

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212123Orig1s000

PRODUCT QUALITY REVIEW(S)



NDA 212123

Office of Pharmaceutical Quality
Integrated Quality Assessment

Contents

NDA 212123	5
EXECUTIVE SUMMARY	6
QUALITY ASSESSMENT DATA SHEET	7
CHAPTER I: DRUG SUBSTANCE.....	17
S.1 GENERAL INFORMATION.....	
S.2 MANUFACTURE	
S.3 CHARACTERIZATION	
S.4 CONTROL OF DRUG SUBSTANCE	
S.5 REFERENCE STANDARD	
S.6 CONTAINER CLOSURE	
S.7 STABILITY	
R REGIONAL INFORMATION	
DRUG SUBSTANCE LIST OF DEFICIENCIES	
CHAPTER II: DRUG PRODUCT	50
P.1 DESCRIPTION AND COMPOSITION.....	
P.2 PHARMACEUTICAL DEVELOPMENT	
P.4 CONTROL OF EXCIPIENTS	
P.5 CONTROL OF DRUG PRODUCT	
P.6 REFERENCE STANDARD	
P.7 CONTAINER CLOSURE	
P.8 STABILITY	
R REGIONAL INFORMATION	
DRUG PRODUCT LIST OF DEFICIENCIES	
CHAPTER III: ENVIRONMENTAL	148
CHAPTER IV: LABELING.....	149
ITEMS FOR ADDITIONAL ASSESSMENT	
CHAPTER V: MANUFACTURING	173
I. MANUFACTURING SUMMARY	
II. DRUG PRODUCT MANUFACTURING.....	
DI. DRUG SUBSTANCE MANUFACTURING	
IV. TESTING FACILITIES / PRIMARY PACKAGING FACILITIES	

V. LIST OF OUTSTANDING INFORMATION REQUEST/DEFICIENCIES:
VI. SIGNATURE BLOCK
CHAPTER VI: BIOPHARMACEUTICSN/A
B.1 BCS DESIGNATION
B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA
B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)
B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD
B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – <i>In-Vitro Alcohol Dose Dumping</i>
B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY
B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS
B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS
B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS
B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS
B.11 EXTENDED RELEASE DOSAGE FORMS – <i>Extended Release Claim</i>
B.12 BRIDGING OF FORMULATIONS
B. 13 BIOWAIVER REQUEST
R. REGIONAL INFORMATION
BIOPHARMACEUTICS LIST OF DEFICIENCIES
CHAPTER VII: MICROBIOLOGY Error! Bookmark not defined.220
S DRUG SUBSTANCE
S.2. MANUFACTURE
S.4 CONTROL OF DRUG SUBSTANCE
S.6 CONTAINER CLOSURE SYSTEM
S.7 STABILITY
P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT
P.2 PHARMACEUTICAL DEVELOPMENT
P.3 MANUFACTURE
P.5 CONTROL OF DRUG PRODUCT
P.7 CONTAINER CLOSURE
P.8 STABILITY

APPENDICES.....
A.2 ADVENTITIOUS AGENTS SAFETY EVALUATION.....
R REGIONAL INFORMATION
MICROBIOLOGY LIST OF DEFICIENCIES
Chapter VIII: Additional Quality DisciplineN/A
DOCUMENT HISTORYN/A

Recommendation: **Approval**

NDA [212123]

Flortaucipir F 18 Injection

Review #[FINAL]

Drug Name/Dosage Form	TAUVID (Flortaucipir F 18 Injection)
Strength(s)	300 – 1900 MBq/mL (8 – 51 mCi/mL) @ EOS NLT 37 MBq (1 mCi)/mL at TOI ¹
Route of Administration	Intravenous Injection bolus
Rx/OTC Dispensed	Rx
Applicant	Avid Radiopharmaceuticals, Inc.
US agent, if applicable	N/A

1. [REDACTED] (b) (4)

SUBMISSION(S) REVIEWED (seq. no.)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	09/30/2019	OPQ, Microbiology, Process/Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Shomo Mitra	Martin Haber
Drug Product	Elise Luong	Danae Christodoulou
Process/Facilities	Laurie Nelson	Krishnakalli Ghosh
Microbiology	Avital (Talie) Shimanovich	Erika Pfeiler
Biopharmaceutics	N/A	N/A
Environmental	Elise Luong	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 # ¹	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	V	(b) (4)	(b) (4)	(2)	(2)	(2)
	V			Adequate	11/29/2016	N/A
	V			Adequate	04/25/2017	N/A

- (1) Letters of authorization from the holder of the DMF's are submitted with the NDA.
- (2) DMF in Biologics. Determined to be adequate by OPQ Microbiology (Review by: Avital Shimanovich, Ph.D., 02/20/2020).

