CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208700Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 208700 (Resubmission)
OPQ Integrated Quality Assessment final
Review Date: 12/13/2017

Drug Product	Lutetium Lu 177 Dotatate / Lutathera
Strength	370 MBq/mL
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Advanced Accelerator Applications
US agent, if applicable	N/A

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505b2**

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. DMFs: See previous IQA

Table 1 Drug Master Files (DMFs)						
DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETE	REVIEWER

A. **Other Documents: IND** (b) (4)

3. **CONSULTS: N/A**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	John Amartey, Ph.D.	ONDP/DNDAPI
Drug Product	John Amartey, Ph.D.	ONDP/Branch VI/Division II
Microbiology	Peggy Kriger, Ph.D.	OPQ/OPF/Microbiology
Facility	Krishnakali Ghosh, Ph.D.	OPQ/OPF/DIA/B1
Project/Manager (R.Ph)	Thao Vu/Steven Kinsley	OMPT/CDER/OPQ/OPRO/ORDP MI/RBPMBI
Application Technical Lead	Eldon E.Leutzinger, Ph.D.	ONDP/Branch VII/Division II
Environmental Assessment (EA)	John Amartey, Ph.D.	ONDP/Branch VII/Division II

Table 2 Documents			
DOCUMENT	**RECEIPT DATE**	**DESCRIPTION**	**Section/reviewer**
Resubmission	7/26/2017	Application + inspectional documents & FDA 483	Krishna Ghosh/OPF

Executive Summary

I. Recommendations

APPROVAL, based on CMC, Microbiology Product Quality and Facility Inspections

A. Recommendation and Conclusion on Approvability

N/A

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

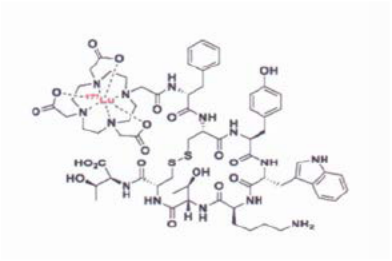
BACKGROUND:

The **Drug Product** is a **ready-to-use radiopharmaceutical** contained in a 30 mL single-use glass vial. The vial fits in a lead pig. The pig with the vial is placed in the (b) (4). (b) (4). The dosage form is a solution for intravenous infusion, at a strength of 370 MBq/mL (10 mCi/mL) (b) (4) The shelf-life is 72 hours (b) (4)

A **Complete Response Letter** was issued 12/19/2016 listing multiple clinical issues, as well as deficiencies identified during inspection of the manufacturing facilities. Those facilities included 'Advanced Accelerator Applications (Meldola, Italy; Ivrea, Italy), and IDB Radiopharmacy B.V., the Netherlands.

A. Drug Substance [USAN Name] Quality Summary

The **Drug Substance** is ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, a radiolabeled peptide, and has the following molecular structure:



The peptide sequence is d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7), containing 8 amino acids, and has a molecular weight of 1535.6 g/mol. There is a -S-S- disulfide linkage between the two Cys amino acids, connecting the two cysteine amino acids of the peptide together. DOTA is attached to the d-Phe end of the peptide through an amide linkage by utilizing one of the carboxylic acid groups in the ligand, and the free amino group of **H_2N**-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7). D-Trp^{4} and Lys^{5} each possesses a N-atom that can be protonated, and in NDA 208700, the counter-ion used is trifluoroacetate, two per peptide. After linking DOTA to the peptide, there are remaining 3 carboxylic acid groups and 3 ring N-atoms for binding to $^{177}Lu^{3+}$. The radiolabel ($^{177}Lu^{3+}$) is bound within the DOTA cavity.

The overall process for production of drug substance is as follows. (b) (4)

(b) (4)

B. **Drug Product [Established Name] Quality Summary**

Product Vial composition consists of an aqueous solution containing **^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate** (370 MBq/mL [redacted]), plus excipients (Acetic Acid, Sodium Acetate, Gentisic Acid, [redacted] DTPA and Sodium Chloride). Each vial will contain sufficient volume of solution (20.5 – 25.0 mL) to allow for delivery of 7.4 GBq ± 10% at time of injection. A dose of 7.4 GBq corresponds to 7.4 x 10^3 MBq, or [redacted] mCi.

