BLA POST-APPROVAL CASE STUDIES FOR ONCOLYTIC VIRUS, IMLYGIC® (TALIMOGENE LAHERPAREPVEC)

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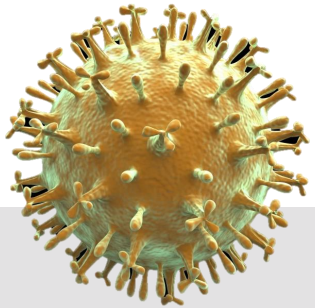
OPENING & AGENDA

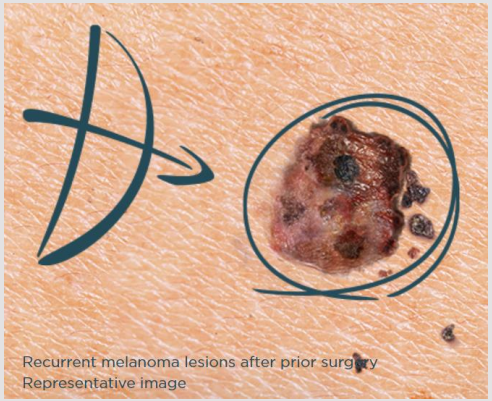


In the midst of a global pandemic, where the development and approval of vaccinations is paramount, and in a biotechnology climate where cellular and gene therapies are becoming abundant, lessons learned from an oncolytic virus that has been approved since 2015 are shared…

- **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 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

GLOBAL FOOTPRINT

- **IMLYGIC® Marketing Application approved in:**
  - United States (FDA – CBER)
  - European Union (EMA)
  - Switzerland (SwissMedic)
  - Israel (MoH)
  - Australia (TGA)



