Food and Drug Administration

CBER Product Review

Gene Therapy Review

Division of Cellular and Gene Therapies
Office of Cellular Tissue and Gene Therapies

1. **BLA#: STN 125518**

2. **REVIEW DATE: October 15th 2015**

3. **PRIMARY REVIEW TEAM:**

Product Quality: (This review contains the CMC reviewers listed in Blue color)	
Reviewer Name	**Review Sections**
R. Vatsan (Primary Reviewer) OCTGT/DCGT	Manufacturing Process, Lot release testing, Stability, E&L, and sections not covered by others.
R. Aksamit OCTGT/DCGT	Testing validation
A. Byrnes OCTGT/DCGT	Derivation and Banks
M. Havert OCTGT/DCGT	AVA testing and Environmental Analysis
OCBQ Reviewers	
C. Wernly OCBQ/DBSQC	Sterility Assays
R. Ballica	Facilities, Container Closure Integrity
L. Ortega	Manufacturing Facilities
N. Waites	Manufacturing Facilities Inspection
Pharmacology/Toxicology and Clinical reviewers	
Y. Huang	Pharmacology/Toxicology
M. O'Leary	Clinical Review (Safety)
R. Le	Clinical Review (Efficacy)
P. Bross	Clinical Review (Safety & Efficacy)
Statistics	
Y. Luo	Biostatistics
Epidemiology/Pharmacovigilance	
M. Alimchandani	
Labeling	
L. Nguyen,	
L. Stockbridge	
RPM	
M. Davidson	

4. **RFI COMMUNICATIONS WITH SPONSOR and SUBMISSION(S) REVIEWED**

Communication/Document	Date
Amendment Sequence # 6	11/26/2014
Amendment Sequence # 10	1/16/2015
Amendment Sequence #18	2/11/2015
Amendment Sequence # 17	2/20/2015
Amendment Sequence #20	2/26/2015
Amendment Sequence # 26	3/17/2015
Amendment Sequence # 28	3/26/2015
Amendment Sequence # 25	4/2/2015
Amendment Sequence # 33	5/15/2015
Amendment Sequence # 34	5/26/2015
Amendment Sequence # 38	7/20/2015
Amendment Sequence # 42	10/6/2015

5. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name:	Imlygic
b. Trade Name:	Imlygic
c. Non-Proprietary/USAN:	Talimogene laherparepvec
d. CAS name:	N/A
e. Common name:	No Common Name as yet
f. INN Name:	Talimogene laherparepvec
g. Compendial Name:	N/A
h. OBP systematic name:	N/A
i. Other Names:	N/A

6. **PHARMACOLOGICAL CATEGORY:** Genetically-Modified Oncolytic Viral Therapy

7. **DOSAGE FORM:** A maximum of 4 mL of talimogene laherparepvec (IMLYGIC) at a concentration of 10^6 (1 million) plaque forming units (PFU) per mL. Subsequent doses should be administered up to 4 mL of IMLYGIC at a concentration of 10^8 (100 million) PFU per mL

8. **STRENGTH/POTENCY:** Single-use vials: 10^6 (1 million) PFU per mL, 10^8 (100 million) PFU per mL

9. **ROUTE OF ADMINISTRATION:** Intra-lesional injection

10. **INSPECTIONAL ACTIVITIES:** PLI inspections Completed 2/13/2015

11. CONSULTS REQUESTED: M. Theoret (CDER Clinical), M. Hazarika (CDER Clinical)

12. PRECEDENTS: First in class

13. ADMINISTRATIVE

A. Signature Block

Signatures of Primary Reviewer (s) **Division of Cellular and Gene Therapies** **Office of Cellular Tissue and Gene Therapies (OCTGT)**	
Name and Title	**Signature and Date**
Ramjay Vatsan PhD CQA Chair, Review Committee Biologist, OCTGT, CBER	
Mike Havert PhD Biologist, OCTGT, CBER	
Robert Aksamit PhD Research Chemist, OCTGT, CBER	
Andrew Byrnes PhD Supv. Research Microbiologist, CBER	
Denise Gavin, PhD Branch Chief, Gene Therapy Branch.	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product, talimogene laherparepvec. The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information, along with post-marketing requirements (PMR) from Amgen (see section Executive Summary), will satisfy the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

II. List Of Deficiencies To Be Communicated

All CMC related deficiencies identified during the BLA review have been fully addressed by Amgen. There are no outstanding CMC deficiencies.

III. Review Of Common Technical Document-Quality Module 1

The common technical document- Quality module was reviewed and found to be acceptable.

IV. Environmental Assessment or Claim Of Categorical Exclusion

The applicant (Amgen) submitted an environmental assessment (EA) in accordance with 21 CFR 25 in the original submission. During the BLA review Amgen was asked to provide a quantitative assessment of product released into the environment in a revised EA. In addition, Amgen was asked to provide additional information on environmental stability, reactivation and latency, and potential for recombination.

The revised EA, submitted as amendment 33 dated May 15, 2015, consists of a risk assessment that follows the recommendations presented in CBER's Guidance for Industry ("Environmental Assessment of Human Drug and Biologics Applications" and "Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products"). The EA provides a quantitative assessment of IMLYGIC environmental exposure and environmental stability. This version of the document was submitted to the BLA as the final version on 10/6/2015.

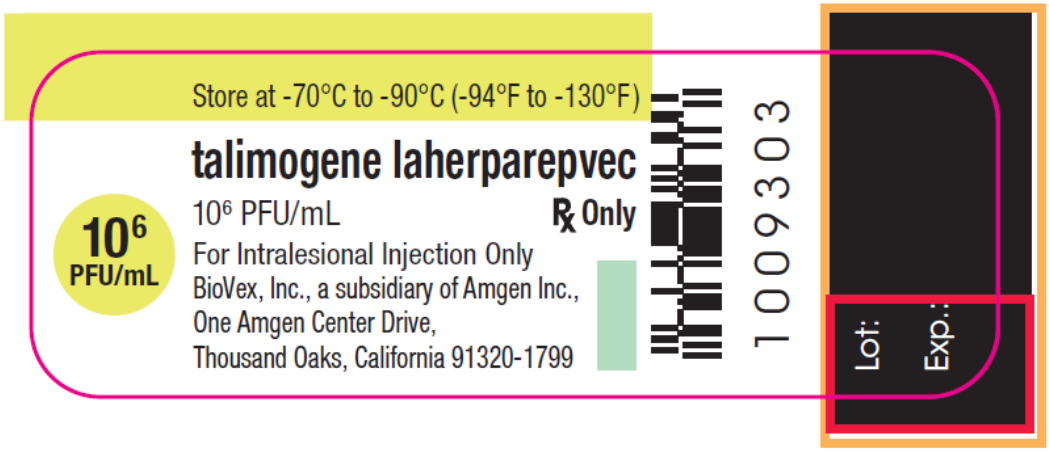
An estimation of environmental release is informed by biodistribution and shedding data collected during clinical trials. In one of these trials, patient samples were collected and evaluated with validated methods to detect both viral DNA and infectious virus. In this study, no detectable infectious virus was recovered from body compartments An estimation of environmental release is also informed by animal biodistribution and shedding data. In these studies extensive loss of infectivity of the virus was observed.

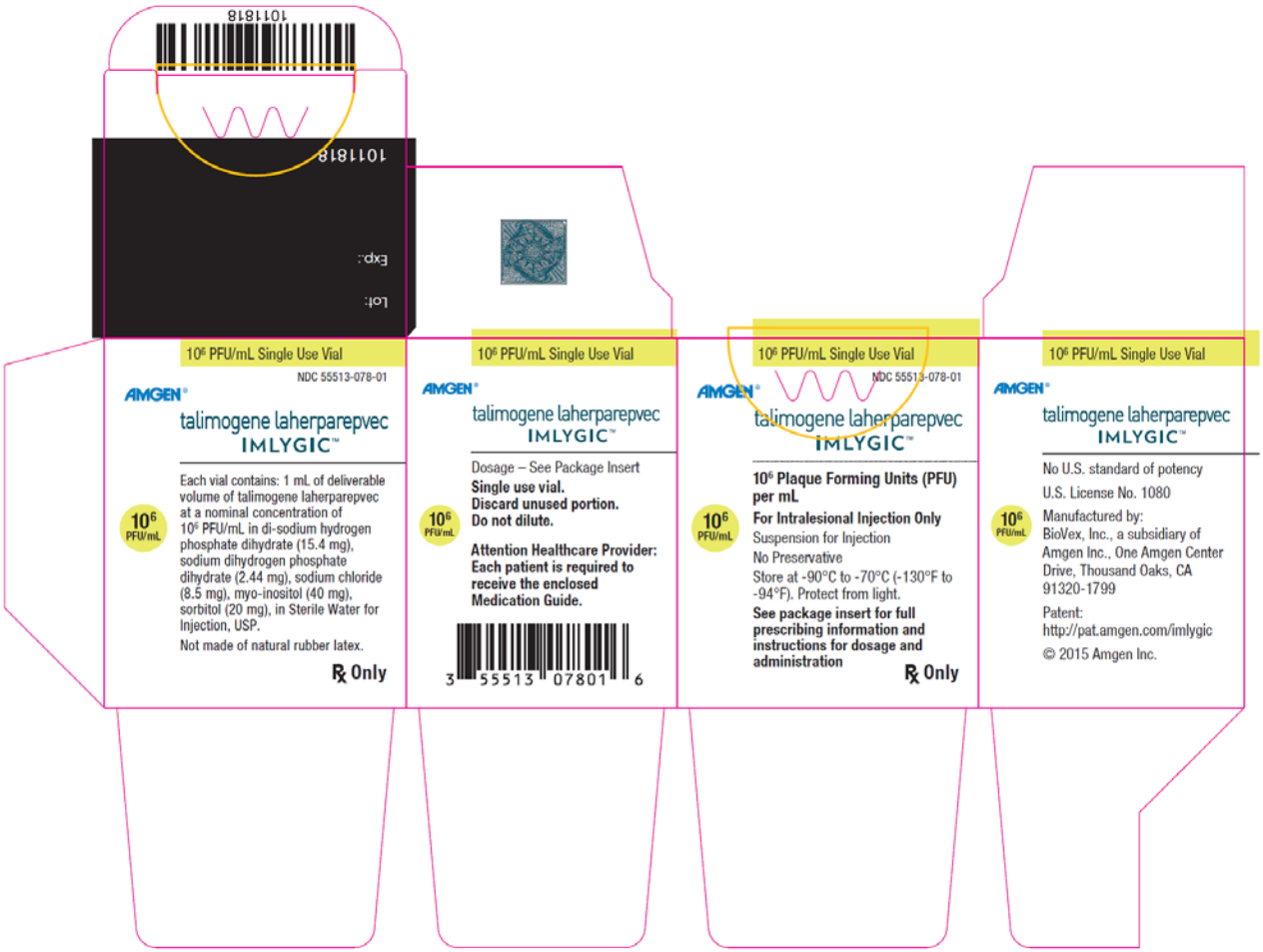
The environmental stability studies of IMLYGIC demonstrated rapid inactivation of the virus. In one study, significant decreases in the amount of recoverable infectious virus occurred within 4 to 8 hours of environmental exposure, and little to no recoverable infectious virus could be detected after 24 hours.

Therefore, the potential environmental exposure and environmental stability of IMLYGIC is expected to be minimal. No significant environmental impacts were identified, and a finding of no significant impact (FONSI) was prepared.

