CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212643Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA [212643]

Gallium Ga 68 PSMA-11 Injection

Review #[Final]

Drug Name/Dosage Form	Gallium Ga 68 PSMA-11 Injection/ Sterile solution
Strength(s)	18.5 MBq/mL – 185 MBq/mL ((b) (4) mCi/mL – 5 mCi/mL) at calibration time
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	University of California San Francisco (UCSF)
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED (seq. no.)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 212643	09/06/2019	CMC (DS, DP), Microbiology, OPF

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Martin Haber	Donna Christner
Drug Product	John Amartey	Danae Christodoulou
Microbiology	Maritere Carattini	John Metcalfe
Process / Facility	Krishnakalli Ghosh	Vidya Pai
Biopharmaceutics	N/A	N/A
Environmental	John Amartey	Danae Christodoulou
RBPM	Anika Lalmansingh	N/A
Application Technical Lead	Eldon E. Leutzinger	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	V		(b) (4)	(1)	(1)	(1)
	II			Adequate	04/27/2020	None
	II			Adequate	04/01/2020	None

(1) DMF in Biologics.
(2) Adequacy for use in NDA product assessed in drug product review.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127621	Thomas Hope

2. CONSULTS

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
N/A			

Executive Summary

I. Overall Recommendation on Approvabilit

Approval, based on CMC Product Quality, Microbiological Product Quality and acceptable CGMP Inspections of all manufacturing facilities associated with NDA 212643.

OPQ recommends [**APPROVAL**] of NDA [212643] for commercialization of [Gallium Ga 68 PSMA-11 Injection/in 0.9% sodium chloride with not more than 10% ethanol, pH 4.0 – 7.0, and strength of 18.5 MBq /mL to 185 MBq/ml ((b) (4) mCi/mL to 5 mCi/mL) at calibration time] with an expiration dating period of [4 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:
^{68}Ga-PSMA-11 for positron emission imaging of prostate-specific membrane antigen (PSA) prostate lesions in men with prostate cancer in men with (1) suspected metastasis who are candidates for initial definitive therapy or with (2) suspected recurrence based on elevated serum-prostate specific antigen (PSA).

Regulatory Context - Designation of Drug Substance:
The active ingredient is that substance after radiolabeling of PSMA-11 which is radioactive, ***HBED(^{68}Ga^{3+})-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 ***HBED(^{68}Ga^{3+})-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-(carboxyethyl)benzyl]-ethyenediamine-N,N'-diacetic acid, and Ahx is amino-hexanoic acid.

(Structure)

(b) (4)

From ATL and author of this Executive Summary:

(b) (4)

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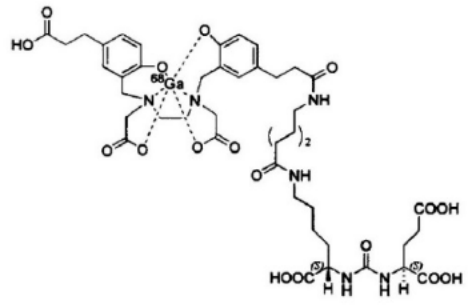
(b) (4)



(b) (4)

(b) (4)

Regulatory Context - Regulatory Status of the Precursor:

(b) (4)

(b) (4)

[redacted]

Product Profile and Critical Quality Attributes (CQA's):
[^{68}Ga]-PSMA-11 is a sterile aqueous solution of **HBED($^{68}Ga^{3+}$)-CC-Ahx-Lys(OH)-CO-Glu(OH)**, $C_{44}H_{59}[^{68}Ga]N_6O_{17}$ (MW 1011.91 g/mol), in Sodium Chloride 0.9% Injection and Ethanol. The strength is 0.5 – 5 mCi/mL. HBED($^{68}Ga^{3+}$)-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 (^{Nat}Ga substituting for ^{68}Ga), and exists as such in solution. See Regulatory Context – Designation of Drug Substance and under Notes.

Both versions (^{Nat}Ga, ^{68}Ga) are subject to the same stability-sensitivities typically possessed by peptides, but the ^{68}Ga version possesses the additional sensitivity (b) (4)

[redacted]

Areas of Unique Focus:

(b) (4)

[redacted]

(b) (4)

III. Summary of Quality Assessments

PRECURSOR (**in relation to Drug Substance**)

(b) (4)

(**adequate**, 4/27/2020).

