

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212643Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 127621

**MEETING MINUTES**

University of California San Francisco  
Attention: Thomas A. Hope, MD  
505 Parnassus Avenue, M-391  
San Francisco, CA 94143-0628

Dear Dr. Hope:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gallium-68 labeled HBED-CC PSMA, Gallium-68 labeled PSMA-11.

We also refer to the meeting between representatives of your firm and the FDA on August 29, 2018. The purpose of the meeting was to discuss a joint venture regarding your proposed NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, MD, PhD  
Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B

**Meeting Category:** Pre-NDA

**Meeting Date and Time:** August 29, 2018

**Meeting Location:** Bldg. 22 Room 1419

**Application Number:** IND 127621

**Product Name:** Ga 68 -PSMA-11

**Indication:** Imaging of metastatic prostate cancer:

**Sponsor/Applicant Name:** University of California; San Francisco- Dr. Thomas A. Hope

**Meeting Chair:** Anthony Fotenos

**Meeting Recorder:** Diane Hanner

**FDA ATTENDEES**

OFFICE OF NEW DRUGS / OFFICE OF DRUG EVALUATION IV/IMMEDIATE OFFICE

- o Lesley Furlong, MD, Deputy Director, Office of Drug Evaluation IV
- o Jagjit Grewal, MPH, Associate Director for Regulatory Affairs, Office of Drug Evaluation IV

OFFICE OF NEW DRUGS / OFFICE OF DRUG EVALUATION IV/ DIVISION OF MEDICAL IMAGING PRODUCTS

- o Libero Marzella, MD, PhD. Director, Division of Medical Imaging Products, (DMIP)
- o Alex Gorovets, MD, Deputy Director, DMIP
- o Anthony Fotenos, MD, PhD, Clinical Team Leader, DMIP
- o August Hofling, MD, PhD, Medical Officer, DMIP
- o Nushin Todd, MD, PhD, Clinical Team Leader, DMIP (phone)
- o Phillip Davis, MD, Medical Officer, DMIP (phone)
- o Sunny Awe, PhD, Pharmacology/Toxicology Reviewer, DMIP
- o Stanley H. Stern, PhD, Health Physics Reviewer, DMIP
- o CAPT Diane Hanner, MPH, MSW, LSW, Senior Program Management Officer, DMIP

OFFICE OF TRANSLATIONAL SCIENCES / OFFICE OF BIOSTATISTICS /  
DIVISION OF BIOSTATISTICS V

- o Sue Jane Wang, PhD, Deputy Division Director, DBV
- o Jyoti Zalkikar, PhD, Biostatistics Team Leader, DBV
- o Xiangmin Zhang, PhD, Biostatistics Reviewer, DBV

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH / OFFICE OF IN VITRO  
DIAGNOSTICS AND RADIOLOGICAL HEALTH/

- o William Jung, PhD, Supervisor Biologist, CDRH
- o Andrew Kang, MD, Medical Officer, CDRH
- o Xin He, PhD, Biomedical Engineer, CDRH

OFFICE OF NEW DRUGS PRODUCTS / DIVISION OF NEW DRUG PRODUCTS (DNDPII)

- o Eldon Leutzinger, PhD, CMC Reviewer, DNDPII
- o John K. Amartei, PhD, CMC Reviewer, DNDPII

OFFICE OF PHARMACEUTICAL QUALITY/OFFICE OF PROCESS AND FACILITIES,  
DIVISION OF MICROBIOLOGY ASSESSMENT (DMA)

- o Daniel Schu, PhD, Microbiologist reviewer, DMA,

**SPONSOR ATTENDEES**

UNIVERSITY OF CALIFORNIA SAN FRANCISCO (UCSF)

- o Thomas Hope, MD, Principal, Investigator/Sponsor, UCSF
- o Ashley Mishoe, PharmD, Cyclotron Facility Manager, UCSF

UNIVERSITY OF CALIFORNIA LOS ANGELES (UCLA)