V. Primary Container Labeling Review

The BLA includes primary and secondary container labeling information for both 10e6 and 10e8 PFU/mL doses. The primary (vial) label contains product generic name, lot number, expiration date, and storage conditions. The route of administration is listed as intra-lesional administration. The label also includes space for dates of manufacture and expiry. The secondary (box) label contains the proper name as required under 21CFR610.60(a)(1), manufacturer's name, address and license number. An example of the 10e6 PFU/mL vial label and secondary container label are reproduced here for information.





CMC comment: The primary container label and the secondary container labels together comply with the requirements for container labeling under 21CFR610.60. The above carton label was received on 9/4/2015.

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Executive Summary for BLA# 125518

Talimogene laherparepvec is a replication-competent attenuated Type 1 Herpes Simplex Virus (HSV-1) that expresses human Granulocyte-macrophage colony-stimulating factor (hGM-CSF). The product's mechanism of action is not fully understood, but may be a combination of viral-mediated tumor cell lysis and stimulation of anti-tumor immune responses. Deletions in the genes for ICP34.5 and ICP47 attenuate virulence, contribute to tumor-selective replication, and alter interactions of the virus with the immune system.

Talimogene laherparepvec is manufactured at BioVex Inc., a wholly owned subsidiary of Amgen (referred to as Amgen Woburn Massachusetts or AWM) located in Woburn, Massachusetts, USA. The talimogene laherparepvec drug substance (DS) is manufactured on (b) (4) to achieve the target dose and directly packaged as the final Drug Product (DP), without further manufacturing. The DP is supplied as a sterile, single use, preservative-free frozen liquid for intralesional injection. Each vial contains 1.0 mL deliverable volume with a nominal dose of 10^6 plaque forming units (PFU) per mL or 10^8 PFU/mL drug product.

The BLA includes process validation reports from (b) (4) DP lots of Talimogene laherparepvec (b) (4) at10^6 PFU/mL, and (b) (4) at 10^8 PFU/mL) at commercial manufacturing scale (b) (4). The BLA also contains batch records for (b) (4) drug product lots (b) (4) at the 10^8 PFU/mL dose, and (b) (4) at the 10^6 PFU/mL dose). The batch records show that the product manufacturing process yields a consistent product with DP titers that are within pre-specified acceptance limits for safety, purity, potency and identity. The AWM manufacturing site has the capacity to produce (b) (4) lots per month at the (b) (4) scale. The shelf life of the DP is 48 months when stored at -80°C $\pm$ 10°C. Although the trend is towards a gradual loss of potency over this period of time, potency remains within pre-set acceptance criteria. Potency is determined by (b) (4) have been validated as quantitative assays. The DP is stored frozen until thawed at the point of use. The BLA contains empirical data to show that, after thaw, the 10^6 PFU/mL and 10^8 PFU/mL drug products may be stored in the original container, protected from light, at 5$\pm$3°C for a maximum of 12 and 48 hours respectively, without the loss of potency.

Amgen lot release specifications with justifications for the specifications are acceptable. All non-compendial lot release tests conducted by Amgen are performed at their Abingdon, UK site, and validation reports were submitted for all assays conducted at this site. All compendial assays are performed at various European contract testing organization (CTO) sites (with back up test sites located in the US) and verification reports for these assays are included in the BLA. The applicant's quality system has control measures that include in-process and end-of-production evaluations and protocols for corrective and/or preventive action to prevent recurrence.

Reviewer Recommendations:
This BLA provides an adequate description of the manufacturing process and characterization of talimogene laherparepvec. After a complete review of the information provided in the original BLA and its amendments, the CMC review team concludes that the manufacturing process, with the test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information along with the post-marketing commitments from Amgen (listed below) will satisfy the CMC requirements for biological product licensure as outlined in the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products.

Required Post-Marketing Requirements for Amgen:
Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct post marketing studies and clinical trials for

certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

Based on our review of the submitted information, we require that the applicant conduct:

1) Completion of the ongoing shedding studies per clinical protocol # 20120324, under IND 12412 (to be reviewed by the CMC, Clinical and OBE review teams).
2) Pharmacovigilance Studies (Please see OBE review for additional information).

VI. Review Of Common Technical Document-Quality Module 3.2

DRUG SUBSTANCE

3.2.S.1.2 Structure

Talimogene laherparepvec is a modified type 1 herpes simplex virus (HSV-1) that has been altered by recombinant methods, including gene deletions (i.e. Us12) and insertions (i.e. GM-CSF into the RL1 gene) as outlined below. The talimogene laherparepvec virions are enveloped and have a diameter of about (b) (4) Each virion contains a capsid that encloses a double-stranded DNA genome of roughly (b) (4)

3.2.S.1.3 General Properties

Talimogene laherparepvec is a replication-competent attenuated HSV-1 that expresses hGM-CSF. The parental virus for talimogene laherparepvec was a 1999 patient isolate (JS1), which was subsequently altered using recombinant methods. The talimogene laherparepvec genome is deleted in the U_S12 gene that encodes ICP47, a protein that interferes with antigen presentation. This U_S12 deletion also results in upregulated expression of US11 (due to the U_S11 gene coming under control of the immediate-early U_S12 promoter), which results in enhanced ability to grow in tumor cells. A hGM-CSF expression cassette was inserted into both copies of the R_L1 gene that encodes ICP34.5, resulting in functional deletion of ICP34.5. Loss of ICP34.5 attenuates the neurovirulence of the virus, while preserving the ability to replicate in tumor cells and lyse them. Expression of hGM-CSF is driven by the cytomegalovirus major immediate-early promoter. The viral thymidine kinase gene is intact and thus talimogene laherparepvec is sensitive to the antiviral drug acyclovir. Preclinical studies indicate that talimogene laherparepvec has improved selectivity for replication in tumor cells, and increased ability to present antigens, when compared to wild-type HSV-1. However, it has not been demonstrated whether or not talimogene laherparepvec retains an ability to replicate in non-tumor cells. Preclinical studies also indicate that talimogene laherparepvec can stimulate increased immune responses, as compared to similar vectors that do not express hGM-CSF. However, clinical studies to support this claim were not included in the BLA.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Informational Summary:

The talimogene laherparepvec (b) (4) and drug product (DP) are manufactured at BioVex Inc., a wholly owned subsidiary of Amgen (referred to as Amgen Woburn Massachusetts or AWM) located in Woburn, Massachusetts, USA. There are additional storage sites (Table 1) and testing sites (Table 2).

Table 1: Drug substance manufacturing facility responsibilities

Facility	Address	Responsibility	US FDA Registration Number / Facility Establishment Identifier

1 page determined to be not releasable: (b)(4)

(b) (4)

[redacted]

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Overview of the manufacturing process:

The following sections describe the manufacturing process and process controls. The optimal operating parameters for process control were determined empirically. Supporting data and justifications were provided in the BLA and are summarized in section 3.2.S.4.5 (Justification of Specifications) of this review.

3.2.S.2.2.1 Batch and Scale Definition

The manufacturing batch for talimogene laherparepvec [redacted]

Lot numbering system: During clinical development Lots had an alpha numeric numbering system. They contained a prefix of BP (Biovex product); four digit date code; Drug doses were designated either with a F (10^6PFU/mL) or a H (10^8PFU/mL), and Order of fill were designated A, B or C (first, second and third fill) (Example: BP0852HA).

For commercial production a fully numeric lot numbering system was implemented. For the [redacted] and fill steps, a unique 9-digit number is assigned on the basis of a specific dose. The first 4-digit number identifies the dose (5006 (10^6PFU/mL) and 5008 (10^8PFU/mL), and the second 5-digit number increases sequentially with each lot of that dose. The second 5-digit number is consistent across all the doses within a lot. A letter is added to the 9-digit number when a second fill of the same dose occurs (alphabetically increasing letter for each additional fill). DP are fully traceable to the lots of [redacted].

CMC Comments:

- *Lot numbering system devised by Amgen is acceptable and is expected to provide an individually identifiable and fully traceable DP lot.*

3.2.S.2.2.2 Cell Culture and Harvest

Description of Cell culture [redacted]

1 page determined to be not releasable: (b)(4)

(b) (4)

3.2.S.2.2.3 Purification and Modification Reactions

Virus Harvest:

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–

2 pages determined to be not releasable: (b)(4)

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Sterile Filtration:
The purpose of the sterile filtration step is to . The drug product sterility was verified by testing.

Information regarding the container closure system is provided in 3.2.S.6 (Container Closure System and Extractables and Leachables).

[redacted]

3.2.S.2.2.4 Filling, Storage, and Transportation

[redacted]

3.2.S.2.3 Control of Materials

3.2.S.2.3.1 Control of Source and Starting Materials

All raw materials used in the manufacture of talimogene laherparepvec are provided by approved suppliers and are identified, tested and released for use according to established procedures.

Materials used in manufacturing are tested by Amgen or approved contract testing laboratories (3.2.S.2.1, Manufacturers) or accepted on the basis of a supplier's certification documentation. Identity testing is performed on all incoming raw materials with the exception of fetal bovine serum (FBS). The identity of FBS is verified by inspection of the label upon incoming receipt and confirmed with the manufacturer's certificate of analysis. Raw materials used in the cell culture, virus production, and harvest steps are listed in table 11. All of the raw materials are received from the supplier pre-sterilized.

Table 11: Cell Culture, Virus Production, and Harvest Raw Materials

[redacted]

(b) (4)

Non-Compendial Grade Raw Materials: Methods used to test non-compendial cell culture and virus production raw materials upon incoming receipt along with their acceptance criteria, are summarized below. These tests supplement the additional testing provided with the supplier's certification documentation.

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2 pages determined to be not releasable: (b)(4)

3.2.S.2.3.2 Control of Source and Starting Materials of Biological Origin

Talimogene laherparepvec source, derivation and (b) (4)

Talimogene laherparepvec is derived from wild-type strain JS1, which was isolated in 1999 from a patient's cold sore and amplified in baby hamster kidney (BHK) cells. JS1 was found to be more cytopathic than laboratory-passaged strain 17+ (Liu et al. 2003, Gene Therapy 10:292-303). JS1 isolation and construction of talimogene laherparepvec is described in Liu et al., 2003. Previous names for talimogene laherparepvec are JS1/34.5-/47-/hGM-CSF, OncoVEX^{GM-CSF} and T-Vec.

Talimogene laherparepvec was engineered as follows. Briefly, the ICP34.5 (R_L1) genes were deleted (b) (4) and replaced with hGM-CSF expression cassettes. The expression cassette contains a human cytomegalovirus immediate-early promoter and a bovine growth hormone polyadenylation signal. Removal of both R_L1 copies greatly attenuates the virulence of the virus (including the neurovirulence) while preserving the ability of the virus to replicate in actively-dividing cells such as tumor cells. ICP47 (encoded by U_S12) was removed next. ICP47 inhibits peptide transporters TAP1 and TAP2 and thereby blocks MHC I antigen presentation. Removal of ICP47 is intended to increase antigen presentation and therefore immune responses to infected cells. In addition, the deletion brings US11 under control of the immediate-early U_S12 promoter, which enhances replication of the virus in tumors. (b) (4) . The final virus was termed JS1/34.5-/47-/hGM-CSF, and this was the (b) (4) material for talimogene laherparepvec. R_L1 deletion was confirmed by (b) (4) . hGM-CSF production was confirmed by (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

5 pages determined to be not releasable: (b)(4)

(b) (4)

[redacted]

[redacted]

[redacted]

*[redacted]

3.2.S.2.4 Controls of Critical Steps and Intermediates

A process performance parameter is a measurement used to evaluate in-process performance. Performance parameters allow direct assessment of product quality (i.e., impurity levels) or process consistency (i.e., step yield). Performance parameters are evaluated against predetermined limits during process validation, and a subset of performance parameters are designated as in-process controls (IPCs) for routine manufacture.