CMC Product Quality:
In the original submission, there were drug substance issues, [redacted]. For drug product, the most significant issues included lack of information, relative to the batch records. Other drug product issues [redacted] **All issues were resolved, and the final recommendation from CMC was approval**.

Microbiology Product Quality:
Similarly, there were multiple Microbiology Product Quality issues [redacted] **All microbiological product quality issues were resolved, and there was an approval recommendation from microbiology**. A determination was made that a review from Microbiology is not necessary, since a recommendation of approval had been made, based on Microbiology Product Quality (Peggy Kriger, email of 9/19/2017).

Facilities Inspection Status:
There were 3 manufacturing sites out of 6 recommended for withhold until correction of the 483 observations are complete. All 483 issues have been addressed, and no re-inspection per the resubmission is needed – by determination of Krishnakali Ghosh, Ph.D. (OPQ/OPF/DIA/B1). **On**

review of the application (Krishna Gosh, OPQ/OPF/DIA/BI), including the inspectional documents and responses to the FDA 483, a determination was made (OPF) that there are no outstanding manufacturing or facility risks preventing the approval of the NDA.

C. **Summary of Drug Product Intended Use**

Proprietary Name of the Drug Product	Lutathera
Non Proprietary Name of the Drug Product	(^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) solution for intraveneous infusion
Non Proprietary Name of the Drug Substance	^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate
Proposed Indication(s) including Intended Patient Population	Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults
Duration of Treatment	N/A
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. **Biopharmaceutics Considerations**

1. BCS Classification: N/A
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies: N/A
   - Biowaiver Requests
   - PK studies
   - IVIVC

E. **Novel Approaches**
N/A

F. **Any Special Product Quality Labeling Recommendations**
N/A

G. **Life Cycle Knowledge Information (see Attachment A)**
N/A

Risk Assessment - Drug Product (b) (4)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking[1]**	**Risk Mitigation Approach**	**Final Risk Evaluation[2]**	**Lifecycle Considerations/ Comments****
		RPN < 25		RPN < 25	

1. Based on CMC and Microbiology Product Quality considerations. Nevertheless, there was a recommendation for withhold on three sites during the original review of the NDA (after a PAI inspection was conducted at the sites) until there was a satisfactory response to an FDA 483 for these sites.
2. Overall Risk Assessment continues to be Low (RPN < 25), based on no new CMC issues uncovered, along with the standing decision of approval by Microbiology Product Quality (no review of resubmission necessary). Additionally, based on a review of the application (Krishna Gosh, OPQ/OPF/DIA/BI) inspectional documents and responses to the FDA 483, a determination was made (OPF) that there are no outstanding manufacturing or facility risks preventing the approval of the NDA.

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E. Leutzinger -S

Digitally signed by Eldon E. Leutzinger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054329, cn=Eldon E. Leutzinger -S
Date: 2017.12.13 15:13:52 -05'00'

Eldon Leutzinger

Digitally signed by Eldon Leutzinger
Date: 12/14/2017 10:16:48AM
GUID: 508da7210002a0781943eff6cc724d1f

NDA 208700
OPQ N208700 Integrated Quality Assessment
Final
Review Date:

Drug Name/Dosage Form	Lutathera/solution
Strength	370 MBq/mL
Route of Administration	Intravenous/infusion
Rx/OTC Dispensed	Rx
Applicant	Advanced Accelerator Applications
US agent, if applicable	N/A

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505(b)(1)**

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. DMFs:

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETE	REVIEWER
(b) (4)	II		(b) (4)		11/17/2016	John Amartey, Ph.D. (CMC)
(b) (4)	II		(b) (4)	2	10/23/2015	Martin Haber, Ph.D.
	III			2	During NDA review	John Amartey, Ph.D. (CMC)
	III			2	During NDA review	John Amartey, Ph.D. (CMC)

[1]The DMF #

[2]Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

3. **CONSULTS: N/A**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	John Amartey	ONDP/Branch VI/Division II
Drug Product	John Amartey	ONDP/Branch VI/Division II
Process	John Amartey	ONDP/Branch VI/Division II
Microbiology	Peggy Kriger	OPQ/OPF/Microbiology
Facility	Krishnakali Ghosh	OPQ/OPF/DIA/B1
Project/Manager (R.Ph)	Thao Vu	OMPT/CDER/OPQ/OPRO/OR DPMI/RBPMBI
Application Technical Lead	Eldon Leutzinger	ONDP/Branch VII/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment (EA)	N/A	N/A