- o Johannes Czernin, MD, Principal, Investigator/Sponsor UCLA
- o Roger Slavik, PhD, Biomedical Cyclotron Director, UCLA
- o Jeremie Calais, MD, Investigator, UCLA
- o Shaojun Zhu, Regulatory Affairs, UCLA
- o Wolfgang Fendler, Investigator, MD, UCLA

- (b) (4)
- (b) (4) Regulatory Consultant to UCLA/UCSF (b) (4)
  - (b) (4) Regulatory Consultant to UCLA/UCSF (b) (4)
  - (b) (4) Regulatory Consultant to UCLA/UCSF (b) (4)  
(b) (4) (phone)

## 1.0 BACKGROUND

The Sponsor is participating in an initiative which includes both the University of California San Francisco (UCSF) and the University of California, Los Angeles (UCLA). They requested a Type B (Pre-NDA) meeting on June 22, 2018, and the briefing package was included with the request. The primary objective of the meeting was to discuss Gallium Ga 68 Labeled HBED-CC PSMA (68Ga-PSMA-11) for the imaging of patients with metastatic prostate cancer and their path forward to an NDA submission.

The meeting was granted on June 27, 2018, and it was scheduled for August 29, 2018.

FDA sent Preliminary Comments to Dr. Thomas Hope on August 23, 2018.

## 2.0 DISCUSSION

### **OPENING FDA PREAMBLE COMMENT:**

In your submitted data from the prospective biochemical recurrence trial, we note that the majority of 68Ga-PSMA-11 PET-positive patients appear to have had no histopathology correlation or imaging follow-up. Concern over these extensive missing data influences our responses to the clinical questions below.

### **MEETING DISCUSSION- FDA PREAMBLE COMMENT:**

**Please see the meeting discussion captured under Question 6 (below).**

### **Question 1:**

Does the Agency agree that the prospective clinical trial data collected at UCLA and UCSF can be pooled into 1 final CSR for BCR and 1 final CSR for primary staging?

### **FDA RESPONSE To Question 1:**

We agree with your proposal to submit one CSR focused on the combined UCSF/UCLA prospective biochemical recurrence trial and another CSR focused on the combined UCSF/UCLA prospective pre-prostatectomy trial. We request that your NDA also include as detailed a summary as possible of data excluded from your submission but collected with your protocol at sites outside of UCLA and UCSF. See also FDA response to Question 2, below, for requested

approach to reporting on the evidence available from the literature, since it is premature to exclude a pivotal role for this evidence in supporting the efficacy of 68Ga-PSMA-11.

**MEETING DISCUSSION- Question 1:**

**The Agency agreed with the Sponsor that the additional available data from the University of Michigan site, currently estimated at approximately 100 patients, should be included in the official NDA submission. As the trial has not matured at this site to date, the Agency agreed that blinded reads and correlation with the composite endpoint are not requirements.**

**Question 2:**

Does the Agency agree that a side-by-side comparison of the efficacy and safety data from the Phase 3 prospective studies and meta-analyses is acceptable and that data pooling is not necessary?

**FDA RESPONSE To Question 2:**

Module 5 clinical study reports should be presented separately for the combined UCSF/UCLA prospective biochemical recurrence trial, combined UCSF/UCLA prospective pre-prostatectomy trial, review of biochemical recurrence publications, and review of pre-prostatectomy publications. The Module 2 Summary of Clinical Safety should present safety data pooled from all four of these sources. Additionally, each reviewed publication should be categorized as either describing adverse events, not describing adverse events but specifically mentioning adverse event monitoring, or not describing adverse events or adverse event monitoring.

**MEETING DISCUSSION- Question 2:**

**None.**

**Question 3:**

Does the FDA agree that the results from the prospective BCR clinical study and meta-analysis in BCR patients provide adequate evidence of the diagnostic efficacy of PSMA-11 Ga 68 Injection PET/CT in BCR and no additional studies are needed to support an NDA?

**FDA RESPONSE To Question 3:**

The totality of the results summarized in your meeting package, including prospective trial data and literature review for both biochemical recurrence and pre-prostatectomy settings, appear adequate for 505(b)(2) NDA submission. Determination of adequacy of the submitted evidence to support marketing approval will be an NDA review issue.