IPCs are classified as critical or key, depending upon the impact on product quality or process consistency. IPCs have specified limits, which when exceeded result in predetermined outcomes as outline below:

1) Rejection limits (established based on patient safety considerations)
2) Action (set within the characterization or historical manufacturing ranges shown to have no impact on drug substance product quality or process performance)
3) Control limits (statistically derived current normal limits of variability- used to monitor potential process trends)

- An excursion to an action or rejection limit requires an investigation which includes an assessment of impact to the product and processes, investigation of potential root cause and, if required corrective and/or preventive actions to prevent recurrence.
- A rejection limit excursion, if confirmed, will result in lot rejection.
- If an IPC action limit is exceeded, resolution of the investigation is a pre-requisite for lot disposition and can result in lot rejection if product impact is determined. The action limits for key consistency parameters may be refined based on additional data if justified and approved by quality through the change control process.
- Control limits are set and monitored across multiple lots. It confirms that the manufacturing process is operated in a state of statistical control and helps to identify potential process trends or shifts.

- Internal control limits are initially established to be the same as the action limits.
- Once adequate manufacturing experience has been obtained (approximately 15 lots), internal control limits are established using generally accepted statistical process control practices.
- Control limits are reviewed periodically and can be revised over time to reflect the expected performance of the manufacturing process.

Process Control Parameter Definitions

- **Critical performance parameter:** A performance parameter that is a direct measure of the impact of the step on quality of the drug substance
- **Key performance parameter:** A performance parameter that is used to assess consistency for a particular process step/stage.
- **Rejection Limit:** A limit that, if exceeded or in some cases equaled, results in lot rejection. Pertains to designated critical performance parameters only.
- **Action Limit**: A limit used to define a range for a performance parameter within which the parameter can vary with the unit operation delivering acceptable performance. When exceeded, it triggers a non-conformance which must be addressed as part of lot disposition and possibly a corrective action based on the investigation.
- **Control Limit:** Control limits are statistically derived limits that represent current normal cause variability of a specific parameter. For parameters not amenable to statistical treatment, limits are set to provide sufficient sensitivity for process monitoring.

Figure 1: IPCs for the drug substance process

1 page determined to be not releasable: (b)(4)

IPC Parameters for the following Key process related impurities, safety and microbial controls are defined:
Process impurities:

Table 17: Critical Impurity Parameter In-Process Controls and Rejection Limits

[redacted]

Table 18: Key Impurity Parameter In-Process Controls and Action Limits

[redacted]

(b) (4)

These IPCs are classified as key as they are used to assess the consistency of control of in the process. The testing and associated action and control limits promote early detection and remediation of potential trends. Any excursion of an action limit requires a non-conformance and associated investigation tied to the release of the lot. In addition to the drug substance IPCs, the drug product is subject to specification testing for sterility and endotoxin (3.2.P.5.1, Product Specifications).

Process consistency: as part of the overall process control strategy IPCs have been established to assess:

–

CMC Comment: Retesting Procedures (response to CMC RFI on 2/11/2015 and 2/26/2015):
The BLA includes a decision tree chart to conduct a retest. Unexpected test results at contract test facilities are investigated, and copies of these investigations provided with the final reports / CoA, and documented within an internal investigation (non-conformance or OOS), as appropriate. For All Critical IPC tests, decision to retest is made only if supported by results of initial investigation. All retests will involve repeat testing. For quantitative assays reportable results are required for OOS results repeats positive). For assays that require multiple independent determinations to obtain one reportable result (e.g. a minimum of reportable results are required.

CMC Comments:

- *The established "In process control" parameters are adequate to evaluate the manufacturing process consistency and to evaluate process deviations.*
- *Another parameter that is required to evaluate process consistency is the of the product, which is evaluated as a part of the final product and supports the claim of manufacturing consistency.*

9 pages determined to be not releasable: (b)(4)

(b) (4)

Sterile Filtration

[redacted]

3.2.S.2.6 Manufacturing Process Development

From [redacted] clinical and commercial production, there were [redacted] primary generations of the production process for talimogene laherparepvec

Table 28: Summary of Drug Substance Manufacturing Processes

[redacted]

1 page determined to be not releasable: (b)(4)

- [redacted]

[redacted]

CMC Comments for manufacturing Process development:

- *Process development and change are well-documented.*
- *All process changes were made based on scientific reasoning and to progressively improve product quality (see comparability information for product change reviewed under section 3.2.P.2.6, Comparability).*
- [redacted]

Process Characterization:

[redacted]

Definitions

Operating Parameter (Process Parameter): A parameter that can be directly controlled (process parameter). Operating parameters are typically thought of as "inputs".

Critical Operating Parameter: An operating parameter that must be controlled within a defined range to ensure that product quality is met. This classification is based on process characterization studies and/or other relevant data, including platform knowledge, engineering analyses, scale-up data, vendor data, and risk assessments.

Key Operating Parameter: An operating parameter that does not significantly impact final product quality but must be controlled within a defined range to ensure that key performance parameters and process control criteria are met. This classification is based on process characterization studies, and/or other relevant data, including platform knowledge, engineering analyses, scale-up data, vendor data, and risk assessments

Non-Key Operating Parameter: A non-key operating parameter has no significant impact on quality or process performance parameters. These are identified from process characterization, FMEA exercises, development

studies, other relevant data, including platform knowledge, engineering analyses, scale-up data, vendor data, and risk assessments.

Operating Parameter Ranges:

Characterization Range (CR): Range for an operating parameter that is evaluated for process and product impact during process characterization (is expected to be 2 to 3x Operating Range (OR) in most cases).

Operating Range (OR): A range for an operating parameter that is listed in manufacturing procedures or automation systems (e.g., batch record or automation alarm limits). This is often set based on equipment and/or process capability

Acceptable Range (AR): Range for an operating parameter that is established from process characterization or other relevant studies. Variations within this range will deliver acceptable performance, i.e., performance parameters will be within their action/rejection limits

Failure Modes and Effects Analysis (FMEA):

Process characterization included a risk assessment (FMEA) of the impact of operating parameters on process performance, which took into account risk severity, frequency of occurrence, and detectability. These analyses provided risk-based rankings of operating parameters to both provide preliminary classification and to identify parameters needing further evaluation. The FMEA captured experience from process development and manufacturing, as well as an understanding of the commercial manufacturing facility and equipment. Parameters identified as low risk were classified as non-key and not evaluated further. The remaining parameters were evaluated further prior to final classification. Evaluation included performing additional studies if warranted.

3.2.S.3 Characterization

(b) (4)

13 pages determined to be not releasable: (b)(4)

Drug Substance Testing:

(b) (4)

9 pages determined to be not releasable: (b)(4)

[redacted]

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment
N/A

3.2.S.7.3 Stability Data
N/A

DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product
Talimogene laherparepvec is supplied as a sterile, single use, preservative-free frozen liquid in a cyclic olefin polymer (COP) plastic resin vial for intralesional injection. Each vial contains 1.0 mL deliverable volume of talimogene laherparepvec at a nominal drug product potency of 10^6 PFU/mL or 10^8 PFU/mL after product thaw.

3.2.P.2 Pharmaceutical Development
The drug product is manufactured by [redacted] to a target concentration that will deliver a nominal drug product potency of 10 PFU/mL or 10^8 PFU/mL after product thaw (see section 3.2.P.2.2.2 for information on the calculation of overages).

- The [redacted] sodium chloride, [redacted] sorbitol, and [redacted] myo-inositol at a pH range of [redacted]
- The [redacted] is filled, stoppered, capped, inspected, labeled and frozen to -80°C ± 10°C, and is maintained in a frozen condition until thawed at the point of use.

3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 Drug Substance
The drug substance manufacturing process is described in detail in 3.2.S.2.2 (Description of Manufacturing Process and Process Controls), and the development of the drug substance process is presented in 3.2.S.2.6 (Process Development History).
3.2.P.2.1.2 Excipients
The excipients selected for the formulation of talimogene laherparepvec are:

- disodium hydrogen phosphate dihydrate:
- sodium dihydrogen phosphate dihydrate,

- sodium chloride
- sorbitol and
- myo-inositol

All excipients have been used in parenteral products and are tested to United States Pharmacopeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (PhEur) and/or Japanese Pharmacopeia (JP) as provided in the following table:

Table 38: List of DP Components

Component	Grade	Function	Quantity per Label Claim (1.0 mL)	
Active				
talimogene laherparepvec	In house[a]	Active Substance	10^6 PFU/mL	10^8 PFU/mL
Excipients				
Disodium hydrogen phosphate dihydrate	(b) (4)	(b) (4)	15.4 mg	15.4 mg
Sodium dihydrogen phosphate dihydrate			2.44 mg	2.44 mg
Sodium chloride			8.50 mg	8.50 mg
Myo-inositol			40.0 mg	40.0 mg
Sorbitol			20.0 mg	20.0 mg
Water for injection	USP, (b) (4)		(b) (4)	(b) (4)

qs = quantum sufficit

[a] Tested to internal specifications (3.2.S.2.4, Control of Critical Steps and Intermediates)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Development of the talimogene laherparepvec drug product formulation occurred in (b) (4) stages (see table below for a list of product configurations for the (b) (4) stages: early (b) (4) Commercial studies).

The final formulation used for the Phase (b) (4) studies and for commercialization is reviewed here.

Phase (b) (4) studies and for commercial use:

- Contains talimogene laherparepvec formulated in (b) (4) sodium chloride, (b) (4) sorbitol and (b) (4) myo-inositol at pH (b) (4)
- The solution pH was selected based on previously demonstrated HSV-1 stability in this pH range (Lancz & Sample 1985).
- (b) (4) was used in purification steps preceding formulation and provides (b) (4) capacity at pH (b) (4) in a liquid state.
- Sodium chloride was added as a (b) (4)
- Sorbitol and myo-inositol were added as (b) (4)

The effect of these (b) (4) components on the following product characteristics were evaluated: (1) Infectivity upon thaw (2) effect of freeze thaw cycles in the (b) (4) on virus infectivity, (3) effect of

(b) (4) on virus infectivity, (4) infectivity of different virus (b) (4) when stored in the (b) (4) and at -80C.

