LFB Biomanufacturing

Case study: implementation of a new BioProduction Unit

* 2nd colloque BioProduction by Polepharma
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TOURS

Marc Vouillamoz – COO LFB Biomanufacturing
LFB BIOMANUFACTURING: an integrated business unit

✓ 20 years of experience in the development and the manufacture of *monoclonal antibodies* and *recombinant proteins* expressed in mammalian cells
✓ Offering **one stop shop CDMO services**: from Cell Line Development to GMP manufacturing of drug product
✓ Using flexible technologies with almost exclusively disposable systems.
✓ With distinctive customer practice focusing on flexibility and cost efficiency
✓ Pharmaceutical expertise and support of the LFB Group
One-Stop-Shop services: «à la carte» as a fully integrated CDMO

LFB Group

- Analytical (GLP/GMP) Development and Product characterization
- Formulation Development & stability studies
- Project Management
- SCG Process DS
- QA/QC
- Viral safety & Clearance studies
- Planning & Cost Control
- Viral Testing
- CLD & Process Dev / MSAT
- LFB Biomanufacturing
- API Certification
- Supply Chain and Logistics
- Regulatory Expertise & CMC filing strategy support
- GMP Fill & Finishing
- DP Pharmaceutical Release
- Project Team
- Your Needs
- Your Product

LFB

Scientific Advise and Expertise

Outsourced Activities

Program Management

DP Packaging

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History

1997: Founding of MAbgène company

2001: Certification ISO 9001

2003: New GMP facilities established (UP1)

2009: Implementation of 1,000L disposable bioreactor technology

2012: MAbgène becomes LFB BIOMANUFACTURING

2013: UP2 extension project pre-design

2016: New GMP facilities qualified (UP2)

2017: FDA Pre-Licensing Approval Inspection

2018: Implementation of new 2,000L disposable bioreactors

>45 batches @ 1000L Manufactured to date in SUT

300L SS bioreactor + DSP suites
Situation in 2011 and URS needs for the Future…

- Single Use oriented, CDMO Business continuity
- Low CAPEX, high flexibility
- Multiproduct FDA compliant, from clinical to commercial
- Support needs to match COGS for internal or external project
  - Be able to produce at 2000L scale
- DSP capable to process LFB commercial transgenic molecules (polishing steps)
UP2 Project History - a journey to align needs and evolve to the desired technology/capacity

- DD cost landing at final execution: Initial budget +30%
  - Encompassing contingencies.
  - PQ Run in GMP environment

- PROJECT APPROVED for EXECUTION

- Value Engineering exercise: -20% CAPEX saving to fit budget
  - Prioritization
  - Postponed options while maintaining later opportunities upgrade
  - Cost & Value engineering

- Updated full DD = +50% budget increase
  - Full scope for 2x2000L USP/DSP including partial Process Modelling inputs

- DD Process Modelling study
  - Site capability assessments / long range plan, utilities requirement, staffing, COGs models
  - URS update

- Detail Design (DD) = +10% budget increase
  - Building/utilities
  - Process Equipments

- Conceptual Design = base 100 (contingencies 30%)
  - Biotech specialized Engineering company
Lowest CAPEX: existing building fitting, but...
Ideal Project scope construction scheme
Best compromise on the conceptual design

- Best balance between
  - CAPEX and benefits
  - Best global flows & moves
  - Flexibility for further investment
  - Land floor print optimisation
    - While matching LRP needs
  - Centralized « Utility Center »
  - Compatible with existing constraints
  - Acceptable retrofitting or revamping areas
  - Acceptable impact on a running facility
    - Phasing quite complex but doable
Cost Modeling for Next-Generation MAb Production - 2016

- 1000L SUT, 1 suite
- 2x2000L SUT, 2 suites
- 6x2000L SUT, 2 suites + alternative buffer strategy
- Global site extension required

Efficiency loss due to product Changeover and shutdown

Exemple of a process model assumption
6 pack bio model with a single pooling point

Key drivers for factory design or process fitting

- Harvest titer, pooling and splitting strategies
- Gassing demands/utilities needs
- Fed batch duration, global process timing / scheduling
- SplitDown ratio for cell culture/passage
- DSP and buffer prep/storage bottlenecking
- Process Intermediate stabilities / holding times
- DS Storage requirements
- Warehouse space requirements V/S safety stock
- Liquid and solid waste management
- Local QA requirements
- HSE safety levels as well as insurances expectations

- Water demand PW and/or WFI scheduling
- Product changeover times/frequencies
- Column handling/packing/storing strategies
- Staffing requirement
- Working shift models / workplaces
- GMP monitoring & Data Integrity, MES, ERP
- Automation strategy (Roadmap to e-Plant)
- Power supply constraints/emergencies
- External risks (eg: storm/flooding…)
- Expected flexibility and later improvements
- Process intensification expectations….
Actual LFB Biomanufacturing landscape

**GMP ZONES**
- **UP1:** 1000L in SUT
- **UP2:** 6*2000L in SUT
- **DSP In SUT**

**Support:**
- **Utilities:** 1600 m²
- **Warehouse:**
- **Technical floor:**
- **Offices:**

**PILOT/CLD LABS**

**ALES II**
- **Support:** 1600 m²

**UP2:**
- 535 m²

**GMP ZONE**
- **Media / Buffer Prep**
GMP Manufacturing Areas

• **UP1**:
  - GMP area: 1000L
  - Low - Medium titer (<1.5g/L)
  - Oriented to Phases I and II material
  - Or small scale / demand commercial needs
  - Up to 7g/L at 200L scale USP

• **UP2**:
  - GMP area up to 6*2000L USP capacity
  - Multiproduct ready
  - Scale-out approach compatible
Project pictures – Q2 -> Q3 - 2015
Project Pictures – Q1->Q2 - 2016
Project Picture – Q4-2016

[Images of a cleanroom environment with individuals in protective suits and equipment.]
Future Flexibility to match time and cost
Disposable USP PLATFORM
GMP batch readiness to industrial Scales

- Optimization
- Adjustments
- Scalability Proof of concept
- Facility fit design / Gap Assessment & Risk Analysis
  - Process model definition
  - Small scale Batch reference

50 L
200
1000 L
2000 L

Process Reproduction

Tech Transfert

GMP up or scale-out scaling manufacturing strategic decisions

Classical FedBatch Scale-out approach assessment
High Density Cell Culture Or perfusion
Large Scale manufacturing demand

CONFIDENTIAL
In-House manufacturing or CMO?

**Points to consider - when outsourcing to your CMO**

- Variable costs based on supply demand by avoiding under-utilization of your own factory and reducing risks in case of delays/failure
- Low (or no) investments / minimal commitments to be contracted
- Higher flexibility and speed to market thanks to available capacities
- Let you keep focused on next product development
- Be ready to find alternative supplier when demand is growing
- Maintain price competition pressure

➤ **Finally, consider to tech transfer back in-house the product while maintaining outsourced materials to „buffer“ the growing market demand and reduce the risk of a market supply shortfall.**

**Remember : Don’t put all your eggs in the same bucket!**
One-stop shop: From DNA to Drug Substance

CHO and Proprietary EMABling® CLD Platforms

« Platform-type » and customized process development options

Cost and time efficient to satisfy customer’s needs using latest disposable technologies

More than 45 batches produced at 1000L scale

Commercial manufacturing and FDA approval from 2017

Pharmaceutical expertise and support of the LFB Group

www.LFBbiomanufacturing.com
Thank You

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