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119863	Flortaucipir F 18 Injection (Avid Radiopharmaceuticals, Inc.)

2. CONSULTS

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
N/A			

Executive Summary

I. Overall Recommendation on Approvability

Approval, based on CMC Product Quality, Microbiological Product Quality and acceptable CGMP Inspections of all manufacturing facilities associated with NDA 212123.

OPQ recommends **APPROVAL** of NDA [212123] for commercialization of **Tauvid (Flortaucipir F 18 Injection) 300 – 1900 MBq/mL (8 – 51 mC/mL) at EOS** with an expiration dating period of **[5.5 - 10]** 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 (5/14/2020) of [approval] supporting the approval of all manufacturing facilities associated with NDA 212123.
- The proposed labeling and labels [have] adequate information to meet the regulatory requirements.

II. Product Quality Review Context

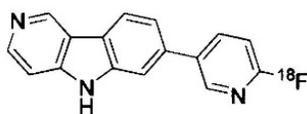
Indication and Intended Population:

There has been an unmet need for a biomarker of aggregated tau NET pathology in the diagnosis and management of Alzheimer’s Disease (AD), which is the basis for submission of NDA 212123 by Avid Radiopharmaceuticals (wholly owned subsidiary of Eli Lilly) for TAUVID (Flortaucipir F 18 Injection) for PET imaging in the context of the following indication: Diagnostic agent for PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles of AD.

TAUVID will be used with PET imaging to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD).

Regulatory Context - Designation of Drug Substance:

7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole is a small molecule with the following structure.



$C_{16}H_{10}[^{18}F]N_3$

Molecular weight: 263.0859 (exact mass)

¹⁸F (β^+ , 0.635 MeV, max; γ^\pm , 511 KeV, 134%; $t_{1/2}$ 109.7 min)

The active ingredient in Fluoroestradiol F 18 Injection is that substance which is radioactive, 7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole (21 CFR 310.3 (n)), interpreted as the drug substance, 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 7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole as the entity that furnishes the “action” expected of an active ingredient.

Regulatory Context - Regulatory Status of the Precursor:

Because the radiolabeled entity is produced (b) (4)

That also impacts strength and specific activity determinations, outcomes that create a chain-effect ultimately transferred to the patient dose, consequently intensifying the criticality of the Precursor,

Together, all of these factors raise the controls for the Precursor to the level of scrutiny as for an API, justifying its placement under the section for drug substance.

Product Profile and Critical Quality Attributes (CQA's):

Flortaucipir F 18 Injection is a clear, colorless and sterile (b) (4) solution of 7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole, C₁₆H₁₀[¹⁸F]N₃, in Sodium Chloride 0.9% Injection with (b) (4) Ethanol (b) (4) and is provided as a multi-dose vial (described in 3.2.P.7 as a Bulk Product Vial), apyrogenic 30 mL or 50 mL clear Type (b) (4) vial closed with rubber stopper (b) (4) and a 20 mm aluminum crimp seal. Unit doses provided by the radiopharmacy are 370 MBq in 10 mL (b) (4)