Summary of Formulation Development Activities to Determine Composition and Storage Temperature for Talimogene Laherparepvec:

Formulation Selection: The sorbitol/myo-inositol formulation provided the best overall stability compared to the other formulations tested during storage at (b) (4) and -80°C ± 10°C

Formulation Robustness: Formulation is robust to changes in pH and excipient concentrations. Variations larger than expected manufacturing variability did not affect stability

Storage Temperature: The drug product is stored at temperatures of -80°C ± 10°C. As a frozen liquid, viral stability at this temperature exceeds 1 year, with no significant loss of activity

Table 39: Summary of Talimogene Laherparepvec Formulation Composition

Formulation Component	Role of Component
(b) (4)	(b) (4)
(b) (4) sodium chloride	(b) (4)
(b) (4) sorbitol, (b) (4) myo-inositol	(b) (4)

CMC Comment on the Formulation development:

Formulation development is well documented. Available data suggests that the formulation is capable of preserving the virus infectivity at -80°C for long duration (see additional evidences from stability studies 3.2.P.8.3) and for short durations at (b) (4)

3.2.P.2.2.2 Overages

Overages are calculated at the time of (b) (4) to obtain the desired (10^6 or 10^8PFU/mL) DP concentration. Factors affecting the losses include thermal stress, adsorption to product contact surfaces, freezing and subsequent thawing prior to use.

Overage involves a concentration overage for both 10^6 PFU/mL and 10^8 PFU/mL, and a volume overage.

- (b) (4)

- [redacted]

- All 10^8 PFU/mL drug product lots met the specification of [redacted].
- All 10^6 PFU/mL drug product lots met the specification of [redacted]

Table 40 summarize the drug product process data comparing the initial drug substance potency, the target potency for dilution, and the results for final drug product potency specification testing for 18 commercial scale lots.

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.2.2.3 Physicochemical and Biological Properties

The drug product development studies presented in 3.2.P.2.2 (Formulation Development) were conducted to evaluate the stability of talimogene laherparepvec as a function of pH, (b) (4) type, (b) (4) concentration, excipient concentration and virus concentration under accelerated, stressed conditions and real-time storage.

The dual mechanism of action of talimogene laherparepvec described in 3.2.S.3.1 (Elucidation of Structure) includes direct cell lysis due to replication of the virus in tumor tissue, which is a local effect at the injection site, and indirect induction of an antitumor immune response, which is a systemic effect through release of tumor antigen and production of hGM-CSF.

- The quantity of expressed hGM-CSF is determined using a hGM-CSF (b) (4) .
- The (b) (4) of hGM-CSF produced from tumor cells is assessed using (b) (4)

Stability properties presented in 3.2.P.8.1 (Stability Summary and Conclusions) demonstrate that the formulation remains within stability acceptance criteria at the recommended condition of -80°C ± 10°C using stability indicating assays.

Stability of drug product subjected to light exposure and freeze/thaw has been evaluated and demonstrates that drug product formulations are stable under conditions that may be encountered during use.

CMC comments:

- *Immune effects of talimogene laherparepvec have not been demonstrated in human studies, using validated methods.*
- *The physiochemical and biological properties of the product are clearly defined and verified using validated test methods.*
- *Results show that the DP has to be protected from light, and this information should be included in the product label.*

3.2.P.2.3 Manufacturing Process Development

The commercial production lots of DP are derived from (b) (4) lots. The final lot size in terms of the number of filled vials depends on the desired strength (titer) of the product.

Manufacturing Process History:

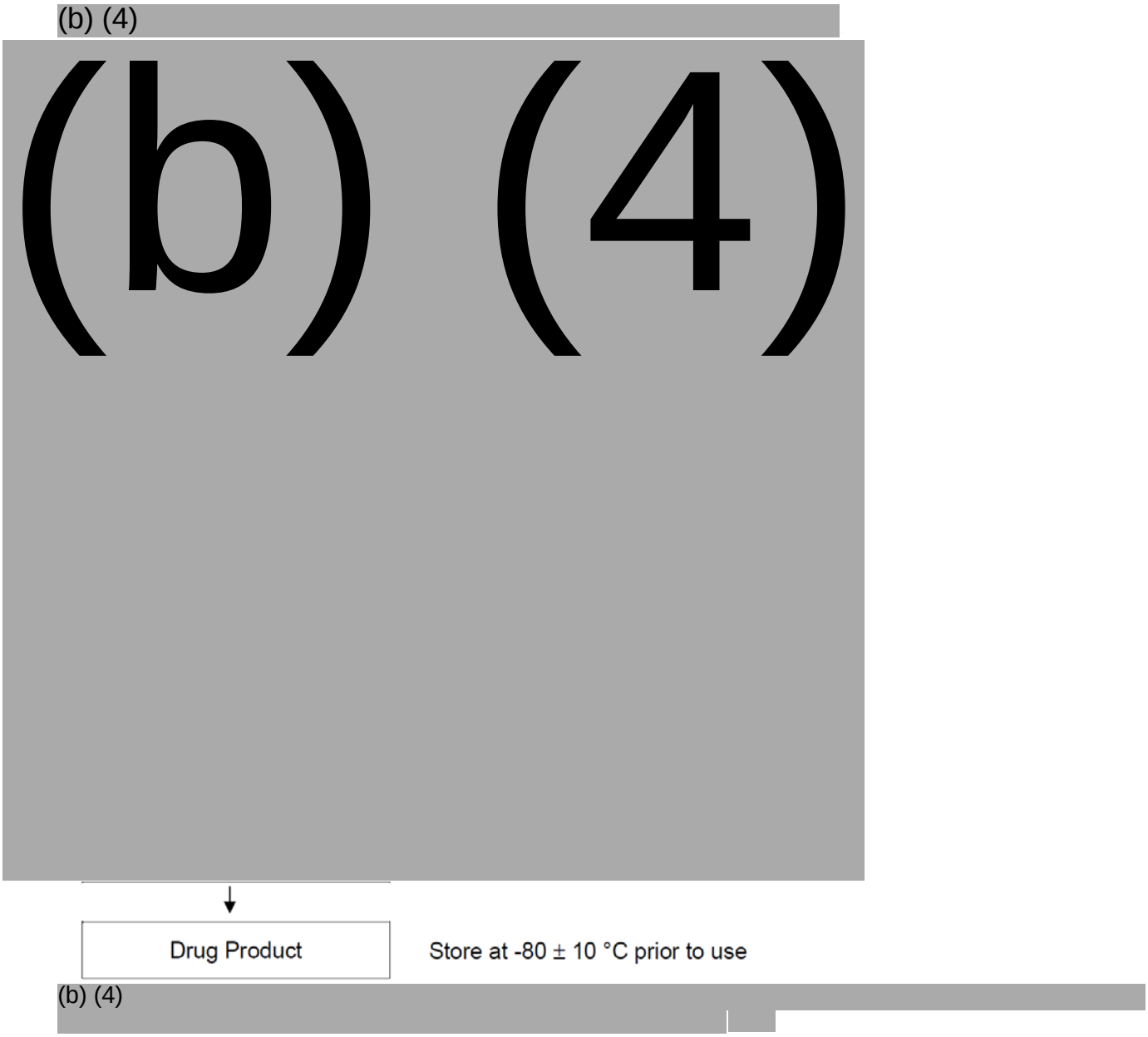
Changes to the drug product process have been largely driven by changes in the drug product formulation, container, manufacturing site, and to improve robustness and scalability. The changes to the drug product

1 page determined to be not releasable: (b)(4)

Process validation was performed for Process (b) (4) prior to these changes. Supplemental process validation was conducted after implementation of the changes in order to demonstrate continued control of the process. Both primary and supplemental process validation are described in 3.2.P.3.5 (Process Validation and/or Evaluation). The comparability of the drug product before and after the facility and equipment changes was also evaluated 3.2.S.2.6 (Comparability).

DP Process Characterization:

A significant output from process characterization was an understanding of how the drug product manufacturing process impacts talimogene laherparepvec quality attributes. An overview of the process and the primary function of each process step are provided in the figure below.



Primary drug product quality attributes potentially impacted by the drug product process include:

- Sterility
- Potency (b) (4)
- Fill volume

Effective control of these attributes is accomplished through a combination of design, procedural and testing controls. As described below, process characterization was performed as appropriate to support the development of an effective control strategy for these attributes.

Control of Sterility: The drug product process begins with a sterile filtered (b) (4)

The ability of the drug product process to produce sterile drug product has been validated (3.2.P.3.5, Process Validation and/or Evaluation) and sterility testing is performed on every drug product lot (3.2.P.5.1, Specifications). Media fill qualification has also been completed (3.2.P.3.5, Process Validation or Evaluation) and will be performed periodically (3.2.P.3.5, Process Validation and/or Evaluation).

As the controls around sterility are design and procedural, and subject to validation, qualification and ongoing testing, no additional characterization studies were performed.

Control of Fill Volume: Each vial contains a minimum of 1.0 mL deliverable volume of talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL after product thaw.

The fill volume is checked in-process by periodically weighing the filled vials. The fill weight criteria is based on the weight of empty assembled vials, the known density of drug product, the hold-up volume of the primary container system and syringe and the specified fill volume with appropriate tolerances.

Control of Potency: Talimogene laherparepvec is inherently labile and losses in activity are expected during the drug product manufacturing process, due to thermal stress and adsorption to product contact surfaces. As described below, measures have been established to control losses in the drug product process and ensure process consistency.

These include:

- Selection of drug product vials (3.2.P.7, Container Closure System) with -80°C ± 10°C storage requirements.
- Control of exposure to controlled room temperatures throughout the drug product process (3.2.P.3.3 (b) (4), Filling and Freezing).
- Implementation of a controlled rate freezing process (3.2.P.3.3, (b) (4), Filling and Freezing) to minimize talimogene laherparepvec losses and provide consistent performance.

Even with appropriate controls in place, process characterization studies and analysis of manufacturing data have demonstrated a consistent reduction in potency inherent to drug product processing from (b) (4) through product freezing. Factors affecting the losses include:

- thermal stress,
- adsorption to product contact surfaces,
- freezing and subsequent thawing prior to use.

Filling, Stoppering and Capping: The purpose of the filling step is to aseptically dispense an accurate volume of formulated (b) (4) drug product into the vials. The automated filling process is described in detail in the DMPQ review. Briefly, a (b) (4) automated filling machine is used for filling.

2 pages determined to be not releasable: (b)(4)

- (b) (4)

Process Characterization Conclusions:

- The talimogene laherparepvec drug product manufacturing process has been characterized, building on knowledge gained through process development and clinical manufacturing.
- Operating parameters have been identified and classified through a combination of risk assessments, analysis of data from development and manufacturing and targeted process characterization studies.
- They have been categorized and acceptable ranges established and justified.

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

- Results indicate that talimogene laherparepvec is compatible with disposable syringes for a period of time sufficient for administration of drug product.
- In addition, as for all injectable products, immediate administration is recommended because of the absence of preservative.
- It is also recommended that talimogene laherparepvec remain frozen until immediately prior to thawing and administration.

(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

All (b) (4) DP manufacturing is performed at Amgen's Biovex manufacturing facility located at 34 Commerce way, Woburn, MA, USA (AWM). All Stability, DP and IPC tests are performed in their (b) (4) . DP Release safety testing is performed by (b) (4)

CMC Comment: *The Woburn, MA site was inspected as a part of the BLA review. Please see the PLI inspection report for details on the inspection. UK sites were not inspected by FDA, however, the Abington facility was inspected and certified by Medicines and Healthcare Products Regulatory Agency (MHRA), UK for final release and stability testing for talimogene laherparepvec.*

3.2.P.3.2 Batch Formula

Talimogene laherparepvec is supplied as a sterile, single use, preservative-free frozen liquid for intralesional injection. Each vial contains 1.0 mL deliverable volume of 10^6 PFU/mL or 10^8 PFU/mL drug product after product thaw.

