



**Manufacturing and Operations in Biotech -
Challenges of GMP protein production
for a small biotech company**

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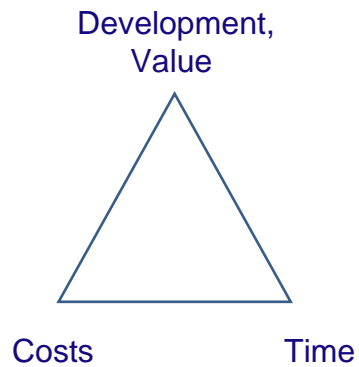
MED DISCOVERY
Corporate Information

- ✦ Founded in 2002 as a spinoff from University Hospital of Lausanne (Urology department)
- ✦ Med Discovery is dedicated to Uro-genital cancers
- ✦ Development of therapeutic protein-based drugs by using natural human proteins as template
- ✦ Med Discovery in 2009
 - ✦ Headquartered in Plan-les-Ouates, Geneva. 14 employees (8 Ph.D.s)
 - ✦ Director Operations & Preclinical Safety, Director Clinical Affairs
 - ✦ R&D : discovery, validation, analytical, manufacturing of biologics
 - ✦ Extensive clinical and R&D networks
- ✦ Lead compound (MDPK67b) in GMP manufacturing process development
 - ✦ GLP toxicology studies Q3/Q4 2009
 - ✦ IND filing beginning 2010

GMP MANUFACTURING CHALLENGES

Optimization of resources

- ✦ Manufacturing as crucial step in early biotech drug development



MANUFACTURING OF BIOPHARMACEUTICALS

Define your needs

- ✦ Intended use and quality requirements:
 - ✦ Research grade material
 - ✦ GLP/GMP-like material for preclinical GLP toxicology
 - ✦ GMP material for clinical trials
- ✦ How much material is needed?
- ✦ When is the material needed?

REGULATION OF GMP MANUFACTURING

Guidelines and their interpretation

- ✦ General GMP guidelines
 - ✦ 21 CFR Part 210 & 211 – cGMP for finished pharmaceuticals
 - ✦ 21 CFR Part 11 – Electronic records, electronic signatures
- ✦ Guidelines for APIs
 - ✦ ICH Q7A – GMP for active pharmaceutical ingredients
- ✦ Guidelines for API development
 - ✦ ICH Q8 – Pharmaceutical development
 - ✦ APIC – GMP in API development
- ✦ ...are some of the most important but there are many more
 - ✦ ICH :International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
www.ich.org

OUTSOURCED OR IN-HOUSE?

Strategic Choice

✦ In-house Production

Advantages

- ✦ Develop in-house expertise and process know-how
- ✦ Control of costs

Disadvantages

- ✦ Strong in-house investments
- ✦ Resources and competencies not readily available

✦ Outsourcing to a CMO

Advantages

- ✦ Increased speed
- ✦ Quick access to expertise and Facilities

Disadvantages

- ✦ Loss of direct control
- ✦ Communication, management capacity

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- ✦ Outsourcing as logical choice for small biotech
- ✦ External advice might be required

CMO SELECTION

Main Criteria

- ✦ Expertise, experience and reputation
 - ✦ USP (microbial vs. mammalian production), DSP
 - ✦ Analytical service
 - ✦ Track record, clinical batches
 - ✦ Accreditations for GMP (EMEA, FDA, ..)
 - ✦ Financial stability
- ✦ Adequate facility capacities
 - ✦ Fermentor sizes, capacity availability
- ✦ Responsiveness, resource and capacity availability
- ✦ Company culture
 - ✦ Small vs. large CMO
 - ✦ Priority
- ✦ PRICE
 - ✦ FTE/time based vs. objective based pricing with risk sharing

CMO SELECTION

Tender - Collaboration Phases

- ✦ Strain construction and Development
- ✦ Technology transfer
- ✦ Cell banking
- ✦ Process and Analytical Development, Repeatability
- ✦ Scale-up
- ✦ cGMP manufacturing
 - ✦ Formulation
 - ✦ Stability
 - ✦ Fill & Finish
- ✦ (Regulatory support)

- ✦ Economic Feasibility Checks at all phases

CMO SELECTION

Key points

- ✦ Do both parties understand the project and what is needed?
Detailed scoping of analytics, fermentation, DSP, regulatory
 - ✦ Opportunities, expectations
 - ✦ Minimize/delay expenses ('Fast track') vs. increasing value of project (time to market)
- ✦ Assessment of technical and economical feasibility, schedule, risks
 - ✦ Robust, scalable process
 - ✦ Cost of goods (yield, productivity)
- ✦ Clearly defined, strong project management, low staff turnover
 - ✦ Involved staff
 - ✦ Communication (by phone and on-site)
 - ✦ Definition of formal GO / NO-GO milestone and report
 - ✦ Delays, overrun costs
 - ✦ On-site visit, expert audit

CASE STUDY

Protease Inhibitor MDPK67b manufacturing

- ✦ Transfer of in-house process to small CMO for GMP process development: Protein'eXpert/PX'Therapeutics, Grenoble, France
 - ✦ E.coli, soluble protein
 - ✦ In-house lab scale process, shake flask (total > 2 grams mainly for R&D, analytical development and non-GLP animal studies)
- ✦ PX:
 - ✦ Successful strain construction and GMP cell banking
 - ✦ Development of 5 liter process and analytical methods
- ✦ Collaboration stopped during 30 liter upscaling due to technical and capacity problems
 - ✦ Protein degradation due to process duration and temperature increase (no prior scale down of process)
 - ✦ Additional equipment required
 - ✦ Fermentor size limitations (yield below expectation, increased needs)
 - ✦ Accumulating cost and time overruns

CASE STUDY

Protease Inhibitor MDPK67b manufacturing

- ✦ Decision to change CMOs (after 12 months)
- ✦ Evaluation of CMO alternatives (3 months)
 - ✦ 28 CMOs identified
 - ✦ CDA with 10 CMOs, technical discussions
 - ✦ Offers ranging from 0.8 M€ to 2.7 M€ including
 - optimization of existing process
 - completion of analytical development
 - production of tox batch
 - ✦ 4 CMOs selected for detailed evaluation and on-site visits
- ✦ Set-up of a broad bioprocess development partnership with Canadian CMO Laborium Biopharma
 - ✦ Subsidiary of Validapro Biosciences Inc., Montreal
 - ✦ Risk sharing development approach
- ✦ Tech transfer: 1 year of delay, 1 M€ additional costs