Risk-Based Speed: Approaches for Fast to FIH and Accelerated Commercial Process Development

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Presentation Outline

- BMS Biologics Portfolio
- CMC Development Timeline
  - Fast to First In Human
  - Commercial CMC Development for Breakthrough Designation
- Right First Time Scorecard
- Case Study
# BMS Biologics Portfolio

<table>
<thead>
<tr>
<th><strong>PHASE I</strong></th>
<th><strong>PHASE 2</strong></th>
<th><strong>PHASE 3</strong></th>
<th><strong>MARKETED</strong></th>
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<td>Pentraxin-2</td>
<td>FROSTVAC</td>
<td>OPDIVO®</td>
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<td>Lirilumab (Anti-KIR)</td>
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<td>YERVONY®</td>
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<td>HuMax-IL8</td>
<td>Ureumab (Anti-CD137)</td>
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<td>EMPLICITI™</td>
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<td>Anti-Fucosyl GM1</td>
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<td>Cabiralizumab (Anti-CSFIR)</td>
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<td>Anti-OX40</td>
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**Immunoscience**

**Fibrotic Diseases**

**Oncology**

Source: [www.bms.com](http://www.bms.com)
CMC Development Lifecycle

Traditional CMC Development

Pre-Clinical
Phase 1
Phase 2
Phase 3
BLA/MAA
Lifecycle

20 mo to develop a Phase 1 process and deliver clinical supplies

Commercial Process Development
Process Characterization
PPQ at Launch Site
Launch Supply
PMCs/FUMs
Lifecycle Management

3-4 Years

Accelerated CMC Development for Breakthrough Status

Pre-Clinical
Phase 1
Phase 2
BLA/MAA
Lifecycle

14 mo to develop and deliver Phase 1 supplies. Launch capable process

Process Characterization
Launch Supply
PPQ at Launch Site (Registrational Stability)
PMCs/FUMs
Lifecycle Management

18 months

Understand the potential for acceleration
 Acceleration Decision

Commercial Process Development. Begin characterization
Base Template of Fast to FIH Timeline and Activities

Key Enablers for Speed:
- Platform processes, analytical methods, specifications
- Template activities and timelines
- Perform activities in parallel
- DS & DP submission-enabling stability with non-GMP Tox material
- Quality Risk Management
- Tox lot production from top six RCB clones
Launch Capable FIH Process

Cell Line Development
- High performing
- Stable with no sequence variants
- No animal derived material contact

Upstream and Downstream
- Enable high performing robust processes
- Platform process controls, equipment
- Platform raw materials that are compendial grade

Analytical Methods
- Compatible with Commercial launch requirements
- Includes impurity characterization (ex. HCP)
- Leverage platform and compendial methods

Formulation and Vial Presentation
- Platform formulation and vial.
- Minimize change for commercial process.
Approach to Commercial Process Development

Governance Alignment
- Review by exception. Timely alignment on risks. Reduces time at governance

Commercial Process Development by Exception
- Leverage prior knowledge. Enables parallel development and characterization

Standard Work Practices
- Tools and templates guide routine work

Platform Process, launch capable FIH process
- Position papers document technical strategy and platform processes

Knowledge Management and Prior Knowledge

Right First Time Scorecard

Quality Risk Management
• Approach planned for all Drug Substance PPQ
• Position paper documents the approach
• One bioreactor with data from 3 consecutive batches
• Leverage prior knowledge demonstrating equivalency of equipment train
• Filtration reprocessing qualification done in lifecycle as qualifying events occur (supporting small scale data and protocol included in the BLA)
Drug Product Commercial Development: Risk Based Speed

- **Faster Process Development**
  - Lab, pilot and full scale equipment qualification. Enables use of data from multiple scales.
  - Matrix approach to covers min and max for multiple presentations
  - Limited experience at scale, mitigated by leveraging small scale models

- **Decrease Number of Batches at Full Scale**
  - Combine LTSS and PPQ
  - Matrix approach
  - Leverage data from engineering runs at site and scale for BLA filing and lifecycle.