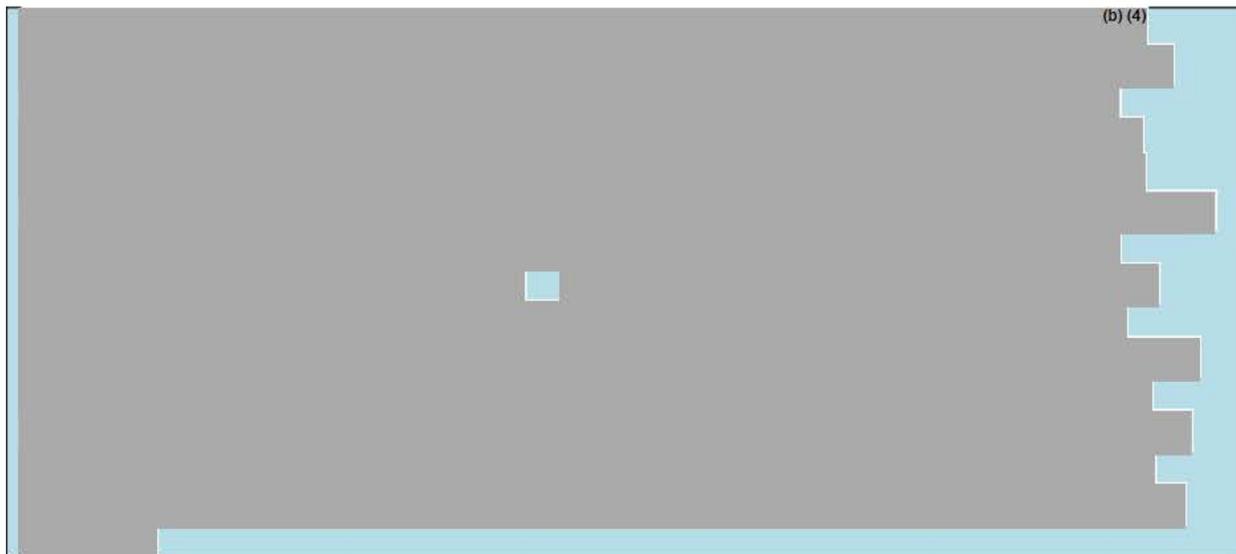
Expiration dating is from 5.5 to 10 hours, post EOS, where the length of the dating period depends on the radioactivity yield of the production batch. Patient dose is set at (b) (4)

Areas of Unique Focus:

➤ Radiolabeling Chemistry:

The radiolabeling reaction for creation of 7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole follows a (b) (4) mechanism, well-established in terms of

applicability and outcomes. The most important issue with respect to the process for 7-[6-(¹⁸F)fluoropyradin-3-yl]-5H-pyrido[4,3-b]indole relates to the **radiosynthesizer** that will be used in the production of product, the exact type (model) and all those matters associated with its use (**ancillary items**).



➤ **Quality Controls:**

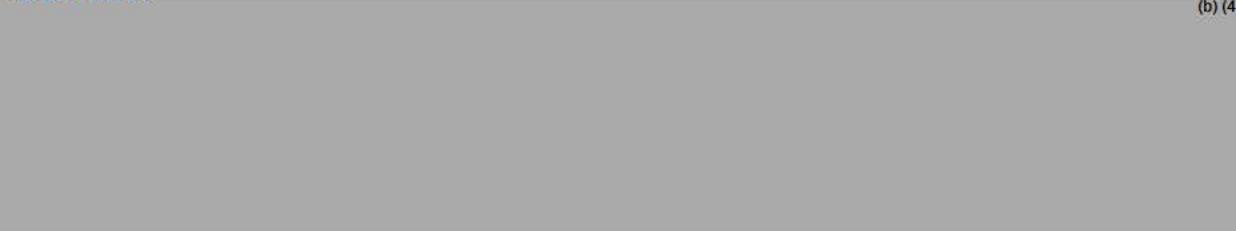
Overall, there are numerous deficiencies in the analytical methods and acceptance criteria that cause concerns about the overall readiness to be employed in real-time analytical quality controls in a manufacturing environment. These deficiencies are not so much with the underlying principles of methodology, but rather the **absence of critical information showing the level of their method development and validation, some discrepancies in the data provided, and the quality of some of that data** (primary review by Elise Luong, Ph.D.).

➤ **Product Packaging and Stability:**

The intent of the firm is to ship product in both vials



(**Stability**)



(b) (4)

(Post-Approval Protocol and Stability Commitment).

