

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202008Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-008

AMYVID™
(Florbetapir F 18) Injection

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Avid Radiopharmaceuticals, Inc.
3711 Market Street 7th Floor
Philadelphia, PA 19104

INDICATIONS AND USAGE

Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations (1).

Limitations of Use

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Amyvid have not been established for:
 - Predicting development of dementia or other neurologic condition;
 - Monitoring responses to therapies (1).

Presentation: The drug product is supplied as a multidose vial and administered as a single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b) (4) flush of

0.9% Sodium Chloride Injection to ensure full delivery of the dose.

Establishments Evaluation Report (EER) Status: Acceptable 26-MAR-2012

Note – 8 Cardinal Health facilities where the product will be produced were found acceptable.

Consults:	EA –	Acceptable
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm –	N/A
	Microbiology –	Acceptable
	Pharm Toxicology –	Acceptable

Original Submission:	September 17, 2010
Amendments:	
Amendment	09-Nov-2010
Amendment	07-Jan-2011
Amendment (QR, CC)	31-Jan-2011
Amendment (EG)	17-Jan-2011
Amendment	20-Dec-2011
Amendment	29-Feb-2012
Resubmission:	7-Oct-2011
Post-Approval CMC Agreements:	None at this time.

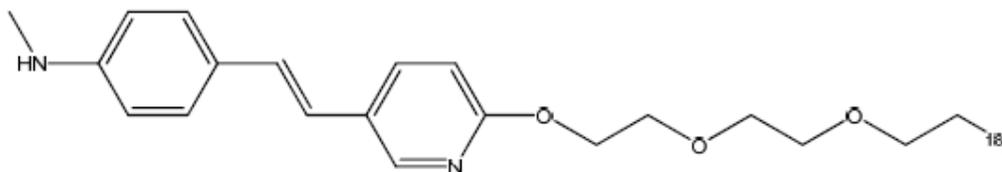
Labeling

Labeling as been found acceptable.

Drug Substance

The drug substance florbetapir is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity approximately (b)(4) and has ranged from (b)(4). The specific activity is required to be (b)(4) at exp (b)(4) of Drug Substance in Drug Product NLT 500 MBq/mL and NMT 1900 MBq/mL at EOS and is required to be NLT 37 MBq/mL at expiry. The shelf-life (expiry) specifications mean that a 370 MBq maximum human dose of Florbetapir F 18 Injection will contain not more than 50 µg of florbetapir F 19 and will be contained in not more than 10 mL of a solution that is 10% v/v in ethanol.

Chemical structure, molecular weight and molecular weight are provided below:



Chemical Formula: $C_{20}H_{25}^{18}FN_2O_3$

Molecular Weight: 359.43

Elemental Analysis: C, 66.83; H, 7.01; F, 5.01; N, 7.79; O, 13.35

Stability data support a re-test period of (b)(4) for the florbetapir precursor AV-105.

Conclusion

Drug substance is acceptable.

Drug Product

Florbetapir F 18 Injection is produced as a sterile solution for intravenous injection in a 10 ml, 30 ml or 50 mL multi-dose vial containing 500 mBq/mL (13.5 mCi/mL) to 1900 mBq/mL (51.4 mCi/mL) of Florbetapir F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.5 mg of sodium ascorbate, USP, 0.1 mL dehydrated alcohol, USP and 0.9 ml of 0.9% sodium chloride injection, USP.

The unit dose is prepared by the radio-pharmacy and is 370 MBq (10 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 ml, therefore a maximum of 45mg of sodium ascorbate, USP, 1 mL dehydrated alcohol, USP and 0.9 ml of 0.9% sodium chloride injection, USP may be present in the human dose. For

smaller unit dose volumes (less than 10 mL), the ratios of sodium ascorbate, dehydrated alcohol, and 0.9% Sodium Chloride Injection are maintained. The composition of the drug product is not altered (no dilution) after manufacture of the multi-dose vial of the drug product in preparation of the unit radio-pharmacy doses. A concentration of (b) (4) is needed to maintain Drug Substance radiochemical purity over the shelf-life of the product. The formulation (b) (4) remains within the physiologically compatible range of pH 5.5 to 7.5. The Drug Substance remains soluble in formulation in this pH range and stability studies have not shown sensitivity of Drug Substance to pH within this range. The Osmolality of Drug Product formulation was experimentally determined (b) (4). The Osmolality was calculated (b) (4).

The recommended single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b) (4) flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. Subsequent to administration, the subject is imaged for 10 minutes using a PET camera. A 10 minute scan has been shown to provide good quality PET images.

The proposed expiration dating period of 10 hours after EOS, or when either the shelf-life specific activity or strength specification is reached, whichever is soonest is acceptable.

Conclusion: Drug product is adequate.

Overall Conclusion: From CMC point of view, the NDA is recommended for Approval.

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/s/

ERIC P DUFFY
03/30/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 28 March 2012
From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch VII, DNDQA-III, ONDQA
Through: Ali Al-Hakim, Ph.D.
Branch Chief, Branch VII, DNDQA-III, ONDQA
Subject: CMC Recommendation for NDA 202008.