Table 2 Documents			
DOCUMENT	**RECEIPT DATE**	**DESCRIPTION**	**Section/reviewer**
0000	03/31/2016)	Original Submission	John Amartey, Ph.D.
0021	07/13/2016	Labeling	"
0023, 0024	08/05, 12/2016	IR's	"
0028	09/09/2016	IR	"

Executive Summary

I. Recommendations

APPROVAL, pending satisfactory correction of the FDA 483 observations for three of six manufacturing sites.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

Recommendations:
CMC – Approval
Microbiology – Approval
Manufacturing facilities – Withhold

All CMC issues identified for the drug substance and drug product, and the associated DMF's (b) (4) are resolved. There are no issues (b) (4) based on an acceptable DMF (b) (4) held by (b) (4) (reviewed by Martin Haber, Ph.D., 10/123/2015) in conjunction with NDA (b) (4), the latter approved (b) (4)

Issues for Microbiology are resolved, and their recommendation is approval. Remaining are multiple observations (FDA 483) regarding 3 out of 6 manufacturing facilities. These 3 sites are recommended for withhold. As indicated by Krishnakali Ghosh of OPQ/OPF, some of the corrective actions on the 483 observations will take until January to complete. During this cycle, we did not perform a drug product labeling review.

ISSUE		STATUS
CMC (Drug Substance)	(b) (4) [redacted]	**Resolved**

		STATUS
CMC (Drug Substance)	(b) (4) [redacted]	**Resolved**
		Resolved
(Drug Product)		**Resolved**
		Resolved
Microbiology	Multiple issues (b) (4) [redacted] .	**Resolved (recommend Approval); see Microbiology Review (attached)**
Facilities	Based on FDA 483 observations, there are 3 sites (10010 Colleretto Giacosa, Italy; 47014 Meldola, Italy; Baarle-Nassau, 5111 PV, the Netherlands) that will be withheld, due to inadequate responses to address the issues. Many of these issues involve microbiology.	**Three manufacturing sites out of 6 are recommended for withhold until correction of the 483 observations is complete**

2. Action letter language, related to critical issues such as expiration date: N/A
3. Benefit/Risk Considerations: see Risk Assessment at end of executive summary.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

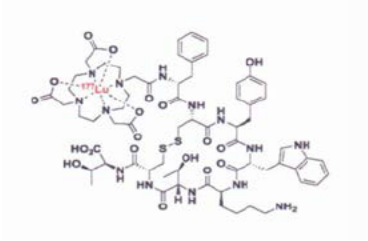
INTRODUCTION:

The **Drug Product** is a ready-to-use radiopharmaceutical. The aqueous solution of product is contained in a 30 mL single-use glass vial (far left-side in the following picture). The vial fits in the lead pig shown in the center. [redacted] The pig with the vial is placed in [redacted] The dosage form is a solution for intravenous infusion, at a strength of 370 MBq/mL (10 mCi/mL) [redacted]

Vial composition consists of an aqueous solution containing **^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate** (370 MBq/mL [redacted]), plus excipients (Acetic Acid, Sodium Acetate, Gentisic Acid, [redacted] DTPA and Sodium Chloride). Each vial will contain sufficient volume of solution (20.5 – 25.0 mL) to allow for delivery of 7.4 GBq ± 10% at time of injection. A dose of 7.4 GBq corresponds to 7.4 x 10^3 MBq, or [redacted] mCi.

A. Substance [USAN Name] Quality Summary

The Drug Substance is ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate, a radiolabeled peptide, and has the following molecular structure:



The peptide sequence is d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7), containing 8 amino acids, and has a molecular weight of 1535.6 g/mol. There is a -S-S- disulfide linkage between the two Cys amino acids, connecting the two cysteine amino acids of the peptide together. DOTA is attached to the d-Phe end of the peptide through an amide linkage by utilizing one of the carboxylic acid groups in the ligand, and the free amino group of **H_2N**-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7). D-Trp^4 and Lys^5 each possesses a N-atom that can be protonated, and in NDA 208700, the counter-ion used is trifluoroacetate, two per peptide.

