APPLICATION NUMBER:

212642Orig1s000

PRODUCT QUALITY REVIEW(S)
Recommendation: **Approval**

**NDA [212642]**

**Gallium Ga 68 PSMA-11 Injection**

**Review [Final]**

<table>
<thead>
<tr>
<th>Drug Name/Dosage Form</th>
<th>Gallium Ga 68 PSMA-11 Injection/ Sterile solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength(s)</td>
<td>18.5 MBq/mL – 185 MBq/mL (b) 6 mCi/mL – 5 mCi/mL at calibration time</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>IV</td>
</tr>
<tr>
<td>Rx/OTC Dispensed</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant</td>
<td>University of California, Los Angeles (UCLA)</td>
</tr>
<tr>
<td>US agent, if applicable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUBMISSION(S) REVIEWED</th>
<th>DOCUMENT DATE</th>
<th>DISCIPLINE(S) AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original NDA 212642</td>
<td>09/06/2019</td>
<td>CMC (DS, DP), Microbiology, OPF</td>
</tr>
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Quality Review Team

<table>
<thead>
<tr>
<th>DISCIPLINE</th>
<th>PRIMARY REVIEWER</th>
<th>SECONDARY REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Substance</td>
<td>Martin Haber</td>
<td>Donna Christner</td>
</tr>
<tr>
<td>Drug Product</td>
<td>John Amartey</td>
<td>Danae Christodoulou</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Maritere Carattini</td>
<td>John Metcalfe</td>
</tr>
<tr>
<td>Process / Facility</td>
<td>Krishna Ghosh</td>
<td>Vidyai Pai</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Environmental</td>
<td>John Amartey</td>
<td>Danae Christodoulou</td>
</tr>
<tr>
<td>RBPM</td>
<td>Anika Lalmansingh</td>
<td>N/A</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Eldon E. Leutzinger</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>Status</th>
<th>Date Review Completed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td></td>
<td></td>
<td></td>
<td>(1)</td>
<td>(1)</td>
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<td>II</td>
<td></td>
<td></td>
<td></td>
<td>Adequate</td>
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(1) DMF in Biologics.

B. Other Documents: IND, RLD, or sister applications

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>IND</td>
<td>130649</td>
<td>Johannes Czerin</td>
</tr>
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2. CONSULTS

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<th>DATE</th>
<th>REVIEWER</th>
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</thead>
<tbody>
<tr>
<td>N/A</td>
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</table>

Executive Summary

1. Overall Recommendation on Approvability

Approval, based on CMC Product Quality, Microbiological Product Quality and acceptable CGMP Inspections of all manufacturing facilities associated with NDA 212642.

OPQ recommends [APPROVAL] of NDA [212642] for commercialization of [Galium Ga 68 PSMA-11 Injection] in solution with ethanol, water for injection and 0.9% sodium chloride, pH 4.0 – 7.0, and strength of 18.5 MBq/ml to 185 MBq/ml (0.5 mCi/mL to 5 mCi/mL) at calibration time strength(s) with an expiration dating period of (0) hours:

- The applicant [has] provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product.

- The Office of Process and Facility has made a recommendation of [approval] for all the
facilities involved in this application.

- The proposed labeling and labels [have] adequate information to meet the regulatory requirements.

II. Product Quality Review Context

**Indication and Intended Population:**
The proposed indication for $^{68}$Ga-PSMA-11 is positron emission tomography (PET) scanning. It is found capable of detecting PC relapses and metastases with high contrast by binding to the extracellular domain of prostate-specific membrane antigen (PSMA), followed by internalization.