**MEETING DISCUSSION- Question 3:**

**None.**

**Question 4:**

Does the FDA agree that the results from the prospective pre-prostatectomy clinical study and meta-analysis in pre-prostatectomy patients provide adequate evidence of the diagnostic efficacy of PSMA-11 Ga 68 Injection PET/CT in initial staging and no additional studies are needed to support an NDA?

**FDA RESPONSE To Question 4:**

See FDA response to Question 3 above.

**MEETING DISCUSSION- Question 4:**

**None.**

**Question 5:**

Based on the results described in Table 1 and the known mechanism of action of PSMA-11 Ga 68 Injection, does FDA agree that the data provided are sufficient to support a broad indication for PSMA-11 Ga 68 Injection PET/CT (b) (4) and no additional studies need to be conducted?

**FDA RESPONSE To Question 5:**

See FDA response to Question 3 above.

**MEETING DISCUSSION- Question 5:**

**None.**

**Question 6:**

Does the Division agree with UCLA and UCSF providing datasets in legacy format for both Phase 3 studies and the BCR and primary staging meta-analyses?

**FDA RESPONSE To Question 6:**

For description of study start dates after which applicants must use the appropriate FDA-supported standards specified in the Catalog for NDA submissions, see FDA guidance entitled, "Providing Regulatory Submissions in Electronic Format – Standardized Study Data" (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>).

For your prospective biochemical recurrence trial, we recommend submission of clarifying information for each of the 475 patients with positive  $^{68}\text{Ga}$ -PSMA-11 PET findings that describes why they did or did not undergo biopsy, surgery, or follow-up imaging. We also recommend that tabular data from the prospective biochemical recurrence trial include the PSA value of each patient at enrollment and whether each patient had negative or positive conventional imaging at enrollment (including data on the source and localization of any pre-PET positive lesions).

In the clinical study report focused on your review of the biochemical recurrence literature, we recommend reference to the following table outline for specific information we would find helpful in evaluating the strength of this evidence.

|                                                                                                                              | <u>Publication 1</u> | <u>Publication 2</u> | <u>Publication X</u> |
|------------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| Protocol pre-registered (and, if yes, where)?                                                                                |                      |                      |                      |
| NCT identifier number (if any)                                                                                               |                      |                      |                      |
| Number of patients enrolled                                                                                                  |                      |                      |                      |
| Number of patients completing $^{68}\text{Ga}$ -PSMA-11 PET                                                                  |                      |                      |                      |
| Number of PET positive patients with tissue correlation                                                                      |                      |                      |                      |
| Number of PET positive patients with imaging follow-up                                                                       |                      |                      |                      |
| Number of patients with positive conventional imaging at enrollment                                                          |                      |                      |                      |
| PSA distribution among patients and summary of PSA-stratified detection rate and PPV subgroup analyses                       |                      |                      |                      |
| Subgroup analysis of detection rate and PPV stratified by whether PET findings were new compared to other imaging modalities |                      |                      |                      |
| Number of blinded readers used                                                                                               |                      |                      |                      |
| Number and identity of regions interpreted per patient                                                                       |                      |                      |                      |
| Patient-level and/or region-level primary efficacy endpoints?                                                                |                      |                      |                      |

#### **MEETING DISCUSSION- Question 6:**

**The Agency expressed concerns regarding the amount of data that appears to be missing from the sponsor's prospective biochemical recurrence trial, particularly the large number of patients without follow-up histopathology or imaging. The Sponsor clarified that the vast majority of patients were monitored by PSA under radiation therapy, systemic therapy, or active surveillance in alignment with European SIOG guidelines. Similarly, in the sponsor's prospective pre-prostatectomy trial, the sponsor stated that certain patients did not undergo planned surgery due to metastatic disease or preference for radiotherapy. The Sponsor indicated that they will tabulate data for each patient in these trials detailing**

**why or why not patients underwent biopsy, surgery, or follow up imaging. The Agency commented that this approach would be helpful in clarifying the missing data with respect to the prospective studies.**

**For the subset of their prospective patients who had conventional imaging prior to enrollment, the Sponsor also agreed to tabulate whether these imaging results were positive or negative.**

**The need for additional analysis of the supporting literature sources was also discussed. Citing the example table provided in the pre-meeting comments, the Agency indicated that a vigorous investigation of the published data will be necessary to expose any potential bias related to missing data. The Sponsor agreed to complete the fields in the above table for the published studies and to add a field to indicate whether furosemide was administered for PET imaging purposes.**

**Question 7:**

Does the Division agree with our request to waive the requirements for an ISE and an ISS in the UCLA and UCSF NDAs?

