An Effective Third Party Manufacturing Model for Speedy Technology Transfer and Quality Oversight

Simon Hsu, Ph.D., Bristol-Myers Squibb
2014 CMC Strategy Forum
July 21-22, 2014, Gaithersburg, MD
Outlines

- Strategic Sourcing to Korea
- Technology Transfer to Samsung Biologics
- Chemical Import Requirements in Korea
- BMS Model for Third Party Manufacturing
- BMS Technology Transfer Model
- Technical and Quality Oversight
- Conclusions
Strategic Sourcing to Korea

Korea has well developed microbial fermentation industrial but limited track record in mammalian cell culture.

Biologics CMOs are mostly located in Songdo New City, a Free Economic Zone near Incheon.

- Tax breaks, cash grants and inexpensive land

Cost advantage is about 20% – 30% over leading competitors in the West

- Lower labor costs offset by the cost for global talents
- Lower asset-depreciation and over-head costs

Top-notch, Europe- and US-based construction and engineering (C&E) firms for the construction of first Korean CMO facility – Celltrion

- Building cost of Celltrion’s 50,000 L facility was estimated at $120 million, about 40% less than other facilities of comparable size and capacity*.

* Source: “Celltrion Bringing 50,000 Liters of Cell Culture to South Korea in 2006, Triple by 2010”, 04 March 2005 21:40, ICIS Chemical Business
BMS as a CMO Sponsor in Korea Since 2005

- 2005.6.21 BMS signed manufacturing agreement with Celltrion.
- 2007.12.18 FDA approved Celltrion to manufacture Orencia.
- 2013.7.18, BMS and Samsung Biologics (SBL) entered into a 10-year manufacturing agreement.
- 2014.4.22, BMS and SBL expanded manufacturing agreement.
## Successes from 1<sup>st</sup> Tech Transfer to SBL

<table>
<thead>
<tr>
<th>Success</th>
<th>Key Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met initial OOF date set during kickoff: 3 ½ months</td>
<td>1. Good working relationship – trust, respect, quick resolution of issues</td>
</tr>
<tr>
<td></td>
<td>2. BMS’s willingness to share documents, experience, and materials necessary</td>
</tr>
<tr>
<td></td>
<td>3. Common goal – OOF date</td>
</tr>
<tr>
<td>Completed 8 RM co-validation</td>
<td>Collaborative working relationship</td>
</tr>
<tr>
<td>Flexibility and effort by both teams</td>
<td>Fair, and trusting relationship</td>
</tr>
<tr>
<td>Quick turnaround of review and approval</td>
<td>1. Hard working team members</td>
</tr>
<tr>
<td></td>
<td>2. Common goal</td>
</tr>
<tr>
<td></td>
<td>3. Good working relationship</td>
</tr>
</tbody>
</table>
### Opportunities from 1st Tech Transfer

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Improvement Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last minute changes</td>
<td>1. Earlier discussion of process details such as MBRs</td>
</tr>
<tr>
<td></td>
<td>2. More accurate document review first pass</td>
</tr>
<tr>
<td></td>
<td>3. Better sampling plan</td>
</tr>
<tr>
<td></td>
<td>4. Earlier establishment of control strategy, MBRs, and SOPs</td>
</tr>
<tr>
<td>Urgent reviews and approvals</td>
<td>1. Document approval process managed better with more realistic dates</td>
</tr>
<tr>
<td></td>
<td>2. On-site technical discussion and review earlier can reduce overall review and approval cycle time</td>
</tr>
<tr>
<td>Delay in RM co-validation</td>
<td>Earlier completion of RM testing requirements and gap analysis</td>
</tr>
<tr>
<td>Earlier establishment of Bill of Material and procurement of RM</td>
<td>1. Earlier discussion of process details</td>
</tr>
<tr>
<td></td>
<td>2. Earlier establishment of control strategy, and MBRs</td>
</tr>
</tbody>
</table>
Korean Toxic Chemical Control Act

Samples or chemicals imported to Korea need to be registered in the system of the Korean Chemical Management Association (KCMA).

