Efficient Project Management of Biopharmaceutical Development: Insuring on-time and Compliant Development Programs

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Managing Product Development

- Coordination of all development activities essential for uninterrupted product supply and phase-appropriate compliance
  - Analytical development must precede process development
  - Formulation development and product stability essential before initiating clinical trials
  - Process history will drive decisions on specifications
  - Incorporation of QbD early in development will streamline late stage production and reduce process deviations in the plant
Managing Product Development

- Process development activities drive supply of biopharmaceutical for clinical development
  - Initiation of clinical trial dependent on good management of process development
  - Decisions in early development may impact supply at later stages
- Effective project management tools will insure seamless coordination of all internal and external activities
  - Coordination across functional units for better overall project control
Integrated Project Planning

- Confirm goals, strategy, and assumptions
- Define development path and identify key decision points
- Create functional activity workplans and integrate among different functional areas
- Forecast resource requirements
- Identify the critical path
- Develop accelerate/decelerate scenarios
- Assess risks and develop contingency plans
- Document the plan and submit for approval
- Track progress along critical path

Set Development Strategy
- Strategic assumptions
- Key milestones
- Decision points

Develop Baseline Plan
- Activities with needed resources
- Supporting tasks
- Cycle times and key dependencies

Identify Recommended Path
- Acceleration/deceleration options
- Critical path and success factors
- Risks and issues

Finalize Deliverables
- Integrated Development Project Plan
- Critical path
- Stage contract
## Framework for Project Management

### Pipeline Review Committee
- Clearly defined decision makers
- Effective resource allocation
- Management of the development pipeline

### Stage Review Process
- Event-driven
- Business perspective
- Explicit deliverables
- Project contracts
- Stage-by-stage funding

### Structured Development Process
- Flexible guidelines
- Consistent terminology
- Inter-functional linkages
- End-to-end view

### Project Teams
- Small, cross-functional teams representing the entire project
- Effective communication and coordination
- Project focus with clear responsibility and authority for marketplace success

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From Clone to Commercial®
Robust Project Risk Management

- Identify all tasks on the project critical path
  - Critical path defined as the longest chain of sequentially dependent tasks
  - Delay of a critical path task will delay project completion
- Tasks likely to delay completion of the project include
  - Tasks that are resource limited or constrained
  - Tasks with very long or very aggressive cycle times
  - Tasks that are dependent on external sources
- For improvement opportunities, focus on items that directly impact the critical path
  - Efficient handoffs between departments or service providers can accelerate a project
Early Stage Development Activities

- Cell line generation
  - Gene and vector choice, selection criteria, speed vs productivity
- Process development
  - Upstream, recovery, and downstream
  - Process demonstration at development scale
- Analytical development
  - Method development, qualification, and/or validation
  - Reference Material
- Scale-up and cGMP manufacturing
  - Document preparation
  - Technology transfer to plant, engineering run(s)
- Stability testing of process intermediates and final bulk product
Cell Line Generation

- Production cell line is the crown jewel of any process
  - Focus on proper cell line development is essential
- Full documentation will streamline regulatory filings
  - Cell substrate origin and history is required
  - Sources of reagents used and documentation of ADC-free components must be included
- Decisions made during cell line development impact entire program
  - Time and cost to generate cell line with suitable expression levels
  - Cost of proprietary technologies may be offset by gains in time to initial clinical trial
  - Use of transient transfection or pools to make pre-clinical material increases regulatory and technical risk
Cell Line Development Requirements

- Gene encoding desired product must be available
- Appropriate expression vector should be selected
  - Proprietary systems can improve timeline but cost license fees
- Analytical methods must be available
  - Reference material for product comparison during development is essential
  - Potency assay should be available
- Once generated, production cell line must be banked to insure uniform input throughout product lifecycle
  - Two tier system is recommended but not required at initial stages of program
Managing Development to Achieve Goals

- Process development and analytical development are both essential to production of first clinical material
- Project planning should identify critical path tasks and focus resources on these tasks
  - Scheduling resources
  - Ordering materials
  - Sufficient personnel for critical path activities
- Examples of critical path activities that often delay programs
  - Potency assay development and validation
  - Ordering long lead time resins or column housings
  - Batch record preparation and review
Management of Process Development