(b) (4)

III. Summary of Quality Assessments

PRECURSOR (in relation to Drug Substance)

Issues for the precursor were few (Shomo Mitra, Ph.D.). But, of these are (1) the lack of long-term stability data in support of retest period of reference standard, and (2) Illegible block flow diagrams in the development history report (b) (4) that need correction. Both of these issues (**Comments to the firm, 01/07/2020**) are addressed in the responses from the applicant and are now **Resolved**.

DRUG PRODUCT

(Radiolabeling Chemistry).

It is established that the applicant will only employ (b) (4)

(b) (4)

Of the **ancillary issues** are those associated with its use (conveyed to applicant 01/07/2020), most prominent being the (b) (4)

(b) (4)

(**Comment #4**), and the absence of a Validation Cleaning Protocol (**Comment #5**); all are **Resolved**. Since nothing will move forward in a CMC plan if the radiolabeling chemistry cannot produce the intended drug substance molecule, it occupies the centerpiece of the whole production process. At the same time, all the ancillary parts are critical to bringing it all together and moving it forward. The **history of this development** is an essential piece for understanding of the character of the CMC plan and for its capability of producing the final product. But, illegible block-flow diagrams in the development history impedes this understanding, thus forming the issue in **Comment #17** (submission of a legible history development report) – now **Resolved**.

(Quality Controls).

➤ **Specifications.**

In the specifications, there are issues (conveyed to sponsor, 01/07/2020) for quality control final release, including (1) radiochemical impurities, radiochemical identity and specific activity (**Comment #6**). Regards the issue for radiochemical identity per the

lag-time consideration, the applicant commits to revision of the acceptance criterion, and so all parts (a, b and c) of comment #6 are now **Resolved**. Along with these issues there is included a needed strategy for control of (b) (4) contamination in leachables in the Bulk Product Vial (**Comment #2**), now also **Resolved**.

In conjunction with Comment #2, Leachables are being separated out here because not only is there the issue for interactions of the container closure system with the product, but also with direct contact with any surfaces in the radiosynthesizer. This led to another **Comment #11** (lack of demonstration of absence of impurities above the reporting limit from pooled samples) having to do with leaching from (b) (4) (now **Resolved**).

➤ **Analytical Methods.**

The issues for analytical methods range from methodology to their validation, and include discrepancies ranging from descriptions to missing information. **Methodology** issues entail the (b) (4), Radionuclidic Identity and Strength (**Comment #7**), and pH (**Comment #10**). For **validation**, the primary issues involve the (b) (4) for determining a whole range of quality attributes (Radiochemical Purity, Radiochemical Impurities, Flortaucipir F 18 Strength, Chemical Impurities and Radiochemical Identity), **Comment #9**. Each of these issues (#7, #9, #10) are now **Resolved**. There are also discrepancies in the sections describing the analytical procedures and their validation (**Comment #8**), now **Resolved**. The **Integrity of the Reference Standard** is one of the pivotal elements for establishing the soundness of the analytical method for Radiochemical Identity and Purity, and for maintenance of that integrity throughout application of quality controls. There cannot be any corners cut on this point, and it involves not only the original qualification of the standard, but also its stability, and that it is maintained throughout its use (subject of **Comment #16** for long-term stability data) – **Resolved**.

The quality of the results from running an analytical method is very important, not just in terms of being error free from an ancillary standpoint, but also that it is scientifically sound, because it potentially affects the outcome to patients subjected to a product. Quality control is responsible for that data. **A “bad” result can originate from a problem in the method itself, involving method principle, or how it is executed, but which had eluded discovery during methods development and validation, only becoming apparent later. Thus, as a potential “science issue,” as opposed to a math issue, Comment #14** for an Out of Specification (OOS) takes its proper place in the review of the drug product (Review by Elise Luong, Ph.D.). Through an independent review, this OOS issue was also noted by Krishnakalli Ghosh, Ph.D., whose review discipline (CGMP) typically handles OOS events. In this instance, it is a cross-cutting issue. But, based on the aforementioned it goes beyond a “normal” cross-cutting issue in that it is a signal piece in establishing confidence in the quality controls from a scientifically robust perspective. As first noted, the applicant’s procedure for handling OOS results was confounded by the issue of what constitutes an invalidated test result creating the specter that the real issue might continue to elude detection, if their original procedure for dealing with the

OOS amounts to a version of “testing into compliance.” The firm indicated that under no circumstances would it be testing into compliance and proposed a rewrite of the procedure to follow in the event of an OOS.