To do so, the following items are required:

- Information regarding the component - name, quantity, purpose of sample, manufacturer, Client personnel in charge, etc.
- Packing/Commercial Invoice - stating all the components and quantities of the samples to be sent
- Material Safety Data Sheet (MSDS) and Certificate of Analysis (CoA) - MSDS required for chemical registration, CoA required for material release by CMO

The Safety, Health and Environment (SHE) department of a Korean CMO will complete the chemical registration for you.
BMS Model for Third Party Manufacturing (TPM) World Wide

- BMS Biologics TPM model is based on 10 years of experience with CMOs across US, Europe, and Asia.
- BMS Departments that are 100% dedicated to TPM oversight.
  - Biologics Third Party Manufacturing
    - Project Management
    - Strategic Sourcing
    - Process and Analytical Specialists
  - Biologics TPM Quality Assurance
  - Staffed with individuals with prior knowledge of large scale biologics manufacturing
- Matrix support from MS&T, ADT, and PD
- New TPM Facility Construction
  - Emphasis on facility qualification and readiness for cGMP manufacture
- New / inexperienced TPM
  - Significant investment in on-site resources to ensure success
- On-site QA and/or technical offices
Technology Transfer Model

Tech Transfer Protocol

- Approved between BMS and TPM at the onset of tech transfer

<table>
<thead>
<tr>
<th>Transfer of Know-How</th>
<th>Gap Analysis</th>
<th>Small Scale Test Run</th>
<th>Full Scale Dev Run</th>
<th>Full Scale GMP Campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Batch Records</td>
<td>• Facility-Fit</td>
<td>• Vial Thaw</td>
<td>• Upstream</td>
<td></td>
</tr>
<tr>
<td>• SOPs</td>
<td>• Process Adjustments</td>
<td>• Media Preparation</td>
<td>• Downstream</td>
<td></td>
</tr>
<tr>
<td>• Flow Diagram</td>
<td>• Regulatory Impact Assessments</td>
<td>• Cell Counting</td>
<td>• BDS Testing</td>
<td></td>
</tr>
<tr>
<td>• Bill of Materials</td>
<td></td>
<td>• Inoculum Expansion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Training</td>
<td></td>
<td>• Column Packing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Initiate Method Transfer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bristol-Myers Squibb
Defined Teams and Responsibilities

Steering Team Committee
- Joint Steering Committee
- Quality Council
- Quality Agreement
- Legal Contract (Supply Agreement)
- Supply Chain Management
- Go/No-Go Decisions in Each Stage of Technology Transfer

Technical Team
- Training of Process Know-How
- Facility Fit Analysis
- Process Performance Analysis and Recommendation
- Analytical Testing Method Transfer
QA People in the Plant (QA PIP)

Implementation of QA PIP

- Full time presence at the TPM, including time between campaigns
- Factors which influence decision to hire QA PIP
  - Commercial manufacture
  - New facilities
  - 30+ lots per year
  - Long geographical distance (e.g. Asia)
- Staffing:
  - 1 Manager (release authority)
  - 1-3 QA Specialists used for batch review

QA PIP Activities

- Follow BMS SOPs specific for QA oversight of TPM activities
- Review and approval of: batch records, change controls, deviations
- On-site drug substance disposition
- On the floor presence for troubleshooting
Technical Subject Matter Experts (SMEs)

Technical SMEs located at the TPM for initial scale-up / GMP runs and process validation campaigns

- On-the-floor coverage for all manufacturing shifts
  - Ensure process performed correctly
  - Real-time trouble shooting
- Analytical SME’s present to monitor release testing of first GMP lot
- Successful campaigns at TPM results in on-time IND/BLA submissions

Routine production: BMS SME’s frequently at the TPM for select activities

- Column packing
- First few lots of manufacturing campaign
- Troubleshooting manufacturing and analytical issues
Current BMS PIP Model

Proactive approach

- Pre-campaign readiness meetings and gap analysis
- Facility and equipment walk through to ensure facility fit and equipment readiness
- Set expectations with CMO
- PIP trained at the process donor site

Phase-based approach

- Full-time PIP coverage during initial tech transfer and critical campaigns such as PPQ and PAI.
- Multiple functional coverage during technology transfer and PPQ until the manufacturing process is proven robust.

Site-based approach

- On-the-floor coverage depends on proximity and consistent performance of CMOs
- Quality/Technical offices have been set up for CMOs in Asia and Europe
Conclusions

Sourcing to Korea increases our biologics manufacturing capability and gives us the flexibility to respond to global needs of patients.

Sourcing to Korean CMOs can be successful if you have the experience and necessary resources.

Sponsor or License holder assumes overall and final responsibility for the product made at the CMO.

Successful quality oversight of CMO can only be achieved by an effective, integrated cross-functional team.

On-site quality/technical office is an integral part of BMS CMO oversight worldwide.