In the CMC Review # 2 of this NDA, the application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided manufacturing facilities are in acceptable compliance for cGMP and acceptable final package insert and container closure labeling is received.

Since that recommendation, the manufacturing facilities have been found to be in acceptable compliance for cGMP (26-March-2012).

Additionally, Avid Radiopharmaceuticals has submitted following revised labeling on 21-March-2012 (e-mail). The following revised vial and shield labels were submitted:

Bulk Drug Product Vial Label

NDC Code 0001-1200-30 Sterile
Amyvid™ Rx Only
Florbetapir F 18 Injection CAUTION: RADIOACTIVE MATERIAL
Batch No. Date:
For Intravenous Use.
Contains 9.1 to 19 micrograms of florbetapir and 500 - 1900 MBq (13.5 - 51 mCi) florbetapir F 18 at end of synthesis (EOS), with 4.5 mg sodium ascorbate USP, 0.1 mL dehydrated alcohol USP, (b) (4) 0.9% sodium chloride injection USP per milliliter of solution. Store at USP controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Manufactured by "Contract Manufacturing Organization" for Avid Radiopharmaceuticals, a wholly-owned subsidiary of Eli Lilly and Company, Philadelphia, PA 19104
(Other vial sizes will have NDC Codes: 0002-1200-10 or 0003-1200-30
*PETNET Solutions, Inc. Knoxville, TN 37932 or Cardinal Health #14, LLC, Dublin, OH 43017 depending on manufacturing facility.

Bulk Drug Product Shield Label

NDC Code 0001-1200-30 Sterile
Amyvid™ Rx Only CAUTION: RADIOACTIVE MATERIAL
Florbetapir F 18 Injection
_____ MBq (_____ mCi) in _____ mL at _____ °C
Batch No. _____
For Intravenous Use.
Contains 0.1 to 1.0 micrograms of florbetapir, 4.5 mg sodium ascorbate USP, 0.1 mL dehydrated alcohol USP, (b) (4) 0.9% sodium chloride injection USP per milliliter of solution.
Store at USP controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Expires at _____ °C
Manufactured by "Contract Manufacturing Organization" for Avid Radiopharmaceuticals, a wholly-owned subsidiary of Eli Lilly and Company, Philadelphia, PA 19104
*Other vial sizes will have NDC Codes: 0002-1200-10 or 0003-1200-30
*PETNET Solutions, Inc. Knoxville, TN 37932 or Cardinal Health #14, LLC, Dublin, OH 43017 depending on manufacturing facility.

Following CMC related information is provided in package insert:

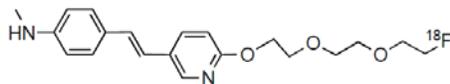
Name of the Drug:

Amyvid (Florbetapir F 18 Injection) for intravenous use

-----DOSAGE FORMS AND STRENGTHS-----
10 mL, 30 mL, or 50 mL multidose vial containing a clear, colorless injectable solution at a strength of 500-1900 MBq/mL (13.5-51 mCi/mL) florbetapir F 18 at End of Synthesis (EOS) (3).

11 DESCRIPTION

Amyvid contains florbetapir F 18, a molecular imaging agent that binds to β -amyloid aggregates, and is intended for use with PET imaging of the brain. Chemically, florbetapir F 18 is described as (E)-4-(2-(6-(2-(2-[18 F] fluoroethoxy)ethoxy)ethoxy)pyridine-3-yl)vinyl)-N-methylbenzamine. The molecular weight is 359 and the structural formula is:



Amyvid is a sterile, non-pyrogenic radiopharmaceutical for intravenous injection. The clear, colorless solution is supplied ready to use and each milliliter contains 0.1 to 19 micrograms of florbetapir and 500 - 1900 MBq (13.5 - 51 mCi) florbetapir F 18 at EOS, with 4.5 mg sodium ascorbate USP, and 0.1 mL dehydrated alcohol USP in 0.9% sodium chloride injection USP. The pH of the solution is between 5.5 and 7.5.

16.1 How Supplied

Amyvid is supplied in 10 mL, 30 mL, or 50 mL vials containing 10 mL, 10-30 mL, or 10-50 mL, respectively, of a clear, colorless solution at a strength of 500 - 1900 MBq/mL (13.5 - 51 mCi/mL) florbetapir F 18 at EOS. Each vial contains multiple doses and is enclosed in a shielded container to minimize external radiation exposure.