**FDA RESPONSE To Question 7:**

We recommend including cross-references to the appropriate summary documents in Module 2 and your cross-referencing rationale in the required ISE and ISS sections of Module 5. See also FDA guidance, “Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” (<https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf>).

**MEETING DISCUSSION- Question 7:**  
**None.**

**Question 8:**

Does the FDA agree with not submitting patient CRFs, patient narratives, or patient profiles for the prospective Phase 3 studies?

**FDA RESPONSE To Question 8:**

For description of FDA guidance focused on the relevance of patient-level CRFs and narratives during the NDA review, see “Attachment B: Clinical Safety Review of an NDA or BLA of the Good Review Practice: Clinical Review Template (MAPP 6010.3 Rev. 1)” (<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM080121.pdf>).

**MEETING DISCUSSION- Question 8:**

**None.**

**Question 9:**

Does the Agency agree that the pharmacology and dosimetry data from the literature is adequate and that an average radiation dosimetry calculated across the published literature is acceptable for use in the product labeling?

**FDA RESPONSE To Question 9:**

Without additional justification and clarification, the data from the three papers that you've identified are not necessarily sufficient as a basis to characterize biodistribution and dosimetry of the product in its labeling. As review issues, we expect the following items to be addressed:

- a) There would need to be a strong justification that such data in some general sense represent the bio- and absorbed-dose distributions of the drug product in its ultimately manufactured and controlled formulation. The papers you cite involve different methods of product preparation, and it's not clear that the sources and radiolabeling methods are equivalent in yielding the same formulations of final product:
  - 1) In the study of Green et al., the  $^{68}\text{Ga}$  PSMA-11 conjugate was purchased as a commercial-grade product from ABX GmbH, and the radiolabeling was done with ITG Garching  $^{68}\text{Ge}/^{68}\text{Ga}$  generators employing an ITG labeling module. On the other hand, the study of Afshar-Oromieh et al. states that the  $^{68}\text{Ga}$  was obtained from a generator of iThemba IDB-Holland bv, Baarle-Nassau, Netherlands, and the source of the conjugate is implicitly cited via reference. The generators/labeling modules are different. Are the conjugate sources the same or different?
  - 2) The paper of Pfob et al. cites iThemba Labs, Somerset West, South Africa as the source of the  $^{68}\text{Ga}$  generator, with the labelling implemented via a fully automated module (Scintomics, Fuerstenfeldbruck, Germany) with GMP-grade disposable cassettes and reagent kit from ABX, Radeberg, Germany. Again, the generator and labeling module are different from those of the other two studies. What about the source of the conjugate?
- b) There would need to be clarification that the studies on which the data are based comport with the product indications within their associated clinical context, where such context might include the administration of any other product either to improve imaging of potential lesions or to safeguard against unnecessary radiation exposure. For example, the patients in the study of Pfob et al. were administered a diuretic (20 mg furosemide) after injection of  $^{68}\text{Ga}$ -PSMA HBED-CC. Those authors explain that

“This was necessary to eliminate activity from the urinary tract, including the bladder, to enhance clinical reporting especially with regard to potential lesions in the prostate or

adjacent to the ureters. Because of the increased urine production and excretion of tracer, a lower absorbed dose in the kidneys is to be expected. Due to the higher frequency of voiding after furosemide application, the 'absorbed dose' of the bladder will remain low."

The rationale to enhance clinical reporting with use of a diuretic suggests that research in the clinical application of <sup>68</sup>Ga-PSMA HBED-CC is still ongoing, and a diuretic could significantly impact biodistribution and radiation absorbed dose. Would the labeling reflect such administration of a diuretic, and if so, how does the diuretic affect biodistribution and radiation absorbed dose?