- (b) (4)

Table 47: (b) (4) and DP Batch Formula

Formulation Ingredient	Total Concentration	Amount per Kg (b) (4)	Amount per 1mL label claim ($10^6$and 10^8 concentrations)
Disodium hydrogen phosphate dihydrate (b) (4)	(b) (4)	(b) (4)	15.4mg
Sodium dihydrogen phosphate dihydrate (b) (4)	(b) (4)	(b) (4)	2.44mg
sodium (b) (4)	(b) (4)	(b) (4)	8.5mg
Sorbitol (b) (4)	(b) (4)	(b) (4)	20mg
myo-inositol (b) (4)	(b) (4)	(b) (4)	40mg
Water for injection (USP, (b) (4)	(b) (4)	(b) (4)	(b) (4)

The (b) (4)

Lot sizes for the drug product (b) (4) and the drug product vials are based on process validation and may be expanded based on pre-approved protocols. The lot sizes are supported by media fill validations 3.2.P.3.5 (Process Validation and/or Evaluation) and drug product stability data 3.2.P.8.1 (Stability Summary and Conclusions) and 3.2.P.8.3 (Stability Data).

The lot sizes for 10^6PFU/mL dose is (b) (4) (DP formulated (b) (4)
The lot size for 10^8PFU/mL dose is (b) (4) (DP formulated (b) (4).

CMC Comments for Batch formula Section:

The rationale and composition of the (b) (4) components were previously reviewed under section 3.2.P.2.2.1 (formulation development).

- *The DP potency is a nominal potency and the (b) (4)*

3.2.P.3.3 Description of Manufacturing Process and Process Controls

Talimogene laherparepvec drug product is manufactured at AWM. In the manufacturing operation, the process is performed in closed systems using disposable, single use components. Any process operation that is open to the environment is performed in a biosafety cabinet or other suitable controlled environment.

- The drug product manufacturing process has been developed and characterized as described in 3.2.P.2.3 (Process History) and 3.2.P.2.3 (Process Characterization).
- The description of the manufacturing process is provided in this section and includes key operating parameters and drug product testing controls associated with the process steps.
- Details of the classification and the establishment of acceptable ranges for the operating parameters are provided in 3.2.P.2.3 (Process Characterization).
- Information regarding the testing controls established for the process is provided in 3.2.P.3.4 (Control of Critical Steps and Intermediates) and 3.2.P.5.1 (Specifications).
- The process validation strategy and results are provided in 3.2.P.3.5 (Process Validation).

- Manufacturing facility, equipment, and cleaning methods used in production (including room air classifications for processing areas) are provided in 3.2.A.1 (Facilities and Equipment, AWM).
- The drug product testing controls include the drug substance in-process control for (b) (4) 3.2.S.2.4 (Control of Critical Steps and Intermediates).
- Drug product specifications for the vial fill volume and for the drug product sterility and potency with acceptance criteria that are described in 3.2.P.3.4 (Control of Critical Steps and Intermediates) and 3.2.P.5.1 (Specifications).

(b) (4)

(b) (4)
(b) (4)

Storage: Drug product vials are stored at -80°C ± 10°C. Vials are shipped on dry ice to ensure the product temperature is maintained during transportation. Transportation validation and stability is summarized in 3.2.P.3.5 (Transportation Validation) and 3.2.P.8.1 (Stability Summary and Conclusions).

CMC Comments for this section:
Manufacturing process and process controls are adequately described in the BLA and appear to be well controlled.

3.2.P.3.4 Controls of Critical Steps and Intermediates
Process controls are used to ensure process consistency and product quality during the manufacture of drug product. Talimogene laherparepvec drug product manufacturing includes aseptic (b) (4) to the target concentration, aseptic filling, stopper placement and capping, visual inspection, primary labeling, and freezing. Testing controls for drug product potency, vial filling, and aseptic processing are captured as drug product specifications. Process testing controls for DP Potency (b) (4) and Sterility are reviewed under section 3.2.P.5.1.

Microbial control strategy: The control strategy to ensure drug product sterility is described in 3.2.S.2.2 (Overview), 3.2.S.2.4 (Control of Critical Steps and Intermediates) and 3.2.P.3.3 (Overview).

(b) (4)

CMC comment on the control of Critical steps and intermediates: *The DP process and critical steps are reviewed under different sections as indicated above, and there are no specific concerns for this section.*

3.2.P.3.5 Process Validation and/or Evaluation
The talimogene laherparepvec commercial drug product manufacturing process was validated at the BioVex, Woburn facility (AWM), by demonstrating that the process, when executed within defined operating parameter ranges, met pre-established performance parameter acceptance criteria.
Process validation occurred in two stages:

- The commercial scale manufacturing process was initially validated in **2011**. Subsequently, the manufacturing facility underwent modifications to support projected long-term commercial production requirements. These modifications included minor improvements to the facility, equipment and

automation, but no changes to scale, step sequence, or process chemistry (3.2.P.2.3 Process Development History).
- In **2013** a supplemental process validation exercise was completed and is discussed in detail in 3.2.S.2.6 (Comparability) and section 3.2.S.2.5 (Process validation).

Process validation for talimogene laherparepvec drug product includes:
- Qualification of major equipment (Section 1)
- Media fill qualification (Section 2)
- Main process validation (Section 3)

Qualification of major equipment (Section 1): This section provides details of qualifying the major pieces of equipment used in producing talimogene laherparepvec drug product as well as for the validation of the sterilization process used for product contact materials.
CMC Note: *Please see a review of the equipment used in the manufacture under the DMPQ review.*

Media fill qualification (Section 2): This section includes results from (b) (4) consecutive media fills, and assurance of sterility for the process validation.
CMC Note: *Please see a review of the equipment used in the manufacture under the DMPQ review.*

Main process validation (Section 3): This section includes drug product release testing data for (b) (4) 10^6 PFU/mL and (b) (4) 10^8 PFU/mL drug product lots from the 2011 initial process validation campaign, and (b) (4) 10^6 PFU/mL and (b) (4) 10^8 PFU/mL drug product lots from the 2013 supplemental validation campaign after the facility expansion. The supplemental validation of the drug product process evaluated the process performance parameters of fill weight, filling yield, filling accountability, inspection rejection rate and drug product sterility prior to freezing.
CMC Note: *This section is reviewed below.*

This section contains
- A summary of DP lots (10^6 and 10^8 PFU/mL) used for Drug Product Process Validation
- A list of exceptions (Exceptional conditions that were used to validate the process criteria)
- (b) (4) Hold Times for all the validation lots
- (b) (4) conditions (number of (b) (4) for the validation lots
- Filling validation (batch size and fill weight checks for the validation lots)
- Inspection rejection rate
- Inspection labeling duration
- Drug product vialing and freezing
- Validation of lot homogeneity
- DP release testing results for the validation lots

A DP Lots with Lot Sizes Used for DP Process Validation: (b) (4) lots of 10^6PFU/mL and (b) (4) lots of 10^8PFU/mL titers were used in this study. These lots were manufactured between 2010 and 2013. The amount of formulated (b) (4) for the 10^6PFU/mL lots weighed from (b) (4) and resulted in filling between (b) (4) vials. The amount of formulated (b) (4) for the 10^8PFU/mL lots weighed from (b) (4) and resulted in filling between (b) (4).

Exceptional Conditions: Assignable causes extrinsic to manufacturing process
(b) (4)
.

Hold Times for validation lots:

1 page determined to be not releasable: (b)(4)

(b) (4)

Inspection and Labeling:
Filled vials are 100% manually inspected by certified operators under standardized conditions at controlled room temperature. The vial inspection reject rate is a process validation acceptance criterion measuring the process consistency. Filled drug product vials were also tested for sterility demonstrating an aseptic drug product manufacturing. The data given below shows that the supplemental validation lots met the process validation acceptance criteria. Vials that pass visual inspection are labeled automatically or manually.

(b) (4)

(b) (4)

Drug Product Vial Freezing:
Labeled drug product vials are loaded onto trays and transferred to a controlled rate freeze chamber. The appropriate freezing cycle is then initiated per approved manufacturing procedures to a final freezing temperature of (b) (4). The freezing cycles of the supplemental validation lots were executed within defined operating parameter ranges as described in (3.2.P.3.3, Description of Manufacturing Process and Process Controls).

Vial Unloading:
Upon completion of the freezing the talimogene laherparepvec drug product vials at a target temperature of -(b) (4), exposure time at controlled rate temperature where the vials are unloaded from the controlled rate freezer (CRF) and bulk packaged is monitored to ensure the overall exposure is within the acceptable range.
Acceptable range for unloading is(b) (4) minutes/tray the unloading rates for 5 representative lots are:
(b) (4)
The acceptable time is the same for both 10 and 10 PFU/mL lots.

Validation of Lot Homogeneity:
Lot homogeneity was assessed for each lot during process validation. Homogeneity samples were taken after the controlled rate freezing step, which is the final unit operation that may affect quality attributes of the drug product. (results confirm to specifications and not reproduced in this review)

(b) (4)

(b) (4)

CMC Overall Comments for Process validation section: *The Talimogene DP Process validation is adequately evaluated and documented.*

- (b) (4)

Release Testing Results and Specifications for the Drug Product Initial Process Validation Lots (10^6 PFU/mL Drug Product) in 2010 and supplemental validation results for 10^6 PFU/mL lots are included in the BLA and not reproduced here. All the validation lots met specifications. Supplemental validation test results for 10^8 lots are given below.

Table 52: DP Release Testing Results for Validation Lots

Release Specification Testing for the 10^8 PFU/mL DP Supplemental Process Validation Lots						
Test Purpose	Test Property	Method	Specification	(b) (4)		
General Properties	Identity Appearance pH	(b) (4)				
Content	(b) (4)					
Purity	(b) (4)					

Potency		(b) (4)
Safety	Sterility	(b) (4)
	Endotoxin	
	Toxicity	

[a]Results generated were lower than the lowest standard
NE:No evidence of bacterial or fungal contaminants
NATD: No abnormal toxicity detected

3.2.P.3.5 Transportation Validation

Talimogene laherparepvec drug product in 10^6 PFU/mL and 10^8 PFU/mL configurations are transported between the drug product manufacturing site and the distribution sites by aircraft and truck modes.

- The temperature acceptance criterion for talimogene laherparepvec drug product during transport is -80°C ± 10°C.
- The drug product is packaged for transport in a qualified shipping container with a calibrated temperature monitoring device.
- The shipper container(s) has been qualified to maintain the required shipping conditions for talimogene laherparepvec drug product of -80°C ± 10°C for up to 96 hours.
- The transport process is qualified to demonstrate that the drug product is not adversely impacted by the process and that the process performs its intended function effectively and reproducibly.

Transport Qualification Program

The Amgen transport qualification process occurs in two stages: insulated shipper qualification and transport process performance qualification. Qualified shippers are required to execute the transport performance qualification studies.

Qualification of Insulated Shipping Containers

Amgen's insulated shipper qualification process consists of component qualification, thermal qualification, and physical qualification.

