APPLICATION OF QUALITY RISK MANAGEMENT TO AN ONCOLYTIC VIRUS, IMLYGIC® (TALIMOGENE LAHERPAREPVEC)

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PRODUCT QUALITY
AMGEN, INC.
Application of quality risk management principles to an advanced therapeutic medicinal product (oncolytic virus) has facilitated control strategy changes and provided the agility necessary react to the unexpected.

• Today’s Agenda:
  ➢ IMLYGIC® Product Introduction and Process Description
  1. Establishing a product quality control strategy
  2. Conducting a virus control strategy risk assessment
  3. Reacting to unexpected risk
PRODUCT INTRODUCTION

- **Product Name:** IMLYGIC® (talimogene laherparepvec)
- **Modality:** genetically modified *oncolytic virus* (HSV-1)
- **Indication:** local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with *melanoma* recurrent after initial surgery
- **Administration:** *intralesional injection* in cutaneous, subcutaneous, and/or nodal lesions by Healthcare Provider
- **Mechanism of Action:**
  - IMLYGIC has been genetically modified to *replicate within tumors* and to *produce the immune stimulatory protein GM-CSF*.
  - IMLYGIC causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote antitumor immune response. Exact mechanism of action is unknown.

HSV-1 = herpes simplex virus type 1
GM-CSF = granulocyte macrophage colony-stimulating factor
QUALITY RISK ASSESSMENT MANAGEMENT PROCESS APPLIED TO IMLYGIC IS ALIGNED WITH ICHQ9

- Risk assessments covering different areas of production were performed
- FMEAs, PrHAs executed to identify and mitigate risks including the following areas:
  - Product Quality
  - Virus Control
  - Manufacturing Process
  - Raw Materials
  - Environment/Utilities
  - Drug Product Transport

Figure above taken from ICH guideline Q9 on Quality Risk Management
FMEA- Failure Mode and Effects Analysis
PrHA- Preliminary Hazard Analysis
KEY DIFFERENCES BETWEEN CLASSIC BIOLOGICS AND ONCOLYTIC VIRUS (IMLYGIC) MANUFACTURING

**Monoclonal Antibody**
- One production substrate – production cell line
- Purification process includes dedicated viral clearance steps
- Long term storage of drug substance – forward processing following disposition
- Drug product can be manufactured to order and labelled at time of manufacture

**Oncolytic Virus**
- Two production substrates – production cell line and viral seed stock
- Purification process designed to retain enveloped viruses - no viral clearance steps
- No long term storage of drug substance - forward processing at risk
- Drug product stored frozen - special considerations in place to enable flexibility in product labeling
• Challenge: Establish a commercial stage product quality control strategy for a new modality

  – Important considerations included…
    • Clinical specifications established a comprehensive product quality and product safety testing regimen

  – Approach…
    • Execution of a Product Quality Risk Assessment (PQRA) utilizing Quality by Design principles to define a phase appropriate control strategy for critical quality attributes

  – Outcome…
    • Documented risk analysis, evaluation and acceptance (as applicable)
    • Specification parameters transitioned to in-process control parameters, testing placed at appropriate points in the manufacturing process, removal of redundant testing
THE IMLYGIC PQRA WAS A TWO-STEP APPROACH THAT ASSESSED THE OVERALL RISK LEVEL OF CRITICAL QUALITY ATTRIBUTES

Step 1. Identify Critical Quality Attributes (CQAs) and Score Severity of CQAs

- Identify attribute categories
  - Process impurities
  - Function attributes
  - General attributes
- Identify individual attributes within each category
- Assess severity of each individual attribute
- Output of Step 1 is used to prioritize risk assessments

Step 2. Assess Likelihood of Occurrence and Detectability to Determine Overall Risk level

- Prioritize attributes with a severity score at or greater than a pre-determined threshold
- Identify and assess risks to product quality at each unit of operation in the manufacturing process
- Assess likelihood of occurrence and detectability
- Overall Risk Level determined through a combination of Severity, Likelihood and Detectability scoring
- Output of assessment is used to communicate and identify mitigations for Overall Critical and High Risks

Example of Output from Step 1

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Analytical Method</th>
<th>Potential Biological Impact</th>
<th>Overall Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Concentration</td>
<td>Virus Infectivity (Virus Titer)</td>
<td>Impact: Improper patient dose Safety: High dose could impact patient safety Efficacy: High or low dose could impact product efficacy</td>
<td>Numerical Value based on pre-determined scoring thresholds “7” used as an example</td>
</tr>
</tbody>
</table>

Example of Output from Step 2

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Overall Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Concentration</td>
<td>Low</td>
</tr>
</tbody>
</table>
QUALITY ATTRIBUTE RISK LEVEL IS ASSESSED AT EACH UNIT OPERATION; OVERALL RISK DETERMINED THROUGH PRE-ESTABLISHED RISK MATRICES

Product Quality Risk Assessment Example for One Unit Operation and One Quality Attribute

<table>
<thead>
<tr>
<th>Quality Attribute: Product Concentration (Virus Infectivity)</th>
<th>Severity Score : 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit Operation</td>
<td>Can Attribute Be Impacted by Unit Operation?</td>
</tr>
<tr>
<td>Filtration</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Product Concentration Overall Risk Level: Low

