IMLYGIC CASE STUDY: MANUFACTURING AND COMMERCIALIZATION OF AN ONCOCYTIC VIRUS PRODUCT

TIA BUSH
VICE PRESIDENT, SITE OPERATIONS
SERVING PATIENTS IS A PRIVILEGE...
THIS PRIVILEGE COMES WITH SIGNIFICANT RESPONSIBILITIES
TODAY’S OBJECTIVE

• Impart our experience with a “first in class” product
• Discuss how we challenged conventional thinking
• Share what the future holds on our continuing journey
DAWN OF THE BIOCENTURY
ACCELERATING IMPROVED PATIENT OUTCOMES
IMLYGIC® IS FIRST AND CURRENTLY ONLY APPROVED ONCOLYTIC IMMUNOTHERAPY

IMLYGIC (Im-LYE-jick): IMmune bolstering and precise LYsis of cancer cells, achieved through loGICAL design

Talimogene laherparepvec:

- TA limo gene
- LA herpa rep vec

- immunomodulating
- gene therapy
- herpes simplex virus
- replicating
- vector
THE PRODUCT HAS UNIQUE LOCAL AND SYSTEMIC MECHANISMS OF ACTION

- IMLYGIC has a proposed dual mechanism of action
- IMLYGIC® (talimogene laherparepvec) is engineered from herpes simplex virus 1 (HSV-1):
  - Attenuate the virus
  - Increase selectivity for cancer cells
  - Secrete the cytokine GM-CSF
- IMLYGIC is injected directly into a lesion
TALIMOGENE LAHERPAREPVEC PRODUCTION PROCESS OVERVIEW

- Small scale
- Single use
- Cold chain
AMGEN ACQUIRED PRODUCT AND MANUFACTURING SITE

- Formerly BioVex founded in 1999
- Acquired by Amgen in 2011
- Approved in US, EU, CH, AU
- Currently dedicated to the production of IMLYGIC™
  - Biosafety Level 1&2 permit
  - ‘Vial to vial’ facility
  - Single-use, disposable systems
ACQUISITION CREATED NEW OPPORTUNITIES

- Transition from R&D mindset to commercial approach
- Address cultural differences between companies
- Integrate quality and management systems
HOWEVER, THERE WERE CURVES AHEAD
FIRST IMPRESSIONS WERE DECEIVING

**Original Plan**
- Develop and validate -80°C secondary packaging line
- Submit marketing authorizations
- Host regulatory inspections

**Actual Plan**
- Conduct additional process characterization studies
- Complete quality risk assessments
- Conduct validation studies to meet regulatory requirements
- Develop and validate automatic labeling process
- Redesign aseptic core and add restricted access barriers
- Qualify primary container
- Complete extractable and leachable studies
- Develop and validate primary label, carton and seal for -80°C
- Develop and validate cold chain shipment for -80°C
- Develop and validate -80°C secondary packaging line
- Submit marketing authorizations
- Host regulatory inspections
UNIQUE PRODUCT CHARACTERISTICS IMPOSED NEW REQUIREMENTS AND LED TO NOVEL APPROACHES

Business Impact

- Updated manufacturing controls
- Novel testing requirements
- New validation approaches
- Tighter stability and testing criteria
- State-of-the-art packaging line
- Innovative cold chain solutions
- Unique labeling method

These actions allowed Amgen to deliver on our mission to serve patients
Adventitious virus testing performed in parallel

- In vitro and in vivo adventitious virus testing conducted on uninfected parallel culture sample due to interference from Talimogene laherparepvec virus

Drug product solution unable to be sterile filtered

- Extensive aseptic process simulation studies were conducted
- Hold time validations studies were critical

Original process design required manual mixing

- Comprehensive mixing studies were performed to support all mixing steps
- A detailed SOP was written and manufacturing staff were trained
- Regulatory agencies were very interested in this unit operation
CONTROLS TO MINIMIZE IMLYGIC® ADVENTITIOUS AGENT CONTAMINATION RISK BASED ON A MULTILAYERED APPROACH