- c) Finally, it is desirable that product labeling of absorbed dose per activity administered include associated estimates of uncertainty, such as standard deviation, as well as dose values appropriately averaged to account for study cohort-size and uncertainties. As it stands now, there are no estimates of standard deviation in the paper by Green et al. Furthermore, the evident difference between the median dose found the study by Pfob et al. versus mean dose values of Green et al. and Afshar-Oromieh et al. is quite striking. To what are such differences attributed (diuretic administration?), and how would you evaluate appropriately averaged quantities?

**MEETING DISCUSSION- Question 9:**

**The Sponsor confirmed that all 3 sites submitting manuscripts used the precursor/conjugate manufactured (b) (4) and plans to provide the associated release criteria in the NDA. The information collected to date indicates (b) (4)**  
**The**  
**agency indicated that providing this information in the NDA will address the (b) (4) concern.**

**The Sponsor and the agency engaged in a discussion concerning the use of furosemide with PSMA-11. The Sponsor clarified that the vast majority of their prospective clinical trial PET data was acquired using furosemide. The sponsor agreed to combine the data from the two dosimetry articles that did not use furosemide and present their data in tabular format, and in text above mention that furosemide may result in doses lower than reported in the table. The agency agreed with the Sponsors suggested presentation of dosimetry data in the label (table and clarifying text) and suggested the Sponsor consider additional locations throughout the label to present this data. The Agency stated that these dosimetry concerns and others outlined in the pre-meeting comments would ultimately be a review issue.**

**As mentioned in Question 6, the sponsor agreed to indicate whether furosemide was used in each published study that they review.**

**Question 10:**

Given that Ga68-PSMA has been administered safely to thousands of patients without any significant side effects, does FDA agree that no additional preclinical studies need to be conducted to support the NDA?

**FDA RESPONSE To Question 10:**

Yes. The Agency agrees that based on the safety of Ga68-PSMA demonstrated in thousands of patients who have been administered the tracer in addition to the available nonclinical data demonstrating the safety of Ga68-PSMA, no additional nonclinical studies is required to support the NDA.

**MEETING DISCUSSION- Question 10:**  
**None.**

**Question 11:**

Does the Division agree that the information provided by the (b) (4) COA for PSMA-11 precursor is sufficient?

**FDA RESPONSE To Question 11:**

No, although the certificate of analysis (COA) provided in the meeting package summarized the specifications and attributes of the drug substance precursor, the information is not sufficient. The synthesis process of the drug substance precursor, PSMA-11, should be provided in the NDA application. This information may be presented in a DMF Type II, and a letter of authorization (LOA) filed with the NDA application. Describe in the NDA application the preparation of the 5 µg PSMA-11 samples. Additionally, provide stability data for the aliquoted 5 µg samples used for the manufacturing of the drug product.

**MEETING DISCUSSION- Question 11:**  
**None.**

**Question 12:**

Does the Division agree that the information provided by the COA (b) (4) (b) (4) is sufficient?

**FDA RESPONSE To Question 12:**

The COA of analyses (b) (4) are not acceptable for NDA application. The Agency is aware of a DMF (b) (4). Nonetheless, for the (b) (4) Agency is not aware of a filed DMF. If available provide the DMF number and file a LOA from the holder to the NDA application.

**MEETING DISCUSSION- Question 12:**

**None.**

**Question 13:**

Does the Division agree that no specification is required for the drug substance?

**FDA RESPONSE To Question 13:**

Yes, the Agency agree. The drug substance is (b) (4) therefore, the finished drug product specification will ensure the quality of the drug substance and product.

**MEETING DISCUSSION- Question 13:**

**None.**

**Question 14:**

Does the Division have any comments regarding the drug substance?

**FDA RESPONSE To Question 14:**

Yes, see comments in response #11.

**MEETING DISCUSSION- Question 14:**

**None.**

**Question 15:**

Does the Division have any comments regarding the drug product manufacturing process?

