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 (1) ?
  - … 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 µcarriers
    - Standard purification process
  - "From scratch" comparison
    - Between:
      - Stainless steal 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 ≅ 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 PhaseIII 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 µcarriers
  - 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

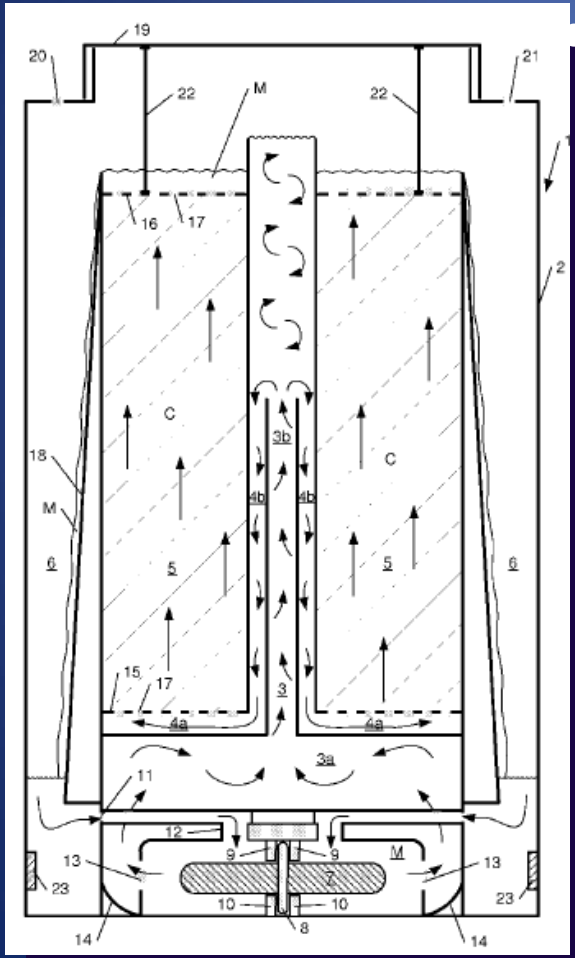
- Consequences
  - No need for a large scale facility:
    - For scaling-up to large scale
    - For manufacturing of PhaseIII efficacy batches
    - Debottlenecking for product development
  - Avoid technical difficulties related to scaling-up adherent cell culture at very large scales:
    - Maximize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

Teaching - Oscar Wilde

- Facts / rationale / perception

"*Truth is rarely pure and never simple*",
The importance of being earnest, 1895, Act1

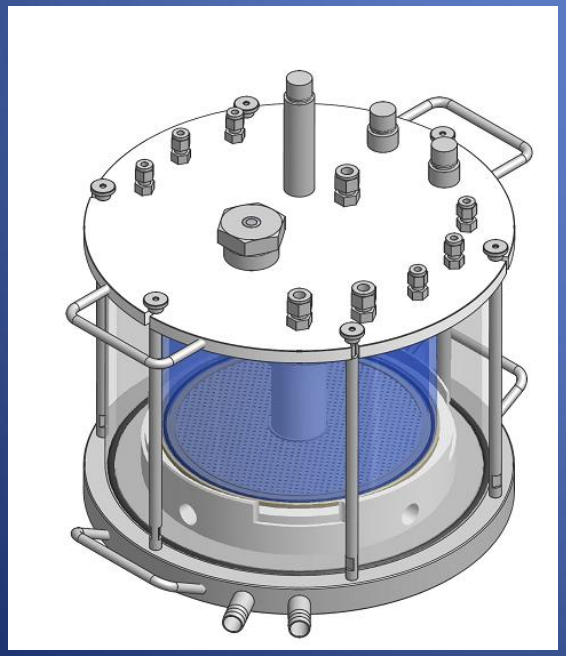
Process Intensification Volumetric Yields