➢ Tradeoffs between achieving high yields vs. speed to clinic
  • Timelines to IND may be increased by 1 year or more
  • However, program risk will be reduced as fewer process changes will be required throughout development
➢ Balance speed and cost, always maintaining quality!
Setting Achievable Goals in Development

➤ “Quick and dirty” process development
  • Reduces initial cost to enable early stage clinical trials
  • Increases risk of scale-up difficulty or batch failure
  • Requires greater costs later in development to optimize process, understand process parameters, and perform product comparability studies

➤ Develop processes that meet anticipated product needs
  • Focus on required yield, product quality, and scalability

➤ Develop process with intended manufacturing scale in mind
  • Same instrumentation at smaller scale preferred
  • Use scale-appropriate unit operations
  • Process steps should consider facility limitations
Coordinate Upstream and Downstream Process

- When possible, use intended production cell line and USP conditions for initial DSP development
  - If use non-optimized bioreactor output for initial DSP work, confirm results with final USP
- Upstream process changes, may alter performance of downstream unit operations
  - Change in ratio of product:contaminants
  - Change in input pH, salt, or protein concentration
  - Increased biomass may provide challenges in harvest or refolding
Analytical Method Development

- Analytical methods are a critical foundation for successful process development
  - Project management must insure concurrent and suitable analytical development at all program stages
  - Other program stages much be coordinated with analytical development
- Well characterized reference standard is key to bridging all stages of product development
  - Reference material must be available from program initiation
  - Initial reference material from discovery lab sufficient for early development
  - Final reference standard should be produced from final process
Technology transfer from development lab to production requires completion of many previous tasks

- Process development and demonstration
- Document preparation and training of GMP operators
- Raw materials sourcing, testing, and release
- Cell bank preparation, testing, and release
- Analytical methods qualification

Scale-up to production scale may be challenging

- Equipment differences
- Handling of larger volumes and longer processing times
  - Intermediate stability information useful
- Clogging or back pressure from increased biomass
Outsourcing and Project Management

Many development activities are outsourced
- Cell line construction, banking, and characterization
- Process development, formulation development, analytical methods development
- GMP manufacturing
- Pre-clinical
- Clinical studies
- Regulatory

Challenges of outsourcing
- Avoiding capacity crunches
- Technology transfer and monitoring of remote site(s)
- Ensuring timelines and proper documentation
- Protecting technology
### In-House vs. Contract Manufacturing

<table>
<thead>
<tr>
<th></th>
<th>In-House</th>
<th>CMO</th>
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<tbody>
<tr>
<td><strong>Product availability</strong></td>
<td>24 – 30 mon</td>
<td>18 – 24 mon</td>
</tr>
<tr>
<td><strong>Technology transfer/ process development</strong></td>
<td>$1.5 – 3 Million</td>
<td>$1.5 – 3 Million</td>
</tr>
<tr>
<td><strong>Cost per lot</strong></td>
<td>$1 – 1.5 Million</td>
<td>$1 – 1.5 Million</td>
</tr>
<tr>
<td><strong>Commitment (FTE)</strong></td>
<td>25 – 30</td>
<td>3 – 4</td>
</tr>
<tr>
<td><strong>Risk of process failure</strong></td>
<td>Company</td>
<td>CMO</td>
</tr>
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Outsourcing and Project Management

- Successful outsourcing results from establishing a core project team with defined responsibilities and established means for resolving issues
  - Maintain focus on ultimate goals so that no single activity consumes excessive time
- Begin preparations for outsourcing and technology transfer as early as possible
  - Management of technology transfer is essential to maintaining timelines
Management of biopharmaceutical product development requires technical expertise in all CMC activities as well as efficient project management tools to understand the duration and dependency of all CMC tasks, ensure seamless integration of all internal and external activities, and drive successful on-time regulatory submissions.

Critical path management provides a robust project risk management and mitigation methodology.
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