**Regulatory Context - Designation of Drug Substance:**
The active ingredient is that substance after radiolabeling of PSMA-11 which is radioactive, $\text{HBED}^{(68)\text{Ga}}\text{-CC-Ahx-Lys(OH)-CO-Glu(OH)}$ (21 CFR 310.3 (n)), interpreted as the drug substance (a Urea-Based PSMA inhibitor), meaning that it “is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, ... of disease...” (21 CFR 314.3)]. The image result is driven by both biodistribution of the chemical system (containing the radionuclide), and the radioactive emissions from the radionuclide. The science is clear here, creating a basis for $\text{HBED}^{(68)\text{Ga}}\text{-CC-Ahx-Lys(OH)-CO-Glu(OH)}$ to be identified as the entity that furnishes the “action” expected of an active ingredient in the regulatory context. HBED-CC is N,N'-bis[2-hydroxy-5-(carboxethyl)benzyl]-ethylenediamine-N,N'-diacetic acid, and Ahx is amino-hexanoic acid.

(Structure)
Regulatory Context - Regulatory Status of the Precursor:

Product Profile and Critical Quality Attributes (CQA’s):
\[^{68}\text{Ga}\]-PSMA-11 is a sterile aqueous solution of HBED\(^{68}\text{Ga}^{3+}\)-CC-Ahx-Lys(OH)-CO-Glu(OH), C\(_{44}\)H\(_{56}\)[\(^{68}\text{Ga}\)]N\(_{6}\)O\(_{17}\) (MW 1011.91 g/mol), in Sodium Chloride 0.9% Injection and Ethanol. The strength is 0.5 – 5 mCi/mL. HBED\(^{68}\text{Ga}^{3+}\)-CC-Ahx-Lys(OH)-CO-Glu(OH) is an independent, discrete molecular species of defined structure, based on its analogousness to its naturally-abundant counterpart (\(^{\text{Nat}}\text{Ga}\) substituting for \(^{68}\text{Ga}\)), and exists as such in solution. See Regulatory Context – Designation of Drug Substance and under Notes.

Both versions (\(^{\text{Nat}}\text{Ga}, {^{68}\text{Ga}}\)) are subject to the same stability-sensitivities typically possessed by peptides, but the \(^{68}\text{Ga}\) version possesses the additional sensitivity

Areas of Unique Focus:
Summary of Quality Assessments

PRECURSOR (in relation to drug substance)

[adequate, 4/27/2020].

DRUG PRODUCT

The issues identified for the drug product can be collected into 4 major categories (Composition, Specifications, Patient Dose, Stability). Within the category of Composition, concerns were raised regarding the absence of the quantity of PSMA-11 (74 Day Letter Comment #2 - Resolved) and the total amount of PSMA-11, with respect to labeling, in the final drug product (74 Day Letter Comment #5 - Resolved).

(Quality Controls)

In the Specifications, the limit for $^{68}$Ga breakthrough is compared to that for the – 74 Day Letter Comment #3 - Resolved.

Patient dose is contingent on a number of factors that include the radioactivity concentration (i.e., strength), volume and stability, and how these factors work together. In this context, for a patient dose of 5 mCi, it appears that dose volume may be too high, relative to the strength and stability. Based on stability data for the validation batches, a recommendation is being conveyed to the applicant that expiration time should be limited by the maximum allowable injection volume (74 Day Letter Comment #4 - Resolved). And, on the theme of Stability, there is a concern

Hence, a 74 Day Letter Comment #1 was conveyed to the applicant requesting stability in support of this expiration date - Resolved.

➢ Establishment of Product Quality Consistency in $^{68}$Ga-PSMA-11
In this context, the primary review recommends for product quality consistency
(Labeling)
There were two issues in the labeling, **(74 Day Letter)**, recalling from the discussion on pages 3-6 that there had been a “miss on chemistry.”

This is now **Resolved** in the revision of labeling (Final Labeling Text, #0014, 10/30/2020) that includes the correct structure as depicted on page 6 of this Executive Summary.

There was also absence of total amount of PSMA-11 (Section 11.1) and absence of consistency in radioactivity units (Section 16.2), **74 Day Letter**, both now **Resolved**.

(Microbiology Product Quality)
The drug product is **and all issues for microbiology, as enumerated and discussed in the Microbiology Review (Maritere Carattini, Ph.D., 02/21/2020) have been adequately resolved.** According to the Microbiology Review, there are no remaining deficiencies and the University of California, Los Angeles (UCLA) has met all regulatory expectations from the perspective of microbiology product quality.