**FDA RESPONSE To Question 15:**

The manufacturing process for the drug product provided in the meeting package appears reasonable. However, FDA has the following comments:

- i. UCLA should provide data or evidence to show that (b) (4) should be included in the components and composition table if present in the drug product.
- ii. Describe how the 5-µg drug substance precursor is prepared (in-house prepared or supplied by a vendor).

Provide data to show stability of the drug substance precursor and include the COA from the supplier.

**MEETING DISCUSSION- Question 15:**

**None.**

**Question 16:**

Does the Division have any comments regarding the final product container/closure?

**FDA RESPONSE To Question 16:**

The information on the three-proposed (b) (4) container-closure systems is acknowledged. For the NDA submission, clearly indicate that the final product container/closure system(s) is (b) (4). Include a description of the components (i.e., glass vial and rubber septum), manufacturer(s) name, and a Certificate of Analysis (COA) to demonstrate the adequacy of the product quality attributes (i.e., sterile, conforms to manufacturer's endotoxins limit, etc.) for the chosen container-closure system(s). If a DMF is referenced for this information, include a Letter of Authorization (LOA) from the DMF holder indicating the specific submission date(s), volume(s), section(s), and page(s) where the product quality information can be located.

The information provided for the container closure system appears reasonable. However, acceptability will depend on the review of the stability and compatibility data to be provided in the NDA application.

**MEETING DISCUSSION- Question 16:**

**None.**

**Question 17:**

Does the Division have any comments regarding the drug product release criteria process?

**FDA RESPONSE To Question 17:**

The drug product release criteria provided appears reasonable. However, FDA has the following comments:

- i. The proposed (b) (4) breakthrough testing protocol is not acceptable. There is insufficient data provided (b) (4) to ensure that the (b) (4) % limit is attainable (Ph. Eur. Monograph (b) (4)). The testing frequency should be weekly until adequate data is collected to justify the proposed change.
- ii. Data should be provided for the validation batches to demonstrate that the ethanol level is controlled.

- iii. Additionally, data is lacking to show that [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] are adequate. Provide the information in the NDA submission.

**MEETING DISCUSSION- Question 17:**

**The Agency stated that the use of the [REDACTED] (b) (4)  
[REDACTED] would be acceptable for the NDA submission.**

**Question 18:**

Does the Division find the proposed commercial drug product specification adequate to support the NDA?

**FDA RESPONSE To Question 18:**

The proposed commercial drug product specification appears reasonable; however, the final decision regarding this specification will be determined once the NDA submission has been received and reviewed by the Agency. For the NDA submission, consider the following:

- a) Include the method used (e.g., gel clot, kinetic, etc.) for the bacterial endotoxins test during routine production. In addition, include a summary of the verification studies (i.e., inhibition/enhancement studies (I/E)) to support the use of the method with the drug product. I/E studies should include: the maximum valid dilution (MVD), product dilution chosen for testing, indication of the product concentration used, the sensitivity of the lysate, acceptance criteria, and the results of I/E testing. Finally, the summary should indicate the dilution that will be used for routine testing.
- b) Include the method used (e.g., membrane filtration, direct inoculation, etc.) for the sterility test. In addition, include a summary of the verification studies to support the use of the method with the drug product.
- c) Include a statement that sterility testing will be started within 30 hours after the completion of the drug product production (See the 2009 FDA Guidance *PET Drugs – Current Good Manufacturing Practice (CGMP)*).

The proposed acceptance criteria seem reasonable; however, adequacy will depend on the review of the information to be provided in the NDA. Additionally, FDA has the following comments.

- i. The Agency reminds UCSF and UCLA that the radiochemical identity testing is a release test. An HPLC validated ITLC test should be performed as a release test for all batches.
- ii. FDA recommends that UCSF provide HPLC chromatograms showing the distribution of the diastereoisomers in the drug product in the NDA application. Lastly, the ITLC

method should be able to resolve clearly the drug substance (b) (4)  
(b) (4)

**MEETING DISCUSSION- Question 18:**

**The Agency agreed that the resolution of the diastereomer would not have to be submitted. The Agency reiterated that the ITLC method should be able to clearly resolve the drug substance (b) (4)**

**Question 19:**

Given that the (b) (4) drug product, does the Division agree that the (b) (4) quality attributes (b) (4) are sufficient for the application if a (b) (4) manufacturing method is being used?