10 mL	NDC 0002-1200-10 (IC1200)
30 mL	NDC 0002-1200-30 (IC1200)
50 mL	NDC 0002-1200-50 (IC1200)

16.2 Storage and Handling

Store Amyvid at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. The product does not contain a preservative. Store Amyvid within the original container or equivalent radiation shielding. Amyvid must not be diluted.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Comments and Recommendation:

The revised package insert submitted on 21-Mar-2012 (e-mail) is acceptable from a CMC perspective. Based on previous reviews and the above information the application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

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/s/

RAVINDRA K KASLIWAL
03/28/2012

ALI H AL HAKIM
03/28/2012

I concur with the reviewer's conclusion.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 202008/000
Orf le: 160
Priority: 1
Stamp Date: 17-SEP-2010
PDUFA Date: 07-APR-2012
Action Goal:
District Goal: 07-FEB-2012

Sponsor: AVID RADIOPHARMACEUT
 3711 MARKET ST 7TH FL
 PHILADELPHIA, PA 19104
Brand Name: Florbetapir F18 (18F-AV-45)
Estab. Name: Florbetapir F18 (18F-AV-45)
Generic Name:
Product Number; Dosage Form; Ingredient; Strengths
 001; INJECTABLE; FLORBETAPIR F-18; 10mCi/1ML

FDA Contacts:

Y. LIU	Project Manager	3017961926
R. KASLIWAL	Review Chemist	3017961386
E. LEUTZINGER	Team Leader	3017961399

Overall Recommendation:	ACCEPTABLE	on 26-MAR-2012	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	PENDING	on 08-NOV-2011	by EES_PROD		
	WITHHOLD	on 20-MAY-2011	by D. SMITH	(HFD-323)	3017969643
	WITHHOLD	on 17-MAR-2011	by A. INYARD	(HFD-323)	3017965363
	WITHHOLD	on 31-JAN-2011	by EES_PROD		

Establishment: CFN: (b) (4) FEI: (b) (4) (b) (4)

DMF No: [REDACTED] **AADA:**

Responsibilities: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-NOV-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3003270485
GIRINDUS AMERICA INC

CINCINNATI, , UNITED STATES 452155528

DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JAN-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-OCT-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: PETNET SOLUTIONS FEI: 3008525965
HOUSTON, , UNITED STATES 770305016

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: PETNET SOLUTIONS FEI:
PETNET SOLUTIONS
, , UNITED STATES

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-DEC-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: PETNET SOLUTIONS FEI: 3007844012
PETNET SOLUTIONS
DALLAS, , UNITED STATES 752076500

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-MAR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: PETNET SOLUTIONS FEI: 3008661394
DES PLAINES, , UNITED STATES 600185909

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-DEC-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: PETNET SOLUTIONS FEI: 3006970766
PALO ALTO, , UNITED STATES 94301

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-FEB-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: PETNET SOLUTIONS, INC. FEI: 3008789905
KNOXVILLE, , UNITED STATES 379322562

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: PETNET SOLUTIONS, INC. FEI: 3006896373
JACKSONVILLE, , UNITED STATES 32007
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-MAR-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: PETNET SOLUTIONS, INC. FEI: 3007283829
ATLANTA, , UNITED STATES 30329
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: POSITRON EMISSION TOMOGRAPHY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-MAR-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: (b) (4)
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-DEC-2010
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

NDA Number: 202008

Established/Proper Name:
Florbetapir F 18

Applicant: Avid
Radiopharmaceuticals Inc.

Letter Date: 27-Oct-2011 Stamp Date: 27-Oct-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		This is a complete response to NDA action letter and is accordingly organized.
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?			Not applicable. The facilities were listed in original application and there is no change in the facilities.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			<p align="center">Not applicable. The facilities were listed in original application and there is no change in the facilities.</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			<p align="center">Not applicable. The facilities were listed in original application and there is no change in the facilities.</p>

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			<p align="center">Not applicable. The facilities were listed in original application and there is no change in the facilities.</p>
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	X		<p>Provided in the original application which was deemed acceptable.</p>

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not Applicable.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		The list of DMF was provided in the original submission and has not changed.

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA 202008**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

{See appended electronic signature page}

11/3/2011

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

11/3/2011

Name of
Branch Chief
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Date

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/s/

RAVINDRA K KASLIWAL
11/03/2011

ALI H AL HAKIM
11/03/2011

NDA 202008

AMYVIDTM
(florbetapir F 18) Injection

Avid Radiopharmaceuticals, Inc.
3711 Market Street 7th Floor
Philadelphia, PA 19104

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment-III
Office of New Drug Quality Assessment
Division of Medical Imaging Products

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Chemistry Review Data Sheet

1. NDA **202008**
2. REVIEW #: 2
3. REVIEW DATE: 09-Mar-2011
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	17-Sep-2010
Amendment	09-Nov-2010
Amendment	07-Jan-2011
Amendment (QR, CC)	31-Jan-2011
Amendment (EG)	17-Jan-2011

CMC Communications	Document Date
CMC Review #1	17-Feb-2011

6. SUBMISSION(S) BEING REVIEWED:

Resubmission	07-Oct-2011
Amendment (labeling)	20-Dec-2011
Amendment (labeling)	29-Feb-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Avid Radiopharmaceuticals, Inc.
Address: 3711 Market Street, 7th Floor
Philadelphia PA 19104
Representative: Alan P. Carpenter, Ph.D.
Vice President, Legal and Regulatory Affairs
Telephone: 215-298-0707
E-Mail: carpenter@avidrp.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AMYVID
- b) Non-Proprietary Name (USAN/INN): Florbetapir F 18
- c) Code Name/# (ONDC only): ¹⁸F-AV-45

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Radiopharmaceutical (PET drug)