(Manufacturing Facilities)

<table>
<thead>
<tr>
<th>Facility</th>
<th>Responsibility</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLA Biomedical Cyclotron Facility-Los Angeles</td>
<td>Production, packaging, labeling, release testing of drug product</td>
<td>Approved¹ 10/26/2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved² 10/26/2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Approved³ 10/26/2020</td>
</tr>
</tbody>
</table>

(1) The inspectional deficiencies identified in the PAI (7.27 – 31/2020) and issued to the UCLA Biochemical Cyclotron Facility are summarized into the areas of

Manufacturing Process – Process Specific

Analytical

Product Specific

All IR’s have been adequately addressed.

Final: UCSF approved 10/26/2020 based on PAI. However, there will be a PAI inspection verification during the next surveillance inspection.
(2) Approved on the basis of previous history.

Final: Approved 10/26/2020

(3) [Signature] approved on the basis of PAI. [Signature] approved on the basis of 706/704 (a) process.


III. Final Analysis of Product Quality Review Issues (~200 words per issue)
No issues remain from the primary reviews from CMC (Chemistry, Manufacturing and Controls) Product Quality, Microbiology Product Quality and Manufacturing Facility Inspection standpoints. Gallium Ga 68 PSMA-11 Injection meets all applicable standards to support the identity, strength, quality and purity that it purports.

IV. There are no remaining issues from the primary reviews from CMC (Chemistry, Manufacturing and Controls) Product Quality, and Microbiology Product Quality concerning the identity, strength, quality and purity of Gallium Ga 68 PSMA-11 Injection. Facility reviews have been completed and the review from OPF is in Panorama, recommending approval of NDA 212642. However, there will be a PAI inspection verification during the next surveillance inspection.

IV. Summary Basis for Product Quality Recommendation (150 words)

V. Lifecycle Considerations
N/A

VI. [OPTIONAL] Draft Text for Complete Response Letter/ Postmarketing Commitment or Requirement
N/A
CHAPTER VII: MICROBIOLOGY

<table>
<thead>
<tr>
<th>Product Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA Number</td>
<td>212642</td>
</tr>
<tr>
<td>Assessment Cycle Number</td>
<td>01</td>
</tr>
<tr>
<td>Drug Product Name/ Strength</td>
<td>PSMA-11 Ga 68 Injection, 0.5 - 5 mCi/mL</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Intravenous injection</td>
</tr>
<tr>
<td>Applicant Name</td>
<td>University of California Los Angeles</td>
</tr>
<tr>
<td>Therapeutic Classification/ OND Division</td>
<td>Radioactive Diagnostic Agent for Positron Emission Tomography</td>
</tr>
<tr>
<td>Manufacturing Site</td>
<td>UCLA Biomedical Cyclotron Facility 780 Westwood Plaza Los Angeles, CA 90095</td>
</tr>
<tr>
<td>Method of Sterilization</td>
<td>Filter sterilization followed by aseptic fill</td>
</tr>
</tbody>
</table>

_Assessment Recommendation: Adequate_

_Assessment Summary:_

List Submissions being assessed:

<table>
<thead>
<tr>
<th>Document(s) Assessed</th>
<th>Date Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>0000</td>
<td>06 September 2019</td>
</tr>
<tr>
<td>0004 (IR Response)</td>
<td>06 January 2020</td>
</tr>
<tr>
<td>0007 (IR Response)</td>
<td>14 February 2020</td>
</tr>
</tbody>
</table>

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable

Remarks: This is a positron emission tomography (PET) imaging drug product

Concise Description of Outstanding Issues: None
Supporting Documents: N/A
S DRUG SUBSTANCE
The drug product is a product quality microbiology review of the drug substance is not applicable.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product** – A clear colorless liquid, packaged in a multi-dose 30 mL glass vial with a rubber stopper and aluminum crimp seal.

