BLA POST-APPROVAL CASE STUDIES FOR ONCOLOYTIC VIRUS, IMLYGIC® (TALIMOGENE LAHERPAREPVEC)
In the midst of a global pandemic, where the development and approval of vaccinations is paramount, and in a biotechnology climate where cellular and gene therapies are becoming abundant, lessons learned from an oncolytic virus that has been approved since 2015 are shared…

• Today’s Agenda:
  ➢ IMLYGIC® Product Introduction
  1. Case Study 1: Operational challenges around ultra-low temperature storage
  2. Case Study 2: Comparability challenges around unique modality
  3. Case Study 3: Considerations for CBER Lot Release Testing
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
GLOBAL FOOTPRINT

• IMLYGIC® Marketing Application approved in:
  ➢ United States (FDA – CBER)
  ➢ European Union (EMA)
  ➢ Switzerland (SwissMedic)
  ➢ Israel (MoH)
  ➢ Australia (TGA)
CASE STUDY #1: ULTRA LOW TEMPERATURE STORAGE

- **Challenge: Ultralow temperature storage conditions (-80ºC)**
  - operationally, this translates into:
    - limited allowable room temperature exposure durations
    - necessity of applying label prior to freezing the product
    - demand fluctuations leading to scrap risk (because of labeling constraint)
    - limited ultra-low freezer availability/procurement in emerging markets
IMLYGIC® DRUG PRODUCT MANUFACTURING FLOW (ORIGINAL)

**Process Step**
- Drug Substance
  - Aseptic Dilution to Drug Product
    - Formulated Bulk (controlled room temperature)
  - Drug Product
    - Aseptic Vial Filling, Stoppering and Capping (controlled room temperature)

**Visual Inspection and Primary Labeling**
- (controlled room temperature)
- Freeze
- Drug Product Vial Unloading from Freezer
- Drug Product (vials stored at -80°C ± 10°C)

**Challenge!**
Commercial demand fluctuations across countries = Scrap risk!
CASE STUDY #1: ULTRA LOW TEMPERATURE STORAGE

• SOLUTION: Vial sleeve
  – Amgen developed polymer “vial sleeve” to enable labeling after freezing
    • Labeling occurs closer to distribution
    • Allows for fluctuations in demand
    • Avoids scrap
  – Simple equipment used to apply vial sleeve, which is labeled at room temperature, to the frozen vial, prior to secondary packaging
  – Approved in all markets!
IMLYGIC® DRUG PRODUCT MANUFACTURING FLOW (POST-APPROVAL)

**Process Step**
- Drug Substance
- Aseptic Dilution to Drug Product Formulated Bulk (controlled room temperature)
- Drug Product Aseptic Vial Filling, Stoppering and Capping (controlled room temperature)

**Visual Inspection and Primary Labeling**
- Controlled room temperature

**Freeze**

**Drug Product Vial Unloading from Freezer**

**Drug Product** (vials stored at -80°C ± 10°C)

**Process Step**
- Apply printed primary label to vial sleeves (room temperature)

**Insert frozen drug product vial into labeled, preconditioned vial sleeve (-80°C)**

**Packaging of sleeved drug product vial into carton**

Public Information
CASE STUDY #1: ULTRA LOW TEMPERATURE STORAGE

Lesson Learned

Decisions regarding modality, formulation selection, and recommended storage condition(s) in early development can have major impact after commercialization.
**CASE STUDY #2: COMPARABILITY FOR A UNIQUE MODALITY**

- **Challenge: Designing comparability assessments for unique modality**
  - **Important considerations include...**
    - Limited analytical toolkit for quantitating attributes of a virus (due to qualitative nature of many methods available for characterizing a virus)
    - Cannot perform BE/PK studies with a viral modality that is injected locally, as possible with monoclonal antibodies or small molecules
IMLYGIC® IS A COMPLEX PRODUCT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight (g/mole)</th>
<th>Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>180</td>
<td>0.7</td>
</tr>
<tr>
<td>denosumab</td>
<td>147,350</td>
<td>16</td>
</tr>
<tr>
<td>talimogene laherparepvec</td>
<td>&gt; 300,000,000</td>
<td>~ 220</td>
</tr>
</tbody>
</table>

Aspirin and denosumab are scaled by diameter
CASE STUDY #2: COMPARABILITY FOR A UNIQUE MODALITY

• SOLUTION: Allot time for holistic comparability assessments & engage with Health Authorities early
  – Per ICH Q5E, comparability assessments are required for manufacturing changes to biotech/biological products,
  – Comparability assessment can be purely analytical; however, if changes are observed in attributes that may warrant further analytical examination, but analytical tools are limited, then nonclinical and/or clinical stud(ies) may be warranted to ensure no negative impact to safety or efficacy.
  – Challenge is that this greatly expands program timelines and can be difficult to design, because PK/BE is not feasible.
CASE STUDY #2: COMPARABILITY FOR A UNIQUE MODALITY

Lesson Learned

For complex biologic products, assume that post-approval manufacturing changes may necessitate holistic (analytical, nonclinical, and/or clinical) comparability assessments.
In accordance with 21 CFR 610.2(a), CBER has the authority to require the submission of samples and protocols (lot release data) for any licensed product for CBER review and confirmatory testing.

**Lesson Learned:** If you are developing a biologic product that is reviewed by CBER, ensure that program timelines, operational logistics, and US-launch and subsequent supply plans account for CBER release.
PUBLIC INFORMATION / RESOURCES

- Amgen - IMLYGIC website
- Amgen - IMLYGIC US Prescribing Information
- EMA - IMLYGIC Approval and Prescribing Information
- FDA - IMLYGIC Approval Information
- FDA - IMLYGIC Approval Letter
- FDA - CBER Lot Release Testing
- TGA - IMLYGIC Assessment Report and Prescribing Information