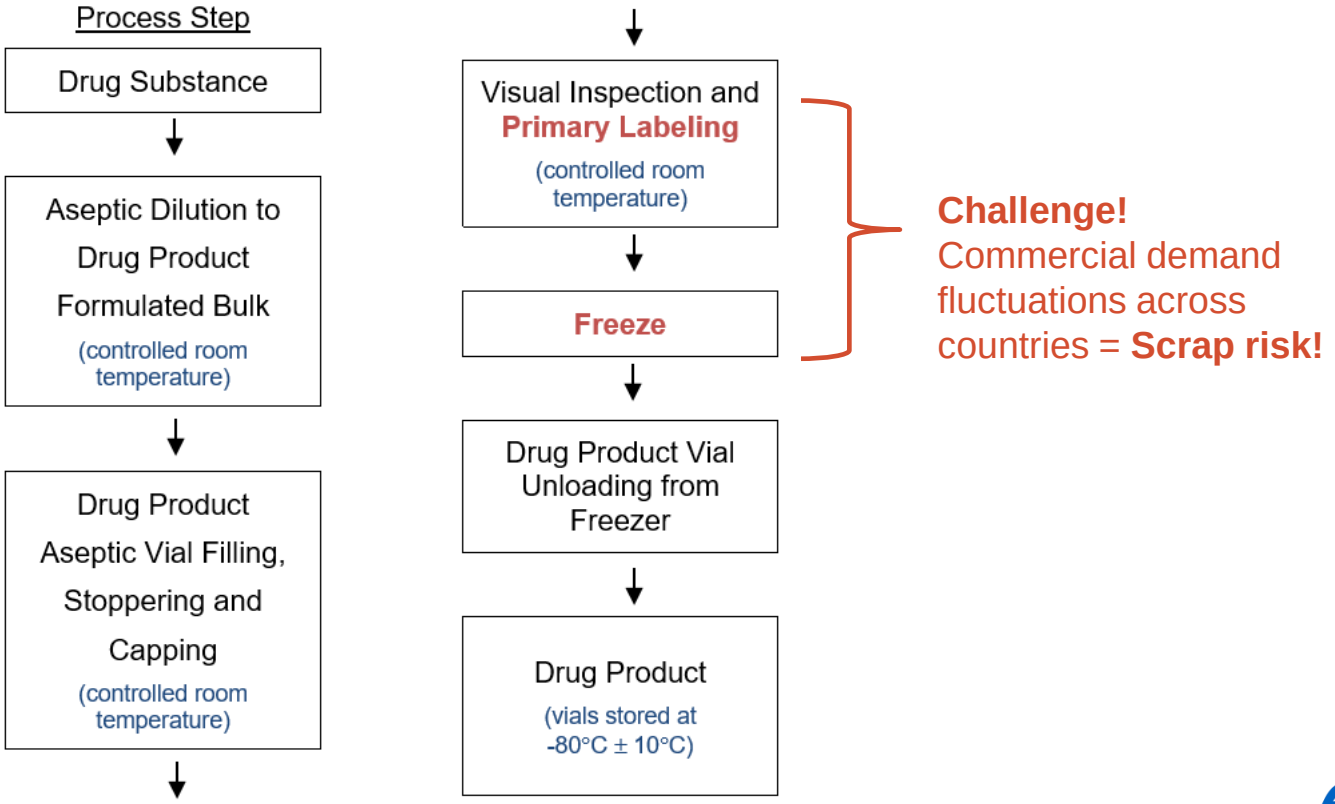


FDA = Food and Drug Administration, CBER = Center for Biologics Evaluation and Research,
EMA = European Medicines Agency, MoH = Ministry of Health, TGA = Therapeutic Goods Administration

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

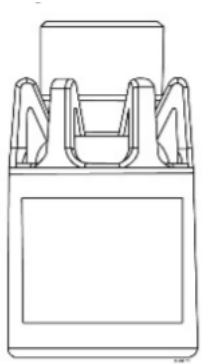
IMLYGIC® DRUG PRODUCT MANUFACTURING FLOW (ORIGINAL)