After linking DOTA to the peptide, there are remaining 3 carboxylic acid groups and 3 ring N-atoms for binding to $^{177}Lu^{3+}$. The radiolabel ($^{177}Lu^{3+}$) is bound within the DOTA cavity. The lanthanides can have large coordination numbers (up to 12), and thus $^{177}Lu^{3+}$ will utilize all of its possible coordination sites to "bind" to all 4 ring N-atoms, and the 3 available carboxylic acid

arms (O-atoms) of DOTA. As a result, the $^{177}Lu^{3+}$ ion is well-buried in the complex, with the metal ion flanked by the 4 N-atoms (below plane of paper) and the 3 carboxylic acid groups (above plane). Because $^{177}Lu^{3+}$ is *engulfed* by the ligand, it has important consequences for *in vitro* stability, and perhaps *in vivo* stability that are potentially of clinical significance. Since the 3 carboxylic acid groups of DOTA are involved in binding to $^{177}Lu^{3+}$, and none remaining, the complex carries no charge (+3 – 3 = 0). The molecular weight of ^{nat}Lu- DOTA^0-Tyr^3-Octreotide is 1609.6.

Lutetium (^{177}Lu, ^{nat}Lu)

Lutetium (Lu), a rare earth, is the last member of the lanthanide period. There are 35 isotopes of Lu. But, of these 35 isotopes, only ^{175}Lu (stable) and ^{176}Lu (3.78 x 10^{10} years) are naturally occurring (97.41% and 2.59% abundance, respectively). ^{177}Lu (the subject isotope in Lutathera) is produced (b) (4) Lutetium has an **electronic configuration** of [Xe]4f^{14}5d^{1}6s^2, with a fully filled 4f-orbital. Lu^{3+} ion is formed by loss of the two 6s-electrons and one 5d-electron, and has an electronic configuration of [Xe]4f^{14}. Another prominent aspect of the lanthanide elements is the preponderance of the very stable +3 oxidation state in their aqueous solution chemistry. Only for Sm, Eu and Yb is there an additional +2 oxidation state. **The single oxidation state of Lu^{3+} translates to assurance of formation of a single molecular entity on complexation with an appropriate ligand (except for the possibility of stereoisomers). Lu is also strongly electropositive, meaning that Lu^{3+} will strongly attract electronegative ions (e.g., O- and N-atoms of simple non-cyclic and multidentate ligands), providing the basis for complexation of $^{177}Lu^{3+}$ with DOTA of DOTA^0-Tyr^3-Octreotate.**

Coordination Chemistry of ^{177}Lu-DOTA^0-Tyr^3-Octreotate

With the 4f-orbital fully filled (7 orbitals x 2 electrons = 14 electrons) in Lu^{3+}, [Xe]4f^{14}, there are no metal orbitals available for overlap with ligand orbitals. But, there is more. It is well-known that there is an energy dependence of atomic orbitals on atomic number. As the atomic number increases across the lanthanide period, the energy of the 4f-orbital decreases and crosses over that of the 5s, 5d, 6s, 5p and 4d-orbitals. When Lu is reached, the energy of the 4f-orbital in Lu^{3+} lies underneath the energies of these orbitals. As a result, the 4f-orbital becomes buried within the electronic configuration. **Consequently, the 4f-orbital is screened by the 5s, 5d, 6s, 5p and 4d-orbital electrons. Due to the shape of the seven f-orbitals, and the screening of the 4f-orbital, the lobes of the 4f-orbitals do not stick out far enough to achieve good overlap with ligand orbitals for covalent bonding to occur, even for those lanthanides that have empty f-orbitals.**

On both counts, chemical bonding in Lu^{3+}-DOTA^0-Tyr^3-Octreotate is necessarily ionic. Although ionic, the bonding in these complexes does not fit the classical definition of a "salt," one that readily dissociates into ions in aqueous solution. Quite to the contrary, metal-ligand coordination complexes (charged and uncharged) exist as stable "discrete molecular entities," with well-defined geometry. That this is so for Lu^{3+}-DOTA^0-Tyr^3-Octreotate is based on a body of evidence from X-Ray Crystallography studies of similar metal-ligand complexes of a lanthanide family member (Gd^{3+}), and their exceptional stability profiles, emulating that as if the bonding in these complexes met the definition of a covalent bond.

