Building a Cell Therapy Supply Chain:

Leveraging digital solutions to manage complexity, reduce risks, and set up for commercialization

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Founded in late 2018, Lyell needed to build its supply chain and manufacturing capabilities to deliver multiple autologous cell therapy platforms with an ambitious timeline. It was a rare opportunity to establish an end-to-end supply chain from the ground up.

**We implemented an early system strategy (pre-IND) that aimed to overcome the complexity of autologous cell therapy and avoid the costly & lengthy cutover from paper to digital.**

The result has been rewarding. We gained the speed, end-to-end visibility and robustness as designed and are positioned for rapid expansion.
Overview: Early System Strategy and Benefits

Use Case: Leveraging Systems to Mitigate Chain Of Identity (COI) Risks

Summary: Lessons Learned
Early system strategy to address challenges in GCT supply chain

**Clinical Facing Challenges**

- Apheresis and Tumor tissue as starting materials
- Maintain Chain of Identity (COI), Chain of Custody (COC) to prevent patient material mix up
- Frequent (>40%) patient apheresis/tissue schedule changes
- Coordinating patient for regiment prior to infusion
- Lack of visibility / real-time status to the end to end patient supply chain

**Manufacturing/Supply Chain Challenges**

- Multiple autologous therapy platforms
- Cryopreservation drug product logistics
- Sole source materials
- Manual workflow
- Duplicated entries in multiple systems
- Lengthy and resource consuming review of 500-1000+ pages of paper batch reports
- Painful to covert from paper to digital
- Long lead-time to scale/expand

**Autologous Cell Therapy: One Chance to Make it Right**
Strategic decisions that enabled Lyell’s early system strategy

What to achieve?
- Patient Scheduling
  - Flexibility / COI robustness
- Speed to clinical trial
- Scalable/Pivotal Ready
- Automated workflow
- Right first time
- Manual Batch Review

Roadmap
- Strategic
- Operational
- People

Strategic Decisions
- Invest in integrated systems early
- Paperless Operations
- Cloud only
- System fit for purpose
- Use out of the box functionalities. Avoid customization
- Automate workflow
- Part 11, Annex 16, HIPAA, Data Privacy Law, Security Compliant
- GMP System Team & CMC Program Management centralized in Supply Chain
- Patient operations and plant scheduling also centralized in Supply Chain
Early system strategy as a countermeasure of the complexity from the cell therapy manufacturing and supply chain

**Paperless Operations**
Streamline operations, built in control (COI) and error-proof

**Workflow automation**
System interfaces facilitate data exchange: ‘create once, use many’

**Agility and scalability**
Cloud enabled systems for rapid deployment and system capacity expansion, security, compliance

**Real-time data acquisition**
Real-time visibility of the end to end patient supply chain

**Advanced Analytics & Insights**
Integrating clinical responses, batch characterization and trending to enable decision making and optimization

Obeya room displays real-time visibility of patient cell journey and performance towards key production and operational deliverables
Lyell’s integrated GMP systems landscape

End to end system integration that enables the delivery of therapy to patients with the defined level of robustness
Workflow automation use cases and benefits

- Benefits
  - Single source of truth (create once)
  - Reduced COI risks of patient mix-up
  - Eliminated duplication & manual work
  - Increased compliance & data integrity
  - One approval workflow in source system
  - Error proofing

- Use cases
  - COI Automation/Propagation (Cell Orch. System -> ERP -> MES)
  - Materials Master / BOM Generation & Refresh (ERP -> MES ERP -> LIMS)
  - Work Order Creation / Automation with COI (ERP -> MES)
  - Inventory refresh (ERP <-> MES ERP <-> LIMS)
  - Equipment Maintenance Status broadcast (CMMS -> MES CMMS -> LIMS)
  - Sample Plan Automation (MES <-> LIMS)

Autologous Cell Therapy: One Chance to Make it Right
The goal of COI control is to ensure patients are treated with the right product

- A critical attribute for cell therapies is the identity and control of the source cells used to manufacture the therapy.

- For autologous cell therapies, the source cells are the patient’s own cells that are collected for processing.

- US and EU regulations have specific requirements regarding identification, tracking, and control of patient derived cells.