Risk assessment based study design: Understand the risk and choose where to spend time and resources

Get the maximum data from minimum investment
Captures the deliverables (standard work) at each stage of the development lifecycle

Organized into categories and stage gates

Ensures organization adheres to standard work

Knowledge management
  – Incorporates lessons learned across programs, so that new assets achieve right first time.
  – It is updated continually as a place to store feedback from HAs and lessons learned across programs

Deliverables Groupings

Analytical Data/ Batch Information
Cell Line
Commercialization / Supply continuity
CQAs/Characterization/Comparability
Documentation
Facility Fit
Lifecycle / Process monitoring infrastructure
Methods
Packaging
Platform Fit
PPQ/Validation
Process Development/Process Characterization
Raw Materials
Reference Material Critical Reagents
Regulatory
Retain Library
Scale-up
Specifications
Stability
Tech Transfer

Categories
1. Analytical
2. Process - Upstream
3. Process - Downstream
4. Process - Drug Product
5. Raw Materials
6. Supply Chain
7. Commercialization

Right First Time Commercialization Scorecard
<table>
<thead>
<tr>
<th>Category</th>
<th>Grouping</th>
<th>Requirement</th>
<th>Target</th>
<th>Timing</th>
<th>Scoring Instructions</th>
<th>Score</th>
<th>Notes</th>
<th>Mitigation / Contingency</th>
</tr>
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</table>
| Analytical        | Specifications            | Specifications include all intended commercial stability methods            | Yes      | Pre-Registrational Stability batches | **Green** = yes  
**Yellow** = in progress or with some gaps identified with mitigation plans  
**Red** = No | | | |
| DS Upstream       | Process Development/ Process Characterization | Scale-down model qualified (include TOST analysis) | Complete | pre PPQ | **Green** = complete, no risks  
**Red** = incomplete | | | |
| Raw Materials     | Raw Materials             | DS and DP Materials Meet platform                                            | Yes      | Pre-Registrational Stability batches | **Green** = Aligns with platform  
**Yellow** = Outliers have acceptable business continuity  
**Red** = Outliers do not have acceptable business continuity | | | |

- CMC team evaluates their status against the standard work in the scorecard
- Risks are discussed at the CMC team. Teams determine how risk will be addressed (accept, mitigate, contingency, avoid)
- Governance ensures each team follows the standard process, endorses actions for the critical risks.
Overall portfolio view of risks, leading into registrational stability/PPQ campaign

- Leverage the analytics from the scorecard across programs.
- Understand and address portfolio wide risks

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<td>Design Space limited due to Accelerated Process characterization timeline.</td>
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<td>Work in progress</td>
<td>Stability profile</td>
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<td>Potential Volume change/vial change</td>
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<td>Work in progress</td>
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Case Study for a Monoclonal Antibody

**Right First Time Scorecard**: Key enabler to assess readiness and CMC risks for breakthrough programs. Team focus on these high risk areas. Proactively identify long lead time items and make investment decisions.

Determine launch readiness: Assess the current state of readiness against future requirements.
If granted breakthrough status, data and approach will need agreement with FDA/EMA.

**Breakthrough CMC Timeline Enablers:**

- No major process or analytical changes between the Phase 1 and commercial process.
- Commercial process development to occur at risk.
- Demonstrate analytical comparability between commercial process. Introduce into registrational trial
- Leverage clinical stability data with representative commercial supplies to establishing/support commercial shelf life.

**Risks**

- Increased lifecycle burden (PMC/FUMs)
- Expect post approval changes to increase robustness and productivity
BMS has several molecules in the pipeline that have the potential for accelerated review of breakthrough status.

Standard work is the key enabler to acceleration on a portfolio scale.

Applying the standard approach for molecules. CMC approach is planned for upcoming accelerated / breakthrough therapeutics.
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