RADIOPHARMACEUTICAL PRODUCTION:

Drug Substance

The manufacture of ^{177}Lu-DOTA^0-Tyr^3-Octreotide (**Drug Substance**) proceeds (b) (4)

(b) (4)

6 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

BACTERIAL ENDOTOXINS – See Microbiology Review
STERILITY – See Microbiology Review

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Lutathera
Non Proprietary Name of the Drug Product	None (ready-to-use solution for infusion)
Non Proprietary Name of the Drug Substance	Lu-177- $DOTA^0$-Tyr^3-Octreotate
Proposed Indication(s) including Intended Patient Population	For treatment of gastroenterpancreatic neuroendrocrine tumors (GEP-NET's)
Duration of Treatment	Four administrations of 7.4 GBq, every 8 weeks
Maximum Daily Dose	7.4 GBq
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations
N/A
E. Novel Approaches
N/A
F. Any Special Product Quality Labeling Recommendations
N/A
G. Process/Facility Quality Summary (see Attachment A)
N/A
H. Life Cycle Knowledge Information (see Attachment B)
N/A

Risk Assessment - Drug Product (Lutathera) – Based on CMC and Microbiology

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation[6]**	**Lifecycle Considerations/ Comments****
Radionuclidic Identity/purity	Purity and CMC quality of ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (b) (4)	25<RPN<60[1]	Information provided to address issues identified in (b) (4) DMF (b) (4) and that provided per (b) (4)	<25[1] (low)	N/A
Radiochemical identity	-Reference standard characterization -Analytical methods	25<RPN<60	Information provided to address issues identified	< 25 (low)	
Radiochemical purity	-Precursor purity[1] -analytical methods	25<RPN<60	Information provided to address issues identified in (b) (4) DMF (b) (4), and that per (b) (4)	<25 (low) <25 (low)	
Chemical Purity	-Precursor integrity, purity and quality[2]	25<RPN<60	N/A	<25 (low)	
Strength (mCi/mL)	-Scale (RAD input)[3]	25<RPN<60	N/A	<25 (low)	
Appearance (reconstituted solution)	-Quality of manufactured Lutathera	25<RPN<60	N/A	< 25 (low)	
pH	-Formulation -Quality of manufactured Lutathera	RPN < 25	N/A	< 25 (low)	
Stability	-Sensitivity of ligand structure (b) (4) in formulation	RPN < 25	N/A	< 25 (low)	
Microbiology[4]		RPN < 25	All issues resolved (see microbiology review)	<25 (low)	

1. DMF (b) (4). Chemical purity (b) (4)
2. Information for the manufacture, purity and quality (b) (4) is in a DMF (b) (4) held by (b) (4), which has been reviewed (Martin Haber, Ph.D., 10/23/2015) and determined acceptable (b) (4) in conjunction with another NDA (b) (4) for (NDA (b) (4) approved (b) (4)).
3. Strength (mCi/mL) – RAD scale is determined by the range of radioactivity to be used with Lutathera. If the radiolabeling fails to meet expectation (RAD yield), the strength will be impacted – that it will meet expectations is validated through studies performed in the NDA.

4. Microbiology – see Microbiology Review (Peggy Kriger, Ph.D., 11/10/2016); RPN = 0 (after modification when applicable) x S x D.
5. Overall Risk Assessment, RPN < 25 (**low to negligible**, based on resolution of all issues for CMC).

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

122 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY

Product Background: Rolling submission, granted an Orphan Designation and a Fast Track review.

NDA: 208700

Drug Product Name/ Strength: Lutetium ^{177}Lu dotatate (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate 370 MBq/mL solution for infusion)

Route of Administration: Intravenous

Applicant Name: Advanced Accelerator Applications USA, Inc.