In any procedure for handling an OOS, there must be **suitable pre-defined test validity criteria** that will be used in an investigation of the root cause. It was unclear whether the decisions on invalidity of a test result were to be handled in this context, and so left vagueness in the original version of the language. These criteria should (of course) be capable of differentiating between method problems and circumstantial-type events so that a ‘result denoted as invalid’ is a result stemming from only occurrences of the latter type. **In the proposed version, the language includes an investigation according to pre-defined test validity criteria and a defined process of how to proceed from the initial test result.** The proposed version is found acceptable in internal discussions among appropriate members of this Branch, as well as by Krishnakalli Ghosh, and finalized in the Memorandum of Teleconference between FDA and representatives of Avid Radiopharmaceuticals, 2/13/2020, thus **Resolving** the OOS issue in Comment #14.

(Product Packaging and Stability).

(b) (4)

Comment #13 is considered **Resolved** relative to fulfillment of the commitment post-approval through a supplement.

(Drug Product Composition and Labeling).

Changes to a drug product in its approved form can be altered in a radiopharmacy as long as those changes are confined to dilution only, so that there is no adverse effect on the formulation. Such change is considered under pharmacy practice. **However, this assumes that there is full compatibility of the given approved form with the diluent.** In relation to compatibility, changes in solubility upon dilution have been known to create a **theoretical risk** of precipitating out during injection, but usually involve the offending ingredient to be in larger concentration than which is present in Flortaucipir F 18 Injection, creating the basis for **Comment #1**. Through solubility data provided by the applicant, the 1:5 dilution of Flortaucipir with 0.9% sodium revealed that this theoretical risk is unlikely to be realized, thus leaving the issue in Comment #1 **Resolved**.

A statement about this included in the labeling (“*Tauvid may be diluted aseptically with 0.9% Sodium Chloride Injection to a maximum dilution of 1:5 by the end user. Diluted product should be used within 3 hours of dilution and prior to product expiry*”) following Avid’s request and the labeling meeting (4/08/2020). There were also some labeling issues in the Full Prescribing Information and How Supplied/Storage, as well as handling sections (**Comment #15**) - **Resolved**. However, as an adjunct to the resolution of this issue, DMIP has decided to remove all references to dilution of the product (1:5).

As of 03/13/2020, it is determined that the PI is satisfactory from a CMC perspective. However, it was communicated to DMIP that the shield and immediate container labels need to be harmonized to include the storage and expiration statements, and this was conveyed with DMEPA’s comments regarding the container closure labels (03/13/2020).

(Microbiology)

All issues for microbiology, as enumerated and discussed in the Microbiology Review (Avital Shimanovich, Ph.D., 02/20/2020) have been adequately resolved, and there are no remaining deficiencies. According to the Microbiology Review, Avid Radiopharmaceuticals has met the regulatory expectations regarding the design of the stability testing program to support Tauvid’s microbiology quality through its shelf-life (10 hours post EOS) at room temperature and stored upright. New manufacturing site qualification will be submitted by submission of a post-approval supplement with a CP.

(Facility Inspections).

In the following table are placed the full range of facilities involved in the production of Tauvid, the responsibility and CGMP status (as of this Executive Summary) as of 5/14/2020.

Facility	Responsibility	Status
PETNET-Knoxville	Drug product production (b) (4)	Acceptable
(b) (4)	"	(1), Acceptable
	"	Acceptable
	Production of (b) (4) precursor	(3), acceptable
	"	Acceptable
		(4), Acceptable
	Precursor release testing	Acceptable
	Provides (b) (4)	N/A

- (1) (b) (4). RAI letter issued to firm and responses received are determined by OPMA to be acceptable.
- (2) (b) (4). RAI letter issued to firm and responses received-determined to be acceptable (OPMA).
- (3) (b) (4). Inspection that was scheduled for (b) (4) is canceled upon strong recommendation from Process/Facilities and is included within the approval recommendation by OPMA management (5/14/2020).
- (4) (b) (4). In conjunction with a 'signed medical necessity form' from DMIP, and product quality determinations (OPQ, OPMA), this facility is included in the OPMA recommendation (5/14/2020) of approval of all manufacturing sites associated with NDA 212123.