<table>
<thead>
<tr>
<th>Manufacturing Process and Facility Design Features</th>
<th>Materials and Components</th>
<th>Operating and Procedural Controls</th>
</tr>
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<tbody>
<tr>
<td>• Closed systems</td>
<td>• Cell substrate proven safety profile</td>
<td>• Stringent bioburden and endotoxin limits using validated methods</td>
</tr>
<tr>
<td>• Robust environmental control and monitoring</td>
<td>• Cell banks and virus seed stocks test free of adventitious agents</td>
<td>• Validated pool hold times and temperature controls</td>
</tr>
<tr>
<td>• Restrictions on personnel and material movement</td>
<td>• Adventitious virus testing of bulk harvest material</td>
<td>• Validated processing durations</td>
</tr>
<tr>
<td>• Validated cleaning and decontamination procedures</td>
<td>• Raw materials and components with predefined specifications for adventitious agents</td>
<td>• Sterility and endotoxin testing prior to release</td>
</tr>
<tr>
<td>• Physical barriers for segregation</td>
<td>• Minimal animal derived materials</td>
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Controls were established to protect both our product and people
ONCOlytic VIRUS TESTING STRATEGY DID NOT FIT NEATLY WITHIN VACCINE OR BIOLOGICAL CATEGORY

<table>
<thead>
<tr>
<th>Category</th>
<th>Implication</th>
<th>Action</th>
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<tr>
<td>Viral Safety</td>
<td>Conventional method of demonstrating viral safety did not apply</td>
<td>Demonstrate viral safety through testing for each lot</td>
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<tr>
<td>Stability</td>
<td>More variables to be accounted for due to ultralow temperature requirements</td>
<td>Conduct extensive stability protocol and data set to cover end to end supply chain and product handling scenarios</td>
</tr>
<tr>
<td>Product Specification</td>
<td>Conventional criteria and methods did not apply</td>
<td>Rely on biological assays to demonstrate potency, strength and purity</td>
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Required extensive planning and education as product was adopted for use
ULTRALOW COLD CHAIN REQUIREMENTS DROVE INNOVATIVE SOLUTIONS THAT WERE AN INDUSTRY FIRST

Primary labeling and secondary packaging line at -80°C

Novel 2-part interlocking carton with cryogenic closure label

Cryogenic shippers to allow direct shipment to healthcare providers
PRE-FREEZE PRIMARY LABELING IMPACTS SUPPLY CHAIN NIMBLENNESS AND INCREASES RISK OF SHORTAGE

**IMLYGIC**

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<th>IMLYGIC Situation</th>
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<tr>
<td>Inventory hold spots</td>
<td>Less buffer in supply chain to accommodate demand discrepancies from supply plan</td>
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<tr>
<td>Long lead times for finished product</td>
<td>Demand built prior to use</td>
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<tr>
<td>Pre-freeze primary labeling</td>
<td>Regional inventory built prior to regional demand being known</td>
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REGULATORY SUCCESS REQUIRED SIGNIFICANT INVESTMENT FROM BOTH AMGEN AND THE REGULATORS

- No clear comparisons for “First in class” product to benchmark
- Required multiple meetings and large number of information requests to understand and evaluate novelty of product
- Did not follow the normal process for well-characterized biologics

Strong collaboration with regulators made IMLYGIC approval possible
WHAT’S NEXT FOR IMLYGIC?

• Complete clinical trials for combination therapies

• Manage complexities of cold chain

• Validate re-use of cryogenic shippers

• Improve productivity and efficiency of the manufacturing process
IN CLOSING

Contributors:
Brian Anderson
Tia Bush
Paul Husak
Richard Reineke
Kathy Sugrue-Richards
Maricarmen Szendrey