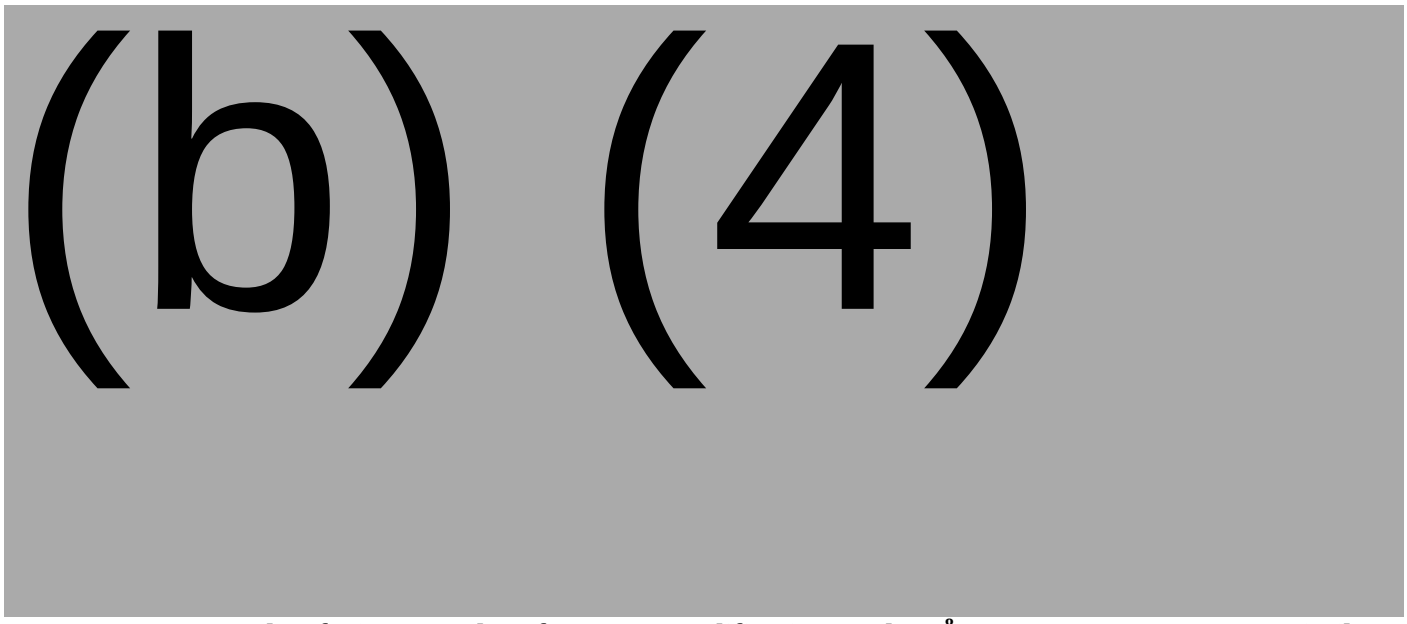
- *Component qualification (CQ):* Evaluation of all components used in Distribution Packaging, in accordance with the intended use of the component.
- *Thermal qualification (TQ):* Insulated shipping containers are challenged in a validated chamber using operating ranges defined by Amgen hot and cold temperature profiles.

- *Physical qualification:* Shipper integrity is tested for shock impact related to drop. The insulated shipping container must remain intact with no damage (i.e., hole or crack) that will allow passage of external environment into the shipper.

Performance Qualification

Performance qualification (PQ): PQ is performed to demonstrate that the global transport process can perform its intended function effectively and reproducibly using a minimum of 3 shipments under actual transport conditions. The PQ verifies that the established quality attributes of the drug product are maintained throughout the transport process and that the approved procedures are appropriate.

Transportation validation data with information on the packaging materials is included in amendment sequence # 10 (1/15/2015). This report summarizes and states that the transportation is validated for temperature maintenance (at -80°C for (b) (4)



Assay Results of Air/Ground Performance Qualification Study 10^8 PFU/mL Lot BP1324HA: Similar to10^6 and not reproduced here.

Conclusions from shipping and transportation validation studies:

Shipping containers used to transport talimogene laherparepvec drug product were qualified to maintain a temperature range of -80°C ± 10°C when challenged against hot and cold thermal profiles. The transport PQ confirmed that talimogene laherparepvec drug product quality is not adversely affected by real world transport conditions and that the process is consistently capable of meeting specifications. Taken together the transport process for talimogene laherparepvec drug product is qualified to maintain the product shipping requirements.

CMC comments on the shipping validations:

Shipping and transportation of the DP is adequately validated

IPC samples are shipped to the testing facilities in the (b) (4) *, however, the included justification and data are acceptable.*

3.2.P.4 Control of Excipients

All excipients in the formulation are specified at a minimum in the current European Pharmacopoeia (PhEur) and United States Pharmacopeia (USP).

3.2.P.4.1 Specifications

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
The drug product excipients, disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, sorbitol, myo-inositol and water for injection (WFI), are tested according to compendial methods. No validations were required or done.

3.2.P.4.4 Justification of Specifications
Derivation and justification for excipient specifications are described in section 3.2.P.2.2.1 (Formulation development).

3.2.P.4.5 Excipients of Human or Animal Origin
Talimogene laherparepvec drug product excipients do not contain materials of human or animal origin.

3.2.P.4.6 Novel Excipient
There are no novel excipients used in talimogene laherparepvec drug product.

3.2.P.5 Control of Drug Product
3.2.P.5.1 Specifications

Table 54: Drug Product Specifications

Drug Product Specification and Tests for 10^6 PFU/mL

Attribute	Parameter	Test Method Description	Test Method Type	Acceptance Criteria
Identity	Identity	(b) (4)		
Appearance	Clarity			
	Color			
	Appearance			
Potency/ Strength	(b) (4)			
Potency				
Purity				

(b) (4)

Attribute	Parameter	Test Method Description	Test Method Type	Acceptance Criteria
General Tests	pH	(b) (4)		
	Osmolality			
	Volume			
	Subvisible Particles			
Safety-Adventitious agents	Sterility			
	Bacterial Endotoxin			
Safety-Toxicity	Abnormal Toxicity			

Drug Product Specification and Tests for 10^8 PFU/mL: Similar to the 10^6 specifications and included in the BLA. Not reproduced in this review.

(b) (4)

- (b) (4)

3.2.P.5.2 Analytical Procedures

Summaries of analytical procedures specific to drug product are listed in the table below and descriptions of the procedures are provided below the table. Detailed assay protocols for non-compendial methods are provided in section 3.2.R. Compendial methods are performed in accordance with current pharmacopoeia.

Table 55: Drug Product Analytical Procedures

Attribute	Analytical Procedure	Test Method Description
Identity	Identity	(b) (4)
Appearance	Clarity Color Visible Particles	
General Tests	pH Osmolality Subvisible Particles Volume[c]	
Purity	(b) (4)	
Potency/Strength	(b) (4)	
Potency	(b) (4)	
Safety-Adventitious Agents	Sterility Endotoxin Abnormal Toxicity	

[d]Test performed by (b) (4)

[e]Test performed by (b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.3 Validation of Analytical Procedures

This section contains summaries of the most recent validations for analytical methods of the drug product that were summarized in section 3.2.P.5.2. The drug product analytical procedures and validation reports are listed in the table below with the validation reports found in 3.2.R.2 (Analytical Method Validation Package). Compendial methods (color, visible particles, pH, osmolality, sterility, endotoxin and abnormal toxicity) were verified to be suitable for use. In some cases, the analytical procedures were augmented based on the outcome of the original method validation. In preparation for commercial production, a number of methods were subsequently revalidated in 2013. This section contains the most recent method validation summaries for the non-compendial methods.

Table 56: Validation of Methods Used to Release Drug Product (10^6 PFU/ml and 10^8 PFU/ml)

Test	Validation Description	Validation Report Number
Identity	(b) (4)	(b) (4)
Clarity		
Color (b) (4)		
Visible particles (b) (4)		
pH (USP, PhEur)		
Osmolality		
Subvisible particles		
Volume		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
Sterility (b) (4)		
Endotoxin (b) (4)		
Abnormal Toxicity (b) (4)		

(b) (4)

(b) (4)

6 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.5 Characterization of Impurities

Impurities can be classified as process-related or product-related. Process-related impurities encompass those derived from or introduced during the drug product manufacturing process.

- There are no process impurities from the drug product manufacturing process.
- Product-related impurities are variants of the desired product that may have properties comparable to those of the desired product with respect to activity or safety.
- These are distinguished from product-related substances which are fully active and have no deleterious effect on the efficacy of the drug substance or drug product.

Product-related Impurities: Product variants include any species that are active per the (b) (4) , whereas viral particles that are not infectious are classified as product-related impurities. Inactive viral particles may include(b) (4)

(b) (4) ds. Additional forms may be included based on their impact on (b) (4) . For example, drug product manufacturing and freeze-thaw cycles can have an impact on (b) (4) , which means that product impurities form due to freeze-thaw process.

In the absence of methods to directly characterize product related impurities in the product, (b) (4) can be used to monitor product purity.

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

3 pages determined to be not releasable: (b)(4)

- (b) (4)

(b) (4)

(b) (4)

3.2.P.5.6 Justification of Specifications

Development of the drug product specifications was performed in accordance with the ICH Harmonized Tripartite Guideline, *Specifications: Test Procedures and Acceptance* Criteria for Biotechnological/Biological Products (Q6B). The specifications and acceptance criteria are intended to ensure safety and efficacy through the control of relevant quality attributes.

- Specifications were established based on historical lot release data, clinical experience, assay variability, and anticipated shelf life of the drug product.
- Lot release parameters were chosen to assure the integrity, purity, potency, strength, and identity of the drug product at release and throughout shelf life.
- The data used to establish the acceptance criteria for the commercial specifications are derived from Process(b) (4) lots, with supportive data provided from Process(b) (4) lots, in order to link the acceptance criteria to relevant clinical experience as appropriate.

Developmental and Commercial Specifications:

- The tests for identity, clarity, potency, strength, purity, adventitious agents, and general tests will remain consistent with the specification used during clinical development.

Tests added for Commercial DP:

- Tests for color, appearance (visible particles), subvisible particles, osmolality and volume were not used during clinical development and are newly added to the commercial specification.

Statistical methods:

The statistical data set used to evaluate the acceptance limits are from release testing results from drug product lots manufactured using the commercial process (b) (4) and used in clinical studies.

Historical batch analyses from the commercial process(b) (4) lots were evaluated to estimate ranges (i.e., tolerance intervals) that contain approximately 99% of the population with 95% confidence (95%/99%).

- The tolerance interval coverage of 99% was chosen due to the limited sample sizes. Tolerance intervals were used for this purpose because they predict the long-term expected behavior of the manufacturing process.

- Two-sided 95%/99% statistical tolerance intervals were used to calculate prospective acceptance criteria for all parameters with numerically reported test values.
- For certain parameters that exhibited excessive skewing in their data distributions, tolerance intervals were computed using a natural log (loge) or logit transformation of the data and the resulting intervals were back transformed, to then be reported in their original unit of measurement.
- The methodology used in this application is recommended by the National Institute of Standards and Technology (NIST, 2006) and Graybill, 1976.
- To assess the historical lot release data against the commercial specification ranges, the data are presented on a trend chart with the acceptance criteria graphically displayed.

For the majority of the product quality parameters, the calculated tolerance intervals were outside of the existing specification ranges used for the control and release of product lots into the pivotal studies and from which clinical experience would have been derived.

Therefore, the commercial specifications for the majority of parameters are reflective of the specification ranges used for the pivotal studies, without revision or amendment. In the one instance where a change was made to a product quality parameter (i.e., (b) (4)), minimum and maximum values calculated from historical data were used, in conjunction with statistically-calculated limits, to inform the commercial specification range.