DRUG PRODUCT

The issues identified for the drug product can be collected into 4 major categories (Composition, Manufacturing, Specifications, and Stability). Within the category of ***Composition***, concerns are raised regards the absence of the quantity of (b) (4) PSMA-11 (**74 Day Letter Comment #1 - Resolved**). In the ***Specifications***, the limit for ^{68}Ga breakthrough is (b) (4) compared to that for the (b) (4) – **74 Day Letter Comment #7 - Resolved**.

(**Manufacturing**)

At UCSF, product is manufactured (b) (4)

(b) (4)

(b) (4)

- **Establishment of Product Quality Consistency in ^{68}Ga-PSMA-11**

(b) (4)

In this context, the primary review recommends for product quality consistency (b) (4)

(b) (4)

(b) (4)

LABELING

There were two issues in the labeling, (b) (4) (**Labeling Comment #1**), recalling from the discussion on pages 3-5 that there had been a "miss on chemistry," (b) (4) This is now **Resolved** in the revision of labeling (Final Labeling Text, #0018, 10/30/2020) that includes the correct structure as depicted on page 6 of this Executive Summary. There was also the need for consistency in the units for radioactivity (**Labeling Comment #2**), and (b) (4) (the firm has submitted a request for this (b) (4) (**Comment #2, IR-2**); both these issues are **Resolved**.

MICROBIOLOGY

The drug product is (b) (4) and all issues for microbiology, as enumerated and discussed in the Microbiology Review (Maritere Carattini, Ph.D., 03/05/2020) have been adequately resolved. According to the Microbiology Review,

there are **no remaining deficiencies and the University of Southern California, San Francisco (USCF) has met all regulatory expectations from the perspective of microbiology product quality**.

MANUFACTURING FACILITIES

Facility	Responsibility	Status
♦UCSF Radiopharmaceutical Facility	Production, packaging, release testing of the drug product	Approved[1] 10/26/2020
(b) (4)		Approved[2] 10/26/2020
		Approved[3] 10/26/2020

(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** (b) (4) **Analytical – Product Specific** (b) (4)

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) (b) (4) approved on the basis of PAI. (b) (4) approved on the basis of 706/704 (a) process.

Final: Approved 10/26/2020

IV. 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.

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

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 212643. However, there will be a PAI inspection verification during the next surveillance inspection.

VI. Lifecycle Considerations

N/A

VII. [OPTIONAL] Draft Text for Complete Response Letter/ Postmarketing Commitment or Requirement

N/A

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212643
Assessment Cycle Number	01
Drug Product Name/ Strength	PSMA-11 Ga 68 Injection, 0.5 - 5 mCi/mL
Route of Administration	Intravenous injection
Applicant Name	UCSF Radiopharmaceutical Facility
Therapeutic Classification/ OND Division	Radioactive Diagnostic Agent for Positron Emission Tomography
Manufacturing Site	University of California San Francisco Radiopharmaceutical Facility 185 Berry Street, San Francisco, CA 94107
Method of Sterilization	Filter sterilization followed by aseptic fill

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed:

Document(s) Assessed	Date Received
0000	06 September 2019
0004 (IR Response)	26 December 2019
0007 (IR Response)	31 January 2020
0009 (IR Response)	19 February 2020
0010 (IR Response)	04 March 2020

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

Remarks: This is a positron emission tomography (PET) imaging drug product (b) (4)
(b) (4)