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<table>
<thead>
<tr>
<th>IMPACT</th>
<th>Product Quality</th>
</tr>
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</table>
| Critical Impact | - The event results in a direct impact to product quality, purity, potency, safety or efficacy  
|                 | - Patient death (i.e. GVHD)                                                    |
| High Impact     | - The event could result in a direct impact to product quality, purity, potency, safety, or efficacy  
|                 | - Patient not receiving therapy                                                |
## FMEA: potential failure modes in autologous patient cell therapy journey

<table>
<thead>
<tr>
<th>Common Root Cause Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batching or Multi-patient areas</td>
<td>Multiple apheresis and infusion at the clinics</td>
</tr>
<tr>
<td></td>
<td>Incorrect patient material is welded onto bioreactor, other equipment.</td>
</tr>
<tr>
<td></td>
<td>Manual aliquot of QC test samples from multiple patients</td>
</tr>
<tr>
<td>Manual entry</td>
<td>Incorrect COI number entered or assigned to patient</td>
</tr>
<tr>
<td></td>
<td>Incorrect COI/lot number is selected</td>
</tr>
<tr>
<td>Material movement</td>
<td>Transfer patient materials from one bag to another</td>
</tr>
<tr>
<td>Labeling</td>
<td>Attach wrong label</td>
</tr>
<tr>
<td></td>
<td>Missing label</td>
</tr>
</tbody>
</table>
Leveraging systems to increase visibility, eliminate, automate & mitigate COI risks and high impact areas

Simplified View
For Illustration Only

Clinical / Aph Site system
Cell orchestration platform
ERP Order Mgmt / Plant Scheduling
Manufacturing MES
Quality Control LIMS

Enrollment Aph/Tissue Scheduling Aph/Tissue Collection Transportation Manufacturing QA / QC Infusion Scheduling & Pkg Transportation Infusion

COI Connection/Verification

Lyell
### Leveraging systems to mitigate COI risks, increase visibility and efficiency

<table>
<thead>
<tr>
<th>Cell Orch. System &lt;-&gt; Plant Scheduling</th>
<th>Cell Orch. System &lt;-&gt; ERP</th>
<th>ERP &lt;-&gt; MES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What:</strong></td>
<td><strong>What:</strong></td>
<td><strong>What:</strong></td>
</tr>
<tr>
<td>• Automate, consolidate, enable flexible scheduling / rescheduling</td>
<td>• Automate the creation of work order with COI in ERP</td>
<td>• Automate the generation of work order with COI in MES</td>
</tr>
<tr>
<td><strong>Why:</strong></td>
<td><strong>Why:</strong></td>
<td><strong>Why:</strong></td>
</tr>
<tr>
<td>• Increase speed, visibility &amp; responsiveness.</td>
<td>• Mitigate COI risks</td>
<td>• Mitigate COI risks</td>
</tr>
<tr>
<td>• Optimize resource allocation / capacity utilization</td>
<td>• Efficiency</td>
<td>• Efficiency</td>
</tr>
<tr>
<td></td>
<td>• Eliminate manual error</td>
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</tr>
</tbody>
</table>

### MES <-> LIMS

<table>
<thead>
<tr>
<th><strong>What:</strong></th>
<th><strong>Why:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Integrate with MES to automate sample plan</td>
<td>• Eliminate manual work</td>
</tr>
<tr>
<td></td>
<td>• Prevent samples and patient mix-up</td>
</tr>
</tbody>
</table>

### MES COI Risk Mitigation

<table>
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<tr>
<th><strong>What:</strong></th>
<th><strong>Why:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Built-in COI verif. w/ materials movement</td>
<td>• Mitigate COI risks</td>
</tr>
<tr>
<td>• On demand labels w/ sys generated COI</td>
<td>• Prevent product / label mix-up</td>
</tr>
<tr>
<td>• Pre-allocate multiproduct workstation</td>
<td>• Prevent manual error</td>
</tr>
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</table>
Early system strategy - lessons learned

**Worked well**

- Early System investment
- Organizational design
- Prioritize with COI risk assessment
- Synchronize continuously based on CMC timeline

**Do Differently**

- Business process and data model before system integration
- System connectivity ahead of time
- System validation approach for cloud based systems and system integrations
- Coordinate across multiple systems and technical expertise for rapid issue resolution
THANK YOU!