Other Considerations:
Several quantitative product quality parameters and associated limits are not derived from clinical experience with the product (as assessed during the clinical program) or statistical assessment but rather were based on formulation development studies, as well as World Health Organization (WHO), United States Pharmacopeia (USP) and/or International Conference on Harmonization (ICH) guidelines.

Vial specifications:

- (b) (4)

Justification of Acceptance Criteria on the Specification and Rationale for Testing:

(b) (4)

(b) (4)

7 pages determined to be not releasable: (b)(4)

Appearance and Description:
The appearance, color, and clarity tests are used to provide a qualitative description of the visible physical characteristics of the drug product, including color hue, opacity and the detection of visible particles.

Appearance-Visible Particles:
Since the visible particle appearance characteristics of both the 10^6 PFU/mL and 10^8 PFU/mL strengths were similar, an identical commercial Appearance specification criterion of (b) (4) will be used for both product strengths.

Appearance- Color:
Color characteristic of the 10^6 PFU/mL and 10^8 PFU/mL drug product strengths is consistent with a colorless hue and whose coloration is less than or equal to the reference standard, (b) (4) The commercial specification acceptance criterion for color of the 10^6 PFU/mL and 10^8 PFU/mL strengths will confirm a lack of product coloration and will be (b) (4)

Appearance- Clarity:
The commercial specification acceptance criterion for clarity of the 10^6 and 10^8 PFU/mL strengths are (b) (4) The acceptance criteria reflect the general opalescent characteristics of both drug product strengths as a virus particle suspension and are based on the variability of the assay and release and stability data generated to date.

pH:
The drug substance pH is not directly adjusted but is controlled by the pH of the formulation buffer (b) (4) The commercial specification limits were aligned with the limits employed during clinical development. The commercial specification criterion for pH of the 10^8 PFU/mL strength is (b) (4) and results will be reported per the specification to one decimal place. The specification range (b) (4) is appropriate based on process history and formulation development studies.

Osmolality:
Osmolality is a general characteristic assay used to provide assurance that the drug product has been properly formulated. Osmolality test results for the 10^6 PFU/mL strength ranged from (b) (4)
Osmolality test results for the 10^8 PFU/mL strength ranged from (b) (4) The commercial specification osmolality acceptance criterion for the 10^6 PFU/mL and 10 PFU/mL strengths is aligned to the critical operating parameter acceptance criterion range of (b) (4) .

Commitment to reevaluate the specifications: As these specification ranges were set using a minimal amount of lot characterization data and a meaningful statistical analysis could not be performed due to the small sample size, Amgen commits to (b) (4) .

Volume:
Amgen intends to use in-process testing to ensure that a patient deliverable volume of 1.0 mL is met. Amgen considers the in-process testing as a Real Time Release Test (RTRT). The RTRT approach provides greater control and a real time evaluation of fill volume compared to the USP compendia fill volume determinations which are based on an average result from a limited number of samples measured at the completion of a filling operation.

The talimogene laherparepvec 10^6 PFU/mL and 10^8 PFU/mL drug product vial fill volume specification will be reported as (b) (4) on the drug product lot Certificate of Analysis, to designate acceptable results against lower and upper fill volume specification limits. The lower and upper fill volume specification limits are (b) (4) , respectively.

Subvisible Particles:
The specification acceptance criteria for this test meet the harmonized requirements for (b) (4)

Sterility:

The test method(s) are used to examine the drug product for the presence of both aerobic and anaerobic bacteria and fungi and is conducted by (b) (4) of the vialed drug product sampled prior to controlled rate freezing into (b) (4) . These methods comply with the current USP and PhEur compendia requirements.

Endotoxin:

This method is used to determine the level of endotoxin present in the drug product and complies with current USP and PhEur compendia requirements. The specification of (b) (4) is appropriate and is in alignment with compendia guidance for endotoxin content in preparations for parenteral or intrathecal routes of administration (b) (4) respectively). A limit of (b) (4) has been established which is well within the defined safety level when calculated based on the maximum dose (4 mL) for talimogene laherparepvec in an adult patient population.

Abnormal / General Toxicity:

Abnormal toxicity (i.e., general toxicity) testing is a direct assessment of product safety on the final drug product at release. Testing is a compendia method compliant with PhEur requirements that is performed at contract testing facilities. The equivalent of (b) (4) by the intraperitoneal route of administration. The commercial specification acceptance criterion for abnormal toxicity of both the 10^6 PFU/mL and 10^8 PFU/mL drug product strengths is (b) (4) as reflected in the absence of toxic effect in both animal species.

CMC Comments on the justification of specifications: *DP specifications are justified and are appropriate,*

3.2.P.6 Reference Standards or Materials

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

In sum, the applicant has appropriate procedures in place to ensure the integrity, stability and continuity of talimogene laherparepvec reference standards. The critical biological activity / potency assays are performed multiple times to directly compare a new reference standard to the previous one, and to ensure that the standards are appropriately bridged.

Amendment 1 section 3.2.8.3 describes stability data for lot (b) (4). In section 1.5 of 3.2.P.6, Amgen states that the expiration date for the reference standard will be determined when sufficient data are available. In response to our questions, Amgen provided further information indicating that stability testing on (b) (4) has been performed at (b) (4) (data not provided) and will be tested at 48, (b) (4) Tests will include (b) (4). Specifications will be the current release specifications. (b) (4) is not currently being assessed due to lack of a suitable reference material, but in amendment 20 the sponsor clarified that they are currently implementing an (b) (4)

In amendment 20, Amgen describes how they will extend the shelf life of a reference standard. Parameters will be trended and the shelf life may be extended if there is no evidence of a significant change in the quality attributes. Any such changes in the expiry date will be documented in a report.

***CMC comments**: Amgen has appropriate procedures and specifications in place for qualifying new lots of talimogene laherparepvec reference standard, and for analyzing the stability of the reference standard. Amgen is in the process of developing an* (b) (4)

Other Reference Standards: The BLA contains COAs for the reference standards used in various assays. For a review of the use of reference standards, please refer to the assay review section. The reference standards are reviewed under section 3.2.S.5 of this review.

3.2.P.8.1 Stability Summary and Conclusion

Stability studies were performed per ICH Harmonized Tripartite Guidelines *Stability Testing of Biotechnological/Biological Products (Q5C)* and *Stability Testing of New Drug Substance and Products (Q1A)* as guidance to establish a 48 month expiry period for drug product at the recommended storage temperature of -80°C. Drug product is stored frozen at -80°C, and long-term stability testing is performed on vials in an upright orientation. There is no potential for liquid contact with the closure during frozen storage. Post thaw, vials are stored at (b) (4) in the upright position, however the inverted position has been demonstrated to have no impact on product quality.

The talimogene laherparepvec stability program consists of (b) (4) lots of 10^8 PFU/mL (including (b) (4) reference standard lots) and (b) (4) lots of 10^6 PFU/mL stored at the recommended storage temperature of -80°C. The overall stability program includes lots from:

- (b) (4)

3.2.P.8.2 Post-Approval Stability Commitment

Amgen commits to continue the ongoing stability studies for the production lots until completion (for a maximum of 48 months for various commercial lots that are currently in the stability study). In addition,

- (b) (4)

1 page determined to be not releasable: (b)(4)

3.2.P.8.3 Stability Data

DP stability was evaluated at -80°C (recommended storage temperature and at stressed storage conditions. Please refer to section 3.2.P.8.1 for a summary of the stability studies.

In addition to the recommended storage condition of -80°C, stability has been assessed for 10^8 PFU/mL and 10^6 PFU/mL under the following conditions:

- (b) (4)

Stability test conditions along with the acceptance criteria and justification for the selected test methods used to determine DP stability during the IND phase are described below.

Table 79: DP Stability Tests and Acceptance Criteria

Parameter	Test Method	Acceptance Criteria [c] (10^8 PFU/mL)	Acceptance Criteria [c] (10^6 PFU/mL)
(b) (4)			

CMC comment: *The methods and tests used in the post approval stability testing are identical to the test methods used during the IND phase, rearranged under different parameters.*

Stability indicating properties of selected parameters:

(b) (4)

Confidence Limits for 48 month Shelf life:
The following set of 2 figures (figure 17 and 18) are representative figures to show the stability of various Talimogene DP lots stored at -80C±10C over 48 month time. The 95% upper and lower confidence indexes (established around the predicted mean and not the individual data points) are marked in dotted lines. The stability data are summarized below. Additional graphs are included in Amendment # 8.

Figure 17: Estimation of DP Shelf Life (10^6 PFU/mL)

1 page determined to be not releasable: (b)(4)

Stability data compiled to date for 10^8 PFU/mL and 10^6 PFU/mL talimogene laherparepvec stored at the recommended storage temperature of -80°C for up to 48 months has remained within the stability acceptance criteria with the exception of two data points for the (b) (4) assays.

- (b) (4) lot of 10^8 PFU/mL drug product (b) (4) exceeded the lower specification limit for virus infectivity at (b) (4) months, this result was investigated, and a repeat assay and (b) (4) subsequent time point results were within specification.
- (b) (4) lot of 10^6 PFU/mL drug product (BP1047FA) exceeded the lower specification limit for (b) (4) at (b) (4) months, this result was investigated and results from (b) (4) subsequent time points were within specification.
- Both out of specification results were investigated and determined to be atypical.

(b) (4)

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(b) (4)

(b) (4)

These experimental stability studies demonstrate that both 10^8 PFU/mL and 10^6 PFU/mL drug product is stable under conditions that may be encountered during clinical use, including storage at (b) (4) for a period of up (b) (4) respectively, in the commercial container protected from light.

- Additionally, experimental stability studies on thawed drug product (at (b) (4) demonstrate no difference when stored either upright or inverted.

CMC comments on the stability analysis:

- *All stability assay results indicate that the DP is losing stability over time and likely to be OOS in less than (b) (4) months.*
- (b) (4)
- *There are a few values that are outside the specified limits (10 (b) (4) ; 10^6 (b) (4) assay). However, since later time point measurements are within the specified limits, the Firm's explanation of atypical result is acceptable.*
- *DP is stable and conforms to specifications for 48 months when stored at the specified storage temperature of -80±10°C, but this may not be extended based on the results of stability studies.*
- *DP continues to be within specifications (stable) after short term (for (b) (4) storage at (b) (4) after thaw for both 10^8 and 10^6 doses, respectively.*

CMC Comments: *Results for each group of studies are presented in BLA. This review does not include all the tables presented in the BLA but has a few tables that are taken as representative data.*
Primary Lots: *are the ones used to determine product stability- these lots were manufactured using the same manufacturing process as the commercial product. Have complete stability data for 48 months.*
Production lot: *are the ones that are currently in commercial production. Have ongoing stability studies.*

Stability information for the 10^8 PFU lots stored at the recommended storage temperature of -80C is included in the BLA and not reproduced here. Please see text for comments on the 10^8 PFU/mL stability.

(b) (4)

(b) (4)

(b) (4)

3.2.A Appendices

3.2.A.1 Facilities and Equipment
Please see DMPQ review

3.2.A.2 Adventitious Agents Safety Evaluation
Non-viral Adventitous Agents
The talimogene laherparepvec manufacturing process incorporates control measures to prevent contamination and maintain microbial control. Information regarding non-viral adventitious agents, including control of microbial contaminants in the manufacturing process is reviewed in Section 3.2.S.2.2 (Description of Manufacturing Process and Process Controls), Section 3.2.S.2.3 (Control of Materials) and Section 3.2.S.2.4 (Control of Critical Steps and Intermediates).