Concise Description of Outstanding Issues: None

Supporting Documents: N/A

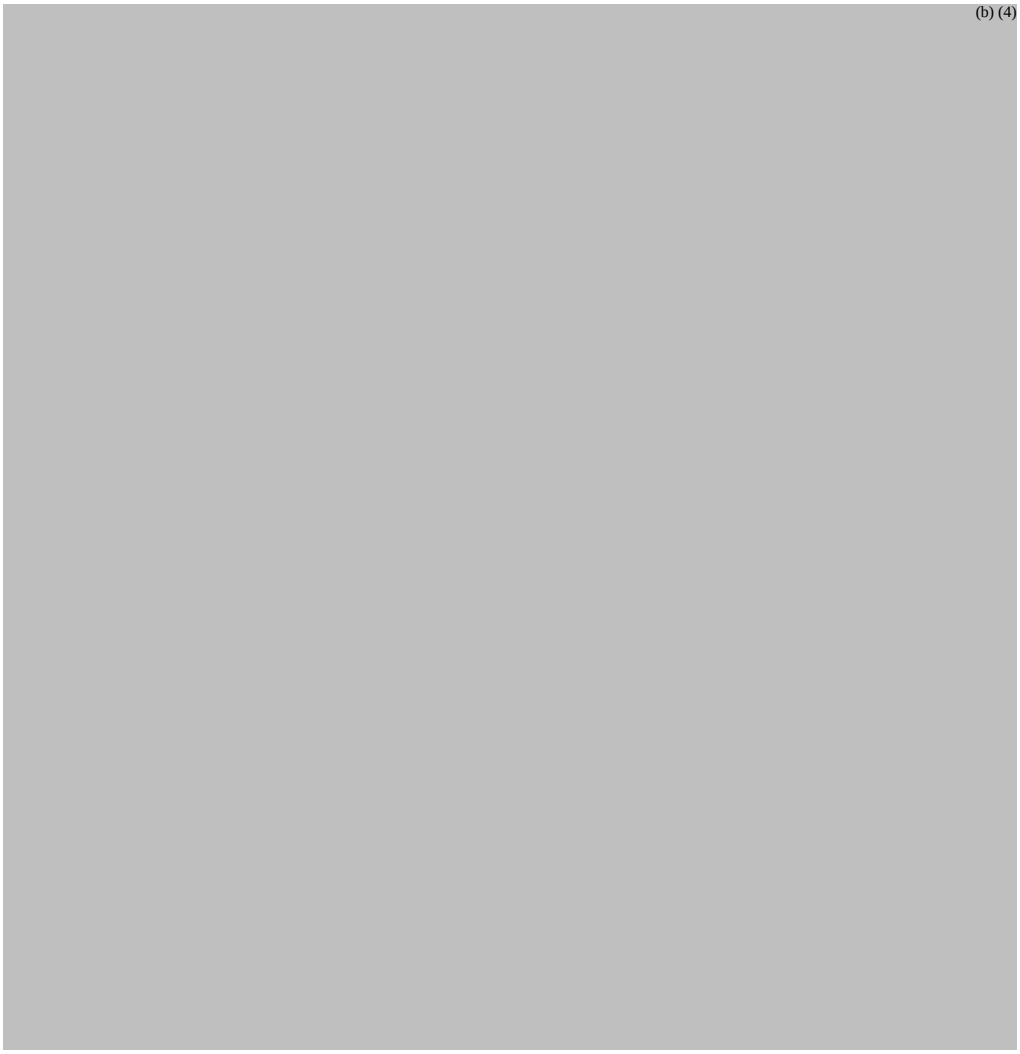
S DRUG SUBSTANCE

The drug product is [redacted] 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 20 mL glass vial with a rubber stopper and aluminum crimp seal.

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



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

  The drug product is packaged in a 20 mL [redacted] glass vial with gray [redacted] rubber stopper, and aluminum crimp seal. The container closure is [redacted]

Assessment: *Adequate*

(b) (4)

(b) (4) See related deficiency and the applicant's response in the Environmental Monitoring Section.

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 four hours of End of Synthesis (EOS) and the container closure system is (b) (4)

Assessment: Not Applicable

Antimicrobial Effectiveness Testing
This information is not required for PET drug products as the subject drug product is administered within four hours of EOS.

Assessment: Not Applicable

P.3 Manufacture
P.3.1 Manufacturers

University of California San Francisco (UCSF) Radiopharmaceutical Facility
185 Berry Street, San Francisco, CA 94107

P. 3.3 Description of the Manufacturing Process and Process Controls
Overall Manufacturing Operation
(Section 3.2.P.3.5, "Process Validation and/or Evaluation")

(b) (4)

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(b) (4)

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:

Test	Test Requirements	Acceptance Criteria	Exhibit Batches [2] Results
(b) (4)		(b) (4)	All passed
Bacterial Endotoxins per USP <85>			All < (b) (4) EU/mL
Sterility per USP <71>			All sterile

(b) (4)

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 Analytical Procedure"; Section 3.2.P.5.6, "Justification of Specifications")

The applicant utilizes the [redacted] bacterial endotoxins test method for PSMA-11 Ga 68 Injection.