**FDA RESPONSE To Question 19:**

No. We acknowledge that the (b) (4) drug product in the case of the UCLA manufacturing process, where the (b) (4) is used. However, we are concerned that (b) (4) will be of sufficient quality for use in producing product for human administration. In addition to the information regarding (b) (4) needs to be validated as part of this assurance. Validation information should include (b) (4) as well as the appropriate assurance of microbiological quality (b) (4)

**MEETING DISCUSSION- Question 19:**

**None.**

**Question 20:**

We acknowledge that FDA requires the use of (b) (4) for the production of products under an NDA. UCLA/UCSF would like to highlight the current issue with acquiring (b) (4) (b) (4) We are concerned (b) (4) Would FDA agree to the use (b) (4) in the commercial production of PSMA-11 Ga 68 Injection if appropriate quality assurances are in place?

**FDA RESPONSE To Question 20:**

See responses 12 and 19

**MEETING DISCUSSION- Question 20:**

None.

**Question 21:**

Does the Division agree that quality attributes of the starting material, target material and a detailed description (b) (4) is sufficient in an application (b) (4) if a (b) (4) manufacturing method is used?

**FDA RESPONSE To Question 21:**

The information presented, and the proposed approach appears reasonable, nonetheless, adequacy will depend on the review of the data to be provided in NDA submission. Furthermore, the Agency has the following comments.

- i. In addition to the description (b) (4) (b) (4) provide data and justification to show that the levels of potential (b) (4) impurities are controlled and acceptable.
- ii. Provide data for at least three validation batches, and side-by-side comparison of the (b) (4) drug product.

**MEETING DISCUSSION- Question 21:**

The Agency indicated that the EU monograph purity levels of no more than (b) (4) (b) (4) seemed acceptable, however, it would be a review issue. The Agency agreed that a limit of < (b) (4) (b) (4) µg/GBq (b) (4) would be acceptable.

**Question 22:**

Does the Division have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

**FDA RESPONSE To Question 22:**

As described in the above FDA response to Question 7, ISE and ISS sections are required in Module 5, even if they only cross-reference the appropriate summary documents in Module 2.

**MEETING DISCUSSION- Question 22:**

None.

**Question 23:**

On the basis of the data included herein, does FDA agree in principle that the UCLA and UCSF NDAs would be eligible for priority review designation.

**FDA RESPONSE To Question 23:**

Your application(s) may qualify for priority review designation; however, this determination will be made at the time of the application filing. You should include your priority review request with the NDA. The request should contain sufficient information to justify that your proposed product would provide a significant improvement in the imaging of prostate cancer. For this purpose, it would be useful to summarize available results, published or otherwise, that compare <sup>68</sup>Ga-PSMA-11 diagnostic performance to that of PET radiotracers currently approved for prostate cancer imaging. Refer to the FDA [Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics](#) for additional information on priority review designation.

**MEETING DISCUSSION- Question 23:**  
**None.**

**Question 24:**

Does FDA have any additional guidance or suggestions for UCLA and UCSF on any aspect of the Ga68-PSMA-11 development program or NDA?

**FDA RESPONSE To Question 24:**

Refer to the 505(b)(2) Regulatory Pathway section below for additional information on submitting a 505(b)(2) NDA. We note that you intend to rely upon published literature in support of your 505(b)(2) NDA(s). You must establish that reliance on the published studies described in the literature is scientifically appropriate. You should also include copies of the published literature in your 505(b)(2) application(s).

We acknowledge your intent to submit separate NDAs for Ga68-PSMA-11 by UCSF and UCLA which will be supported by the same clinical and nonclinical information. We note that this may be a viable plan provided that the second 505(b)(2) NDA is submitted prior to approval of the first 505(b)(2) NDA.

The following additional guidances are suggested in preparation for the NDA submission:

- *PET Drug Applications – Content and Format for NDAs and ANDAs* (2011).
- *PET Drugs – Current Good Manufacturing Practice (CGMP)* (2009).