- 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

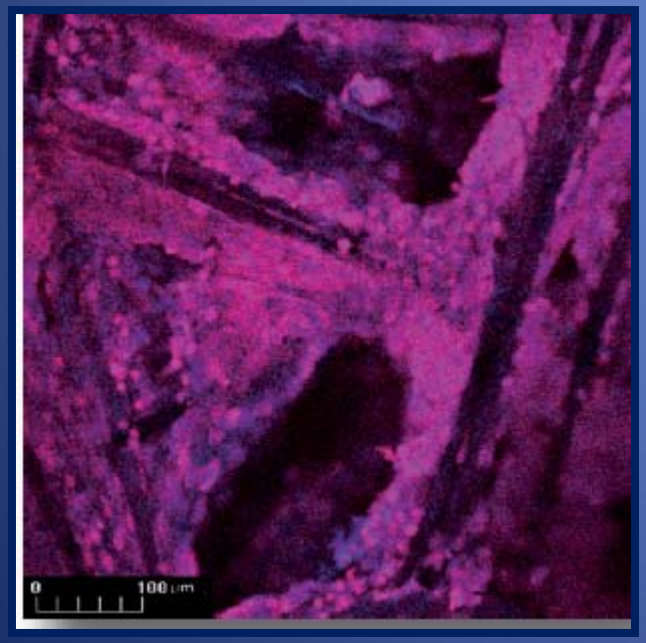
- MDBK – BHV model (1):
  - Screening of cell culture conditions at very small scale (5mL of fixed bed):
    - Screening parameters:
      - Cell density at seeding
      - TOI, MOI, media renewal, harvest time
    - Up to 15 cultures in parallel
    - Predictive of pilot scale experiments
    - Cell densities up to 40 – 60 M cells/mL
    - Viral production per cell similar to stationary cultures

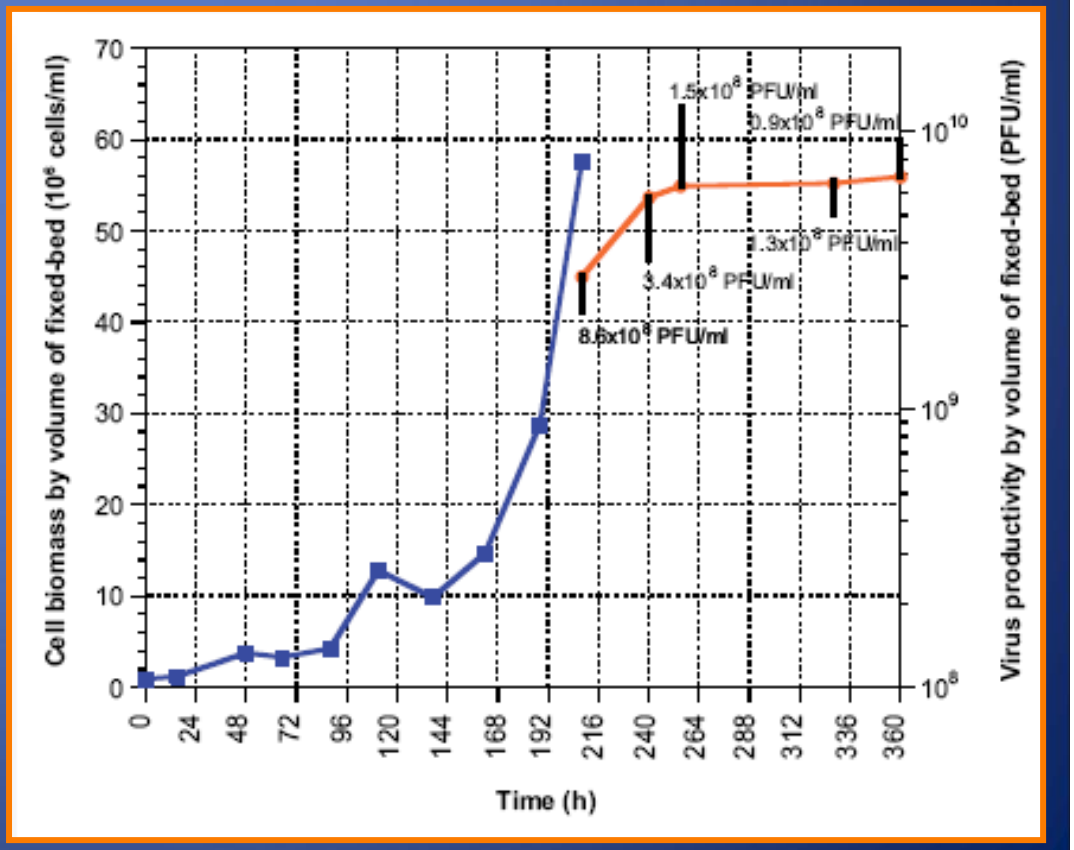
Process Intensification Volumetric Yields

- 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:
    - $1x10^8$ pfu/mL in classical culture
    - $2x10^9$ pfu/$mL_{fixed\ bed}$ in fixed bed
  - Volume reduction: 20

Process Intensification Volumetric Yields

- Mab in CHO model (1):
  - 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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