Viral Adventitious Agents
The strategy to ensure viral safety in the manufacturing process for talimogene laherparepvec is based on a multilayered approach. The (b) (4)

(b) (4)

3 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

3.2.A.3 Novel Excipients
There are no novel excipients used in talimogene laherparepvec drug product

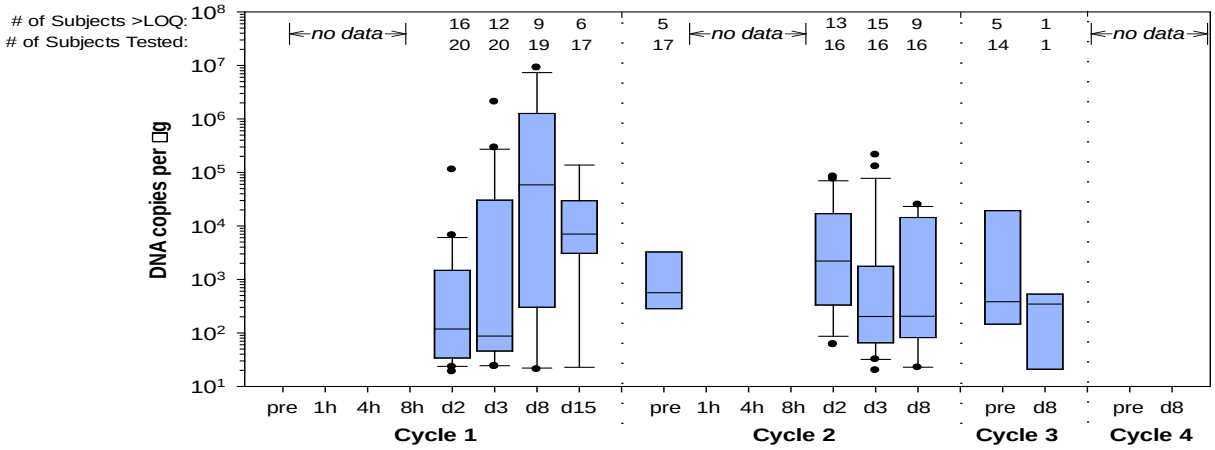
3.2.A.4 Shedding Studies
Talimogene laherparepvec has been attenuated to reduce virulence; however, it is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding and potential for transmission and life-long latency/symptomatic reactivation. To date, there are limited data on product shedding from treated subjects, which serves as a proxy for transmission.

The applicant has an active clinical protocol (Amgen 20120324) that is designed to collect and evaluate samples for shedding with validated assay methods. The applicant expects this study to be completed by the end of 2015 at which time a more complete shedding profile for talimogene laherparepvec is expected to become available. In order to monitor and evaluate transmission of talimogene laherparepvec to Health Care Providers (HCP) and close contacts, the applicant has also proposed a post-marketing study.

Preliminary shedding information for talimogene laherparepvec from the ongoing shedding protocol (Amgen 20120324) is presented in the figures below. In these figures, the number of subjects tested and the number of subjects above the lower limit of quantitation are shown at the top of the plot for each time point.
These data demonstrate the presence of viral DNA at the injection site. A trend of increasing viral DNA at the injection site may indicate some viral replication from day 2 to day 8 (Figure 19). Viral DNA was also detected on the surface of the injection site dressing (Figure 20) and in blood (Figure 21). Very small amounts

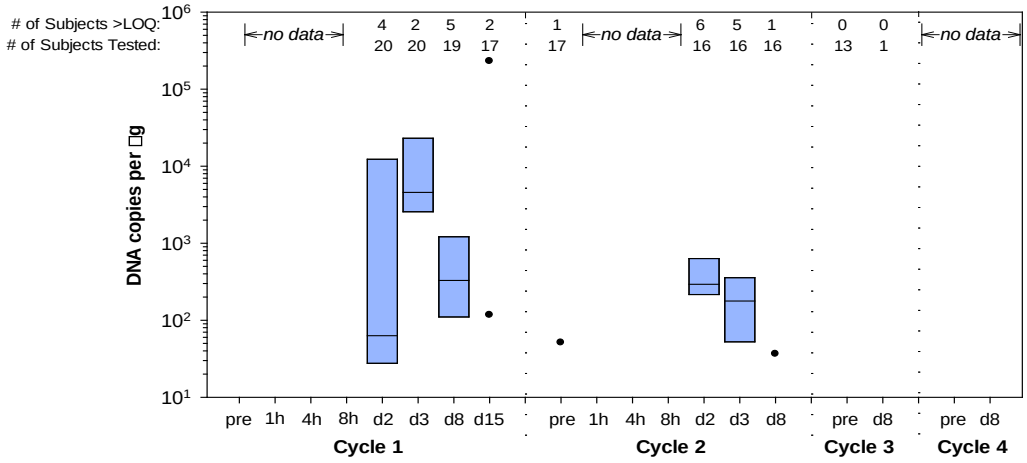
of viral DNA were detected in urine (Figure 22) and no viral DNA was detected in oral mucosa during the first 4 cycles (not shown).

Figure 19: Viral DNA detected by qPCR of swabs of injection site in study 20120312
Available data are presented as a box and whisker plot. There appears to be an increase in viral DNA levels from day 2 to day 8 after the first injection, but a similar increase was not observed after the second or third injections.



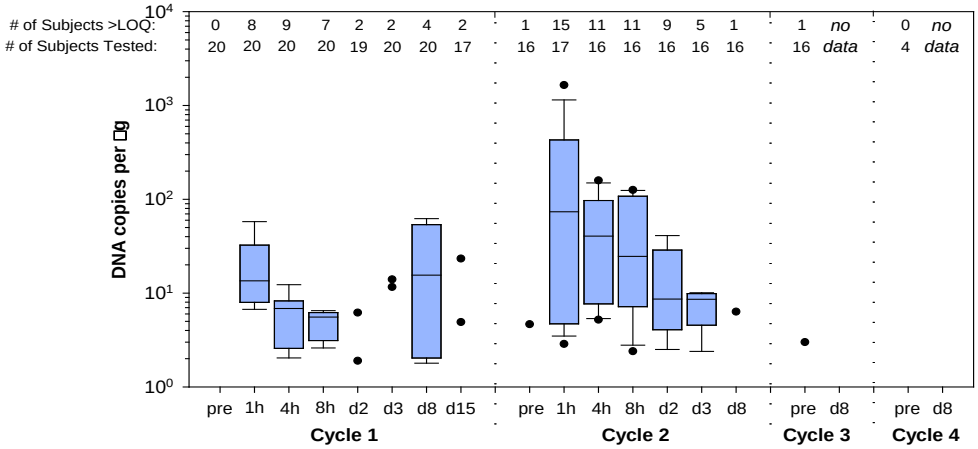
(Alternate text: Figure 19: Shedding data from qPCR results of Injection site swabs are presented as a box and whisker plots. Please see the text for a description of the results).

Figure 20: Viral DNA detected by qPCR of swabs of injection site dressing in study 20120312
Available data is shown as a box and whiskers plot. Viral DNA detected on the dressing surface generally tracked with amount of virus detected at the injection site, indicating that the injection site dressing was not sufficient to contain the virus and prevent surface exposure.



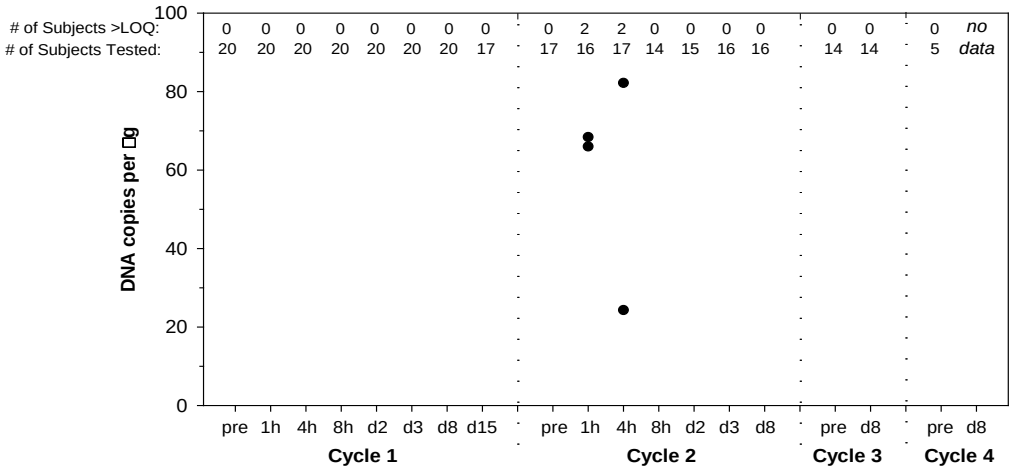
(Alternate text: Figure 20: Shedding data from qPCR results of swabs of Injection site dressing are presented as a box and whisker plots. Please see the text for a description of the results).

Figure 21: Viral DNA detected by qPCR in serum samples in study 20120312
Available data are presented as a box and whisker plot. Viral DNA is detectable within 1 hour of injection. After the first injection the amount of viral DNA appears to increase from 8 hours until day 8. After the second injection viral DNA appears to trend downward over time.



(Alternate text: Figure 21: Shedding data from qPCR results of serum samples are presented as a box and whisker plots. Please see the text for a description of the results).

Figure 22: Viral DNA detected by qPCR in urine samples in study 20120312
Available data presented as a scatter plot. Viral DNA is detectable only after the second injection at a low level.



(Alternate text: Figure 22: Shedding data from qPCR results urine samples are presented as scatter plots. Please see the text for a description of the results).

3.2.R Regional Information

3.2.R.1 Executed Batch Records

CMC Comments on the Batch Records:

Executed batch records are included in the BLA. The information contained in the batch records are summarized throughout the BLA in the form of tables and graphs. Executed batch records confirm the data used in the tables and graphs.

3.2.R.2 Method Validation Package

The method validation package was reviewed. The applicant provided summaries of the detailed method protocols in 3.2.S.4.2 and 3.2.P.5.2. The applicant provided summaries of the validation reports in 3.2.S.4.3 and 3.2.P.5.3. The reviewer compared the detailed method protocols and validation reports with their summaries and concluded that the summaries adequately represent the material submitted as the validation package.

Method protocols generally address the following topics: Purpose, Scope, Responsibilities, Company References/ Associated Documents, Other References/ Regulations/ Standards, Definitions, Health and Safety, Equipment/ Materials/ Reagents, Facility, Method Background, Assay Overview, Preparation of (b) (4) Preparation and Performance of the Assay, Calculations, Acceptance Criteria, Reporting Results, and Assay Training. The assays were performed at (b) (4), Abingdon, UK.

The validation reports state that prospective validation protocols were written for each validation, though not included in the BLA.

(b) (4)

(b) (4)

PRODUCT COMPARABILITY

Description of the Comparability Approach

A brief description of the comparability approach is outlined below. Because we do not agree with this approach, we will review the comparability protocol in detail when it is submitted. Briefly, comparability of the (b) (4) and drug product manufactured at AWM will be demonstrated using:

- (b) (4)

(b) (4)

(b) (4)

2 pages determined to be not releasable: (b)(4)