Rollers (vet vaccines, some human products on CHO and gene therapy)
 - Implement technology for cell therapy



Process intensification Plastic factory

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