Manufacturing Sites:

Advance Accelerator Applications (Italy) srl
Via Ribes 5, Colleretto Giacosa, TO, Italy, 10100

Advance Accelerator Applications (Italy) srl
Via Piero Maroncelli 40, Meldola, FC, Italy, 47014

Method of Sterilization: (b) (4)

Review Summary:
List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
3/31/2016	3/31/2016	N/A	N/A
4/28/2016	4/28/2016	N/A	4/28/2016
5/18/2016	5/18/2016	N/A	N/A
8/05/2016	8/05/2016	N/A	N/A
9/27/2016	9/27/2016	N/A	N/A

Highlight Key Outstanding Issues from Last Cycle: None identified

Concise Description Outstanding Issues Remaining: None identified

Supporting/Related Documents: IND 77219 is referenced for the sterility testing timeframe. Relevant information in a meeting package was reviewed by P. Kriger (077219.doc, dated August 20, 2015). DMF (b) (4) is referenced (b) (4). An LOA dated (b) (4) is provided.

Remarks: The submission is in the eCTD format. Some tables were copied from the submission. The August 5, 2016 and September 27, 2016 amendments are referenced for the responses to information requests from CMC/Microbiology sent to the sponsor on July 21, 2016 and September 19, 2016, respectively.

The Submission is Recommended for Approval.

Note to reviewer: The subject drug product is a sterile, ready-to-use radiopharmaceutical solution for infusion which will be administered intravenously in nuclear medicine settings. The subject drug product is produced (b) (4)

(b) (4)

17 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

P. 8 Stability

P. 8.1 Stability Summary and Conclusion

Proposed Expiry: 72 hours (b) (4)

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification is the same as for release (see above).

Stability storage conditions: 25°C ± 2°C

Test	Time (Hours)			
	0	24	48	72
(b) (4)	X			
Bacterial Endotoxins	X			X
Sterility	X			

Note to reviewer: In the 9/27/2016 amendment response, the applicant did not change the stability information, which indicates that the sterility test is performed (b) (4) However, further clarification will not be requested as the sterility test is only performed once - (b) (4).

Post Approval Stability Commitment
On-going stability will be conducted annually at each manufacturing facility on a single batch produced at the largest possible batch size (b) (4) . These batches used as part of the on-going stability program may also be used as commercial batches.

Reviewer's Assessment: Acceptable

P.8.3 Stability Data

Microbial testing results are provided for 12 primary stability batches, which cover both manufacturing sites, (b) (4) and two possible batch sizes. (b) (4), endotoxins and sterility test results complied with the drug product specification.

Reviewer's Assessment: Acceptable

R Regional Information

Executed Batch Records

Executed lots:

Colleretto Giacosa

- (b) (4) GBq batch size (b) (4) Ci), Lot numbers: LT141118B-03, LT141119B-03, LT141124C-03
- (b) (4) GBq batch size (b) (4) Ci), Lot numbers: LT141113A-03, LT141114A-03, LT141125B-03
- (b) (4) GBq batch size (b) (4) Ci), Lot numbers: LT141119C-03, LT141121A-03, LT141127A-03

Meldola

- (b) (4) GBq batch size (b) (4) Ci), Lot numbers: LT150713A-06, LT150714A-06, LT150720A-06

The batch records for both drug product manufacturing sites confirm that validated (b) (4) were used for the manufacture of the exhibit batches.

Reviewer's Assessment: Acceptable

Comparability Protocols

Reviewer's Assessment: No CP was included in the application.

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

2.A. Package Insert

Storage temperature: below 25°C [(b) (4)], vial enclosed in the original plastic sealed, lead shielded container
Route of administration: IV infusion
Container: Single dose
[(b) (4)] Single-dose vial and discard unused portion is stated in the PI and on vial and container labels. Sterile solution is noted on the container label.

Reviewer's Assessment: Acceptable

Post-Approval Commitments:

Reviewer's Assessment: N/A

Lifecycle Management Considerations

Reviewer's Assessment: N/A

List of Deficiencies:

The Division of Microbiology has no additional comments at this time.

Primary Microbiology Reviewer Name and Date: Peggy Kriger, Ph.D., November 10, 2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 11/14/2016 08:42 53AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Peggy Kriger

Digitally signed by Peggy Kriger
Date: 11/14/2016 08:42 03AM
GUID: 534c169d00067f29cedbaa415df21ba2

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 11/22/2016 04:35 59PM
GUID: 5050dd27000012a4c69bfc70b47660b7