Table 1. Risk Matrix for Preliminary Risk

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>1 Insignificant</th>
<th>3 Minor</th>
<th>5 Moderate</th>
<th>7 Major</th>
<th>9 Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 – Frequent</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Critical</td>
</tr>
<tr>
<td>7 – Likely</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Critical</td>
</tr>
<tr>
<td>5 – Occasional</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>3 – Unlikely</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>1 – Remote</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Table 2. Risk Matrix for Overall Risk

<table>
<thead>
<tr>
<th>Risk Level from Table 1.</th>
<th>Almost certain</th>
<th>Very High</th>
<th>High</th>
<th>Moderately High</th>
<th>Moderate</th>
<th>Slight</th>
<th>Remote</th>
<th>Very remote</th>
<th>Absolutely uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Critical</td>
<td>Critical</td>
<td>Critical</td>
<td>Critical</td>
<td>Critical</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
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<tr>
<td>Medium</td>
<td>Low</td>
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<td>Low</td>
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<td>Medium</td>
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<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
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</tbody>
</table>

Public Information
USE OF VIRUS CONTROL RISK ASSESSMENT TO DETERMINE RISK OF CONTAMINATION THROUGHOUT THE MANUFACTURING PROCESS

• Challenge: Ensuring patient safety from viral exposure in a process designed to retain enveloped viruses
  – Important considerations included…
    • No viral inactivation or viral filtration steps; no validated viral clearance
  – Approach…
    • A comprehensive virus control strategy risk assessment using a failure modes and effects analysis process
  – Outcome…
    • Documentation of procedural and manufacturing preventions and control detections in place to minimize risk of the failure (virus contamination)
    • Justification for the replacement of a broad spectrum adventitious virus test with targeted nucleic acid tests
## Failure Modes and Effects Analysis Approach Used to Score Risk Level for Each Potential Cause of Viral Contamination

<table>
<thead>
<tr>
<th>Risk</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function/Requirement</strong></td>
<td><strong>Potential Failure Modes / Hazards</strong></td>
</tr>
<tr>
<td>No Viral Contamination</td>
<td>Drug Product has a viral contamination</td>
</tr>
<tr>
<td>No Viral Contamination</td>
<td>Drug Product has a viral contamination</td>
</tr>
</tbody>
</table>

Pre-defined risk ranking criteria enable more efficient risk assessment discussions but do not completely eliminate subjectivity in scoring.
USE OF AN ESTABLISHED VIRUS CONTROL RISK ASSESSMENT TO ASSESS RISK OF NEW AND EMERGING VIRUS OF CONCERN

- **Challenge: Assessing risk presented by SARS-CoV-2 pandemic**
  - **Important considerations included…**
    - FDA Guidance for Industry Response to COVID-19\(^1\)
      - Recommendation to perform a risk assessment of the current viral control strategy and implement mitigation strategies
  - **Approach…**
    - Utilize existing virus control strategy risk assessment to determine the specific risk of product contamination with SARS-CoV-2
  - **Outcome…**
    - Determination that there was a low likelihood of transmission from operator into the process because of existing controls and supplemental controls implemented in response to the pandemic

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\(^1\) Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing, June 2020
# IMLYGIC VIRUS CONTROL STRATEGY ASSESSED FOR SARS-COV-2 CONTAMINATION RISK LEVEL

## FDA Guidance to Assess:
- Potential for production cell line to replicate SARS-CoV-2
- Detection of SARS-CoV-2 through routine testing
- Effectiveness of viral clearance/inactivation
- Controls in place for operations in open systems

## Assessment

<table>
<thead>
<tr>
<th>Severity</th>
<th>Potential Cause</th>
<th>Current Prevention Controls</th>
<th>Likelihood</th>
<th>Current Detection Controls</th>
<th>Detection</th>
<th>Risk Level</th>
<th>Risk Control Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>SARS-CoV-2 viral contamination introduced during cell build processing</td>
<td>• Open operations in biosafety cabinet with appropriate grade air quality&lt;br&gt;• Aseptic technique training&lt;br&gt;• Operator gowning&lt;br&gt;• Environmental/ Personnel Monitoring&lt;br&gt;• Supplemental health and safety protocols</td>
<td>1</td>
<td>• SARS-CoV-2 known to replicate in production cell line&lt;br&gt;• Cytopathic effect on cells detected through routine cell viability measurements&lt;br&gt;• Routine in vitro testing of in-process pool</td>
<td>3</td>
<td>Low</td>
<td>None- controls and detections in place capable of minimizing risk of contamination and detection of contamination</td>
</tr>
</tbody>
</table>

The return on the investment of time and resources used to execute a foundational virus control risk assessment include speed and agility in responding to unexpected viral risk such as SARS-CoV-2
CONCLUSIONS....

- Quality Risk Management for an Advanced Therapeutic Medicinal Product (Oncolytic Virus) has been utilized to:
  - Develop a phase appropriate product quality control strategy
  - Establish a foundational virus control strategy
  - React to unexpected risk with speed and agility
PUBLIC INFORMATION / RESOURCES

• Amgen - IMLYGIC website
• ICH Guideline Q9 on Quality Risk Management
• FDA Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drugs and Biological Products Manufacturing