- *Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs* (2012).
- *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (1994).

**MEETING DISCUSSION- Question 24:**

**None.**

**ADDITIONAL DEVICE COMMENTS:**

1. Each PET system may have some difference in system specification, which may affect the image quality and sensitivity and specificity of the study. Please provide the list the PET system(s) used in the Phase 3 clinical study and provide the pre-clinical study evaluation of the PET system(s) for the acceptance of image quality in PET system(s).
2. Please define the positive lesion (abnormal) in the Ga-68 SPMA PET imaging and discuss the difference in SUV (max.) measurement in the PET system used, and the effectiveness of detecting small lesions in early BCR lesions.
3. Ga-68 PET tracer properties are slightly different than any other PET tracer and produce some concern for partial volume effect (PVE), which may affect image spatial resolution, particularly for small lesions. Please discuss the corrective measure you have taken to improve image quality and define spatial resolution limitation and can time requirement.
4. On page 13 in the pre-NDA package, a summary table is shown the efficacy results for phase 3 studies and meta-analysis. For primary objective of sensitivity and specificity of PSMA-11 Ga-68 Injection for the detection of pelvic nodal metastases, the PPV on phase 3 studies was (b) (4) and in the meta-analysis, it was (b) (4). Please explain the reason for the significant difference in PPV.

**MEETING DISCUSSION- ADDITIONAL DEVICE COMMENTS:**

**The Agency agreed that the ACR accreditation was acceptable and this information should be included in the NDA.**

**The Agency indicated that the image interpretation method was in alignment with other approved PET products.**

**With respect to the preliminary differences between PPV values, the Sponsor proposed to include an analysis of false positive patients and report the percent of patients that developed immediate biochemical recurrence and those who had PSMA positive nodes that were noted to be persisting on post-radical prostatectomy imaging. The Agency agreed this would provide the clarity required for NDA review.**

**ADDITIONAL CLOSING DISCUSSION:**

**The Agency reiterated that a detailed summary of why so few patients have biopsy and imaging follow-up results would be important during their review of the NDA.**

**The Agency commented that the indication statement for the label would be a review issue. The indication statement might leverage the data presented in primary prostate setting as supporting with no specific indication for either specific group.**

**The Agency stated that comparative data obtained with other approved drugs for the same indications may be useful to support a priority review determination. Comparative data is not required for general NDA approval, but might be helpful to demonstrate potential improvement in safety or effectiveness over existing approved imaging agents.**

**The Agency asked when they could expect the NDA. The Sponsor indicated they would submit as soon as possible, possibly by year end.**

**3.0 IMPORTANT MEETING INFORMATION**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 27, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at  
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

## **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------|
| 1.        |              |                                                                    |                                         |                                                                   |
| 2.        |              |                                                                    |                                         |                                                                   |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1.        |              |                                |                      |               |
| 2.        |              |                                |                      |               |

## **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that

supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

| <b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature</b> |                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| <b>Source of information<br/>(e.g., published literature, name of listed drug)</b>                                                                                                                                         | <b>Information Provided<br/>(e.g., specific sections of the 505(b)(2) application or labeling)</b> |
| <i>1. Example: Published literature</i>                                                                                                                                                                                    | <i>Nonclinical toxicology</i>                                                                      |
| <i>2. Example: NDA XXXXXX<br/>“TRADENAME”</i>                                                                                                                                                                              | <i>Previous finding of effectiveness for indication A</i>                                          |
| <i>3. Example: NDA YYYYYY<br/>“TRADENAME”</i>                                                                                                                                                                              | <i>Previous finding of safety for Carcinogenicity, labeling section B</i>                          |
| <i>4.</i>                                                                                                                                                                                                                  |                                                                                                    |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

No additional issues were identified that required further discussion.

#### **5.0 ACTION ITEMS**

No additional action items were identified during the meeting.

#### **6.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts distributed for inclusion in the meeting minutes.

-----  
**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/  
-----

LIBERO L MARZELLA  
09/25/2018