- **Drug product composition** – (Section 3.2.P.3.2, “Batch Formula”)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount/ batch</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>^86Ga-PSMA-11</td>
<td>0.5 - 5 mCi per mL</td>
<td>Drug substance</td>
</tr>
<tr>
<td>Sodium Chloride 0.9%, USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol, USP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Description of container closure system** – (Section 3.2.P.7, “Container Closure System”)

The drug product is packaged in a 30 mL USP glass vial with gray rubber stopper, and aluminum crimp seal. The container closure is

**Assessment: Adequate**
The applicant provided an adequate description of the drug product composition and the container closure system is designed to maintain product sterility.

P.2 Pharmaceutical Development
**P.2.5 Microbiological Attributes**

**Container/Closure and Package Integrity**
This information is not required for PET drug products as the subject drug product is administered within three hours of End of Synthesis (EOS) and the container closure system is

**Assessment: Not Applicable**
Antimicrobial Effectiveness Testing
This information is not required for PET drug products as the subject drug product is administered within three hours of EOS.

Assessment: Not Applicable

P.3 Manufacture
P.3.1 Manufacturers

UCLA Biomedical Cyclotron Facility
780 Westwood Plaza
Los Angeles, CA 90095

P. 3.3 Description of the Manufacturing Process and Process Controls
Overall Manufacturing Operation
(Section 3.2.P.3.3, “Description of Manufacturing Process and Process Controls”)

The manufacturing process is outlined in the applicant’s diagram below.

6 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page
## P.5 Control of Drug Product
### P. 5.1 Specification
(Section 3.2.P.5.1, “Specifications”)

The product release specification includes the following microbiological tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Requirements</th>
<th>Acceptance Criteria</th>
<th>Exhibit Batches Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxins per USP &lt;85&gt;</td>
<td></td>
<td></td>
<td>All passed</td>
</tr>
<tr>
<td>Sterility per USP &lt;71&gt;</td>
<td></td>
<td></td>
<td>All &lt; 30 EU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All sterile</td>
</tr>
</tbody>
</table>
Assessment: Adequate
The applicant has met regulatory expectations in regard to product release specification for the subject drug product.

P.5.2 Analytical Procedures – See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures
Endotoxins
(Section 3.2.P.5.2, “Validation Endotoxin Test”; Section 3.2.P.5.6, “Justification of Specifications”, p. 3)

- Endotoxins specification: [redacted] EU/V (0.01 EU/mL)
- Lysate sensitivity: 0.01 EU/mL
- Applicant’s MVD: 0.01
- Reviewer’s calculated MVD:
  \[ \text{MVD} = (\text{endotoxin limit}) \times (\text{sample conc.}) / (\lambda) \]

- The Inhibition/Enhancement study was performed on three lots of the subject drug product using the following dilutions:

- Maximum possible dose: [redacted] mL (provided in the “Justification of Specifications” document)
- Calculated proposed endotoxins specification with maximum dose:
  \[ (\text{[redacted]} \text{ mL}) \times (\text{[redacted]} \text{ EU/mL}) = [redacted] \text{ EU/dose} \]

The endotoxin dose at the proposed endotoxins specification and maximum dose as calculated by this reviewer is within the maximum recommended for PET drug products as defined in USP <85> as no more than [redacted] EU/V, where V is the fill volume.

Information request sent to the applicant on 07 November 2019 and response received on 06 January 2020:
1. The bacterial endotoxins validation report provided in Section 3.2.P.5.3, is acknowledged. However, it is unclear [redacted] For more information please refer to USP <85>, Bacterial Endotoxins Test, which states: “If necessary, adjust the pH of the solution to
be examined (or dilution thereof) so that the pH of the mixture of the lysate and Sample Solution falls within the pH range specified by the lysate manufacturer, usually 6.0–8.0.” Please address the following:

a. **Confirm that the pH of the drug product tested in the endotoxin method validation was within the pH as defined**. If not, then provide updated validation data using the correct product pH.