CASE STUDY #1: ULTRA LOW TEMPERATURE STORAGE

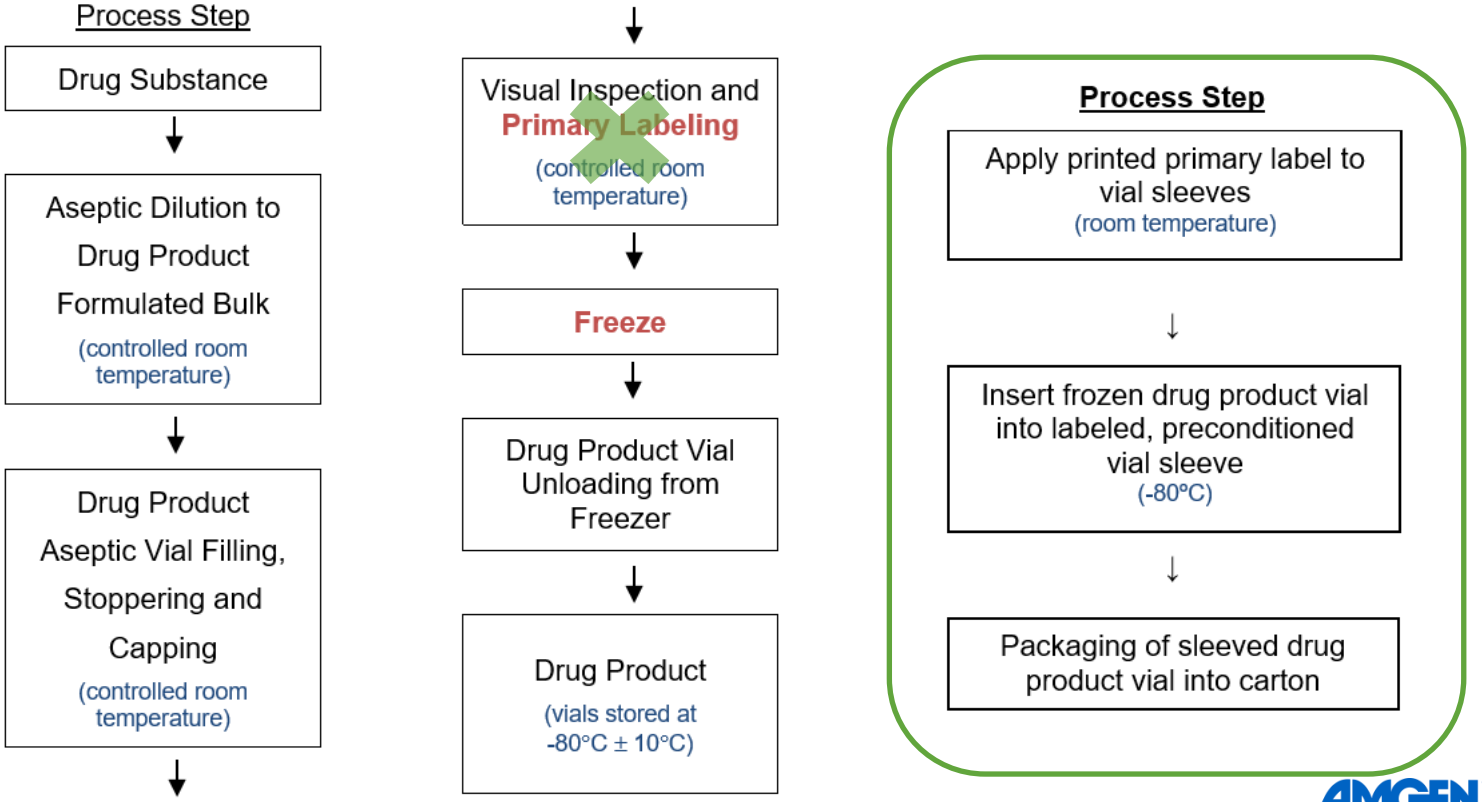
- **SOLUTION: Vial sleeve**
  - **Amgen developed polymer "vial sleeve" to enable labeling after freezing**
    - Labeling occurs closer to distribution
    - Allows for fluctuations in demand
    - Avoids scrap
  - Simple equipment used to apply vial sleeve, which is labeled at room temperature, to the frozen vial, prior to secondary packaging
  - Approved in all markets!

Labeled vial



Vial labeled with vial sleeve

IMLYGIC® DRUG PRODUCT MANUFACTURING FLOW (POST-APPROVAL)



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

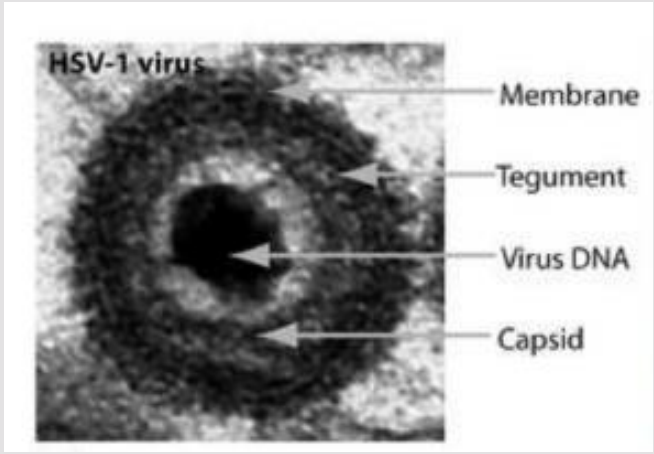
- **Challenge: Designing comparability assessments for unique modality**
  - **Important considerations include…**
    - limited analytical toolkit for quantitating attributes of a virus (due to qualitative nature of many methods available for characterizing a virus)
    - cannot perform BE/PK studies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

IMLYGIC® IS A COMPLEX PRODUCT

Aspirin
MW: 180 g/mole
0.7 nm diameter

denosumab
MW: 147,350 g/mole
16 nm diameter

talimogene laherparepvec
MW: > 300,000,000 g/mole
~ 220 nm diameter$_{Average}$



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

CASE STUDY #3: FDA LOT RELEASE TESTING

Reminder on CBER Requirement

- 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