- Endotoxins specification: [redacted] EU/V ([redacted] EU/mL)
- Lysate sensitivity: [redacted] EU/mL
- MVD = (endotoxin limit) x (sample conc.) / (λ)
  Applicant's MVD calculation: [redacted]
  Reviewer's calculated MVD:
  [redacted]

  Note: The applicant calculated the MVD [redacted]

- The applicant states that [redacted] will be used for routine testing. Inhibition/enhancement study was not provided.
- *Maximum possible dose*: [redacted] mL which is the entire batch (provided in the "Justification of Specifications" document)
- Calculated proposed endotoxins specification with maximum dose:
  ([redacted] mL) x ([redacted] EU/mL) = [redacted] 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 followed by applicant's responses from 26 December 2019:

1. *The bacterial endotoxins information provided in Section 3.2.P.5.2 and 3.2.P.5.6, is acknowledged. However, the bacterial endotoxins enhancement/ inhibition study was not provided. For more information please refer to the FDA guidance, PET Drugs-Current Good Manufacturing Practice (cGMP), p. 26, which states: "We recommend that any new analytical test method be validated, through documented data, to show that it will consistently yield results that accurately reflect the quality characteristics of the product tested." In addition, it is noted* [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. *Provide a summary report with the data collected for the enhancement/inhibition study.*

   Response: The applicant provided an inhibition/enhancement study. The product was tested [redacted]

b. *Confirm that the pH of the drug product tested in the endotoxin method validation was within the pH as defined* (b) (4) *If not, then provide updated validation data using the correct product pH.*

Response: The applicant stated (b) (4)
(b) (4)

c. *Please revise the endotoxins test method to include instructions* (b) (4)
(b) (4)

Response: The applicant stated that the BET method has been validated and further pH testing is not warranted. See response to the information request above (1-b).

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

Response: The applicant states (b) (4)
(b) (4)

2. *Furthermore, the MVD was calculated* (b) (4)
(b) (4) *The maximum valid dilution*

for the subject drug product is (b) (4) *(see calculation below). Provide revised documents reflecting the new MVD.*

MVD = (endotoxins limit) x (sample conc.) / (λ)
Endotoxins limit = (b) (4) *EU/V (*(b) (4) *EU/mL)*
Sample concentration = (b) (4)
λ = (b) (4)
MVD = (b) (4)

Response: The sponsor updated the MVD calculation in Section 3.2.P.5.2.

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 Procedure", p. 5)

The sterility testing of the drug product is performed (b) (4) (b) (4)

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.

The applicant did not provide a bacteriostasis/fungistasis study.

Information request sent to the applicant on 07 November 2019 followed by applicant's responses from 19 February 2020:

The information concerning sterility testing in Sections 3.2.P.5.2 and 3.2.P.5.3 is acknowledged. However, the method suitability testing results were not provided. Please address the following:

a. *Provide the sterility test method validation (i.e., Bacteriostasis and Fungistasis data).*
b. *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 a sterility method validation report conducted with the subject drug product. The study was performed (b) (4) (b) (4) (b) (4). The product showed no bacteriostatic/fungistatic properties.

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 and Conclusions")

Six exhibit batches ((b) (4) 190130PSMA1, 190131PSMA1, 190204PSMA1. (b) (4) 190130PSMA1, 190131PSMA1, 190204PSMA1) were evaluated for stability at the proposed expiry of 4 hours after EOS. The batches were manufactured as proposed in Section 3.2.P.3.3. The vials were stored (b) (4) (b) (4) Samples for testing were taken (b) (4) (b) (4) bacterial endotoxins and sterility testing were performed (b) (4) (b) (4) 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, "Post-Approval Stability Protocol and Stability Commitment")

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 (4 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 (b) (4) The lack of routine

stability studies does not impact the sterility assurance of the subject drug product since it has a short shelf-life (b) (4) 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 all the exhibit batches ((b) (4) 190130PSMA1, 190131PSMA1, 190204PSMA1. (b) (4) 190130PSMA1, 190131PSMA1, 190204PSMA1).

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 Multidose Vial Label-20 mL")

The drug product is labeled as sterile, pyrogen-free, and multi-dose. The subject drug product is stored at (b) (4) 25 ºC and must be used within 4 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: None

Primary Microbiology Reviewer Name and Date: Maritere Carattini, MS, 05 March 2020

Secondary Reviewer Name and Date: John W. Metcalfe, PhD, 05 March 2020

Maritere Carattini

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John Metcalfe

Digitally signed by John Metcalfe
Date: 3/06/2020 03:31:54PM
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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
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