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. Flortaucipir F 18 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 Flortaucipir F 18 Injection. In addition, an approval recommendation was received (5/14/2020) from OPMA management supporting the approval of all manufacturing facilities associated with NDA 212123.

VI. Lifecycle Considerations

Any new manufacturing site qualification will be submitted by submission of a post-approval supplement with a CP.

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

N/A



Eldon
Leutzinger

Digitally signed by Eldon Leutzinger
Date: 5/15/2020 09:49:36AM
GUID: 508da7210002a0781943eff6cc724d1f

131 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental Analysis (EA)

In accordance with 21 CFR 25.31(b), Avid Radiopharmaceuticals, Inc. claims a categorical exclusion from the requirement to prepare an Environmental Assessment as the estimated concentration of the drug product and chemical precursor (b) (4) at the point of entry into the aquatic environment will be below 1 part per billion (ppb) (1 µg/L). To the best of Avid's knowledge, no extraordinary circumstances exist.

The annual peak sales of Flortaucipir F18 Injection in the United States will be less than (b) (4) doses, or (b) (4) kg/year of flortaucipir F19 and (b) (4) kg/year of (b) (4) precursor. Assuming a daily discharge of water to sewage treatment facilities in the United States is approximately 1.26×10^{11} L (Environmental Protection Agency, 2012 Clean Watershed Needs Survey, Technical Data), a maximum expected introduction concentration of flortaucipir F19 will be less than (b) (4) µg/L and of precursor will be less than (b) (4) µg/L.

Assessment: Adequate from a CMC perspective.

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 02/11/2020.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Eldon Leutzinger, Ph.D.; 02/18/2020 I concur with the reviewer's assessment.

Tertiary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D.; 02/18/2020 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TAUVID	Reviewed by DMEPA
Established name(s)	Flortaucipir F18 Injection	Adequate
Route(s) of administration	Intravenous	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	300-1900 MBq/mL (8.1 - 5.1 mCi/mL) flortaucipir F18 at End of Synthesis (EOS)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include	(b) (4)	Adequate

pharmacy bulk package and imaging bulk package.		
---	--	--

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

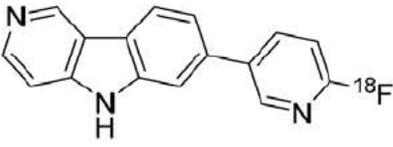
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
<p>Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)</p>	<p>Contradict information is provided. In 3.2.P.1 Description and Composition of the Drug Product, it said <div style="background-color: gray; width: 100%; height: 100%; min-height: 100px; min-width: 100%;"></div> <small>(b) (4)</small> But on the label, it then said "TAUVID may be diluted aseptically with 0.9% Sodium Chloride Injection to a maximum dilution 1:5 by the end user." By doing so, the composition is altered severely.</p>	<p>Any dilution ratio with 0.9% Sodium Chloride will alter the drug product composition. A dilution ratio of 1:5 will alter the <div style="background-color: gray; width: 100%; height: 100%; min-height: 100px; min-width: 100%;"></div> <small>(b) (4)</small></p>

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Solution for injection	Adequate
Strength(s) in metric system	300-1900 MBq/mL at End of Synthesis	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Solution is clear, colorless and no visual particulates	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	The bulk product vial is a multi-dose vial	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name	TAUVID	Reviewed by DMEPA
Established name(s)	Flortaucipir F18	
Dosage form(s) and route(s) of administration	Solution for Injection Intravenous (b) (4)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Sodium Chloride Ethanol	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	0.9% Sodium Chloride Injection and 0.1 (b) (4) Ethanol per milliliter	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	(b) (4) in 0.9% sodium chloride injection USP	Adequate
Statement of being sterile (if applicable)	TAUVID is a sterile, non-pyrogenic radioactive diagnostic agent	Adequate
Pharmacological/therapeutic class	Radioactive diagnostic agent	Adequate