**Response:** The applicant provided results of a new bacterial endotoxins validation study that included the pH measurement of the product samples. The pH of the exhibit batches used in the study was measured and resulted in a pH which is within the manufacturer specification.

b. **Please revise the endotoxins test method to include instructions**

**Response:** The applicant explained

c. **Describe the actions taken in the event of a bacterial endotoxins test failure.**

**Response:** The applicant provided the following actions taken in the event of a BET failure:

2. **In Section 3.2.P.5.6 (“Justification of Specifications”, p. 3), it is stated that the bacterial endotoxins limit**

   **Please clarify the worst-case maximum dose and provide updated documents reflecting the correct endotoxins limit (EU/mL) as needed. In addition, correct the MVD calculation accordingly.**
Response: The applicant updated Section 3.2.P.5.6 (Justification of Specifications) and explained that the worst-case maximum dose is 0(0) EU/mL which translates to a bacterial endotoxins limit of 0(0) EU/mL. It is also explained that the final volume of each batch can fluctuate and so the batch record provides the BET limit as 0(0) EU/dose.

Assessment: Adequate
The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the bacterial endotoxins test that will be performed on the drug product prior to its release.

Sterility
(Section 3.2.P.5.2, “Analytical Procedures”, p. 4)

The sterility testing of the drug product is performed

Actions taken in the event of a sterility failure: A full investigation is initiated to identify the source and route of contamination followed by corrective and preventative actions.

Method Validation: (Section 3.2.5.3, “Validation Sterility Test Method PSMA 11”)

The product showed no bacteriostatic/fungistatic properties.

Information request sent to the applicant on 07 November 2019 and response received on 06 January 2020:
The information concerning sterility testing in Section 3.2.P.5.2 is acknowledged. However, the actions taken in the event of a sterility failure does not include notifying the receiving facility. Confirm that as part of the actions taken in the event of a sterility failure
the receiving facility is immediately notified. Please refer to the Agency’s 2009 Guidance, PET Drugs- Current Good Manufacturing Practice (cGMP), which states: “We recommend the establishment of effective procedures for immediate notification of the receiving facility if there is evidence of an out-of-specification result, and the notification should be documented.”

Response: The applicant provided the following description:

Assessment: Adequate
The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

P.8 Stability
P. 8.1 Stability Summary and Conclusion
(Section 3.2.P.8.1, “Stability Summary”)

Three exhibit batches (68GaPSMA-11102518ST, 68GaPSMA-11102618ST, 68GaPSMA-11103118ST) were evaluated for stability at the proposed expiry of 3 hours after EOS. The batches were manufactured as proposed in Section 3.2.P.3.3. The vials were stored bacterial endotoxins and sterility testing were performed Analysis of the stability results shows that all acceptance criteria were met at the end of the stability study.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment
(Section 3.2.P.8.2, “Postapproval Stability”)

The applicant commits to assess the stability of at least one production batch of the subject drug product annually.

P.8.3 Stability Data
(Section 3.2.P.8.3, “Stability Data”)

There are no stability data associated with the microbiological tests due to the short expiry (3 hours) of the drug product.
Assessment: Adequate
The stability testing for the subject drug product does not include microbiological assays. The microbiological tests are performed The lack of routine stability studies does not impact the sterility assurance of the subject drug product since it has a short shelf-life (3 hours). The applicant has met regulatory expectations with regard to the design of the stability testing program.

R Regional Information

Executed Batch Records
(Section 3.2.R, Regional Information)

Executed batch records are provided for exhibit batches 68GaPSMA11102518ST, 68GaPSMA11102618ST, and 68GaPSMA11103118ST.

Assessment: Adequate
The applicant provides adequate manufacturing records to support the manufacturing process for the drug product.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert
(Section 1.14.1.1, “Draft Vial Label”)

The drug product is labeled as sterile, pyrogen-free, and multi-dose. The subject drug product is stored at 2-8 °C and must be used within 3 hours of the EOS.

Assessment: Adequate
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Reviewer: Maritere Carattini, MS, 21 February 2020
Secondary Reviewer: John W. Metcalfe, PhD, 21 February 2020
Comments: I concur with the primary reviewer's assessment.
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANIKA A LALMANSINGH
11/11/2020 08:51:12 AM

ELDON E LEUTZINGER
11/12/2020 07:35:23 AM