Flortaucipir Chemical name, structural formula, molecular weight	7-(6-[F-18]fluoropyridine-3-yl)-5H-pyrido[4,3-b]indole  262.27 amu C ₁₆ H ₁₀ [¹⁸ F]N ₃	Adequate
If radioactive, statement of important nuclear characteristics	¹⁸ F Half-life: (b) (4) minutes Gamma energy: 511 keV	Adequate
Other important chemical or physical properties (such as pKa or pH)	pH is between 4.5 and 8.0	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Solution	Adequate
Strength(s) in metric system	300 – 1900 MBq/mL (8.1 – 51 mCi/mL)	Adequate
Available units (e.g., bottles of 100 tablets)	30 mL or 50 mL vials	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, colorless solution free of visible particulate matter	Adequate. The description has been provided in the NDA
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	30 mL or 50 mL vial is a multi-dose bulk product vial	Adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at 25 °C (77 °F); excursions permitted to 15 °C to 30 °C (59°F to 86 °F) [See USP Controlled Room Temperature].	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25 °C (77 °F); excursions permitted to 15 °C to 30 °C (59°F to 86 °F) [See USP Controlled Room Temperature].	The storage condition is supported by data and is acceptable.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

In response to CMC comments dated 01/07/20, the applicant has revised the information in the following subsections:

- (a) Subsection 11 Description, '... The clear, colorless solution free of visible particulate matter ...', '...dehydrated alcohol (b) (4) in 0.9% sodium chloride injection USP', and added the molecular formula $C_{16}H_{10}[^{18}F]N_3$ next to the structure.*
- (b) Subsection 16 How Supplied/Storage and Handling, ...'TAUVID is supplied in 30 mL or 50 mL vials containing a clear, colorless solution free of visible particulate matter...'*
- (c) Subsection for Pharmacological Class, '...TAUVID is a radioactive diagnostic agent.'*

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through DMEPA during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Representative examples of a proposed containers)

30-mL Dose Vial Label



3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

FDA Comment (01/07/20): Section 1.14 Labeling, Full Prescribing Information, we have the following comments:

- a. Subsection 11 Description, (i) change 'The clear, colorless solution...' to 'The clear, colorless, and free of particulates solution...' (ii) When alcohol is presented, you must also provide the amount of alcohol in terms of percent volume of absolute alcohol. (iii) Add the molecular formula next to the molecular weight.
- b. Subsection 16 How Supplied/Storage and Handling, change '...clear, colorless solution' to 'clear, colorless, and free of particulates solution'.
- c. Add a subsection for Pharmacological class.

Response (01/16/20): Labeling has been updated to include the molecular formula $C_{16}H_{10}[^{18}F]N_3$, (b) (4) dehydrated alcohol in 0.9% sodium chloride injection USP, the clear, colorless solution is free of visible particulate matter, and the pharmacological class is radioactive diagnostic agent.

EVALUATION: The applicant's responses are adequate. Labeling will be finalized through DMEPA during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The applicant has not updated the multidose vial labels in EDR to reflect the drug product contains (b) (4) dehydrated alcohol.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 02/11/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., 02/16/2020



Danae
Christodoulou

Digitally signed by Danae Christodoulou
Date: 2/18/2020 01:06:28PM
GUID: 5050dd27000012a4c69bfc70b47660b7



Elise
Luong

Digitally signed by Elise Luong
Date: 2/18/2020 10:09:28AM
GUID: 537253e70005b48ebb030e8b349f32e6

57 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following
this page

CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	212123
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Flortaucipir F 18 Injection/300-1900 MBq/mL at End of Synthesis (EOS)
Route of Administration	Intravenous
Applicant Name	Avid Radiopharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Medical Imaging Products
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: Adequate

Assessment Summary:

Document(s) Assessed	Date Received
Initial submission	09/30/2019
CMC IR response	01/13/2020
CMC IR response	02/07/2020
CMC IR response	02/13/2020
CMC IR response	02/20/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is indicated for PET imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles of (b) (4). The drug product is (b) (4).

Concise Description of Outstanding Issues: None

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug product is manufactured in (b) (4). Therefore, no microbiological assessment of the drug substance is performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, descrypt-and-comp, Section 3.2.P.2, micro-attributes, Section 2.3.P, drug-product

- Description of the drug product – The DP is a multi-dose, clear, colorless solution.
- Composition of the drug product –

Ingredient	Quantity/dose	Function
Flortaucipir F 18	370 MBq	API
Dehydrated alcohol (ethanol), USP		(b) (4)
0.9% NaCl Injection, USP (sterile)		(b) (4)

- Description of the container closure system – The applicant states that the container closure systems (CCS) are as follows:

Component	Description	Supplier	(b) (4)
Vial	30 mL/20 mm apyrogenic Type (b) (4) glass (b) (4)	(b) (4)	(b) (4)
	50 mL/20 mm apyrogenic Type (b) (4) glass (b) (4)		
Stopper	20 mm (b) (4) gray (b) (4)		
Seal	20 mm aluminum crimp seal (b) (4)		

In Section 2.3.P, the applicant stated that the drug product can be dispensed from the above CCSs (b) (4).



Assessment: Adequate

The applicant provided a description of the DP in Section 3.2.P.1 and CCSs in Sections 3.2.P.1 and 2.3.P of the 09/30/2019 submission. In the 11/06/2019 meeting with the applicant, the ATL explained to the applicant that the (b) (4)



P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

Section 3.2.P.2, TR-AV-1451-146 Validation of Flortaucipir F 18 Injection

Container Closure Integrity

To demonstrate the integrity of the CCS, the applicant provided a container closure integrity test (CCIT) report VP-028.02, dated 08/24/2009. The CCIT was performed by (b) (4) on the commercial 30 mL/20 mm CCS (b) (4)



The CCIT was performed on the following number of 30 mL/20 mm (b) (4)

(b) (4) units:

Units	Description
Test	36 units manually filled, sealed, and capped with soybean casein digest medium (SCDM). Vials were incubated at 30-35°C for 14 days prior to performing the CCIT.
Positive controls	2 units punctured with a 27G needle which was retained through the test
Negative controls	2

Protocol:

1. Test and positive control units were immersed in 5 Liters of SCDB containing 9.5×10^9 CFU/mL of *B. diminuta*.
2. A vacuum of 24 in Hg was applied to the units for two minutes
3. Units were incubated at 30-35°C for 14 days
4. The vials were examined for growth on days 3, 7, and 14.
5. Units were subjected to a test for growth promotion with ≤ 100 CFU of *B. subtilis*, *C. albicans*, *A. niger*.

Results: Positive control units were turbid. No growth was observed in test and negative control units. The growth promotion test resulted in growth of inoculated organisms.

Assessment: Adequate

A CCIT for the 50 mL/20 mm CCS (b) (4) were not provided. However, CCITs are not required for PET DPs due to the short shelf-life of these DPs; the shelf-life of this DP is 10 hours from EOS. Additionally, the (b) (4). Therefore, no deficiencies requesting CCITs for the additional CCSs will be issued.

Antimicrobial Effectiveness Testing

Assessment: N/A, the DP does not contain a preservative. Antimicrobial Effectiveness Testing (AET) per USP <51> is not required for PET products due to the short shelf life of the DP which minimizes growth of adventitious microorganisms; the shelf-life of this DP is 10 hours from EOS.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

Section 3.2.P.3.1, manufacturers

(b) (4)

Assessment: Adequate

The applicant provided the location of the drug manufacturing facilities.

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

Overall Manufacturing Operation

Section 3.2.P.3.1, descript-and-comp and Section 3.2.P.3.3, mfg-process

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page



Avital
Shimanovich

Digitally signed by Avital Shimanovich
Date: 2/21/2020 07:04:01AM
GUID: 598ca8f5005723e97e9300810ca9b31a



Erika
Pfeiler

Digitally signed by Erika Pfeiler
Date: 2/21/2020 07:09:53AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

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
05/15/2020 04:31:42 PM

ELDON E LEUTZINGER
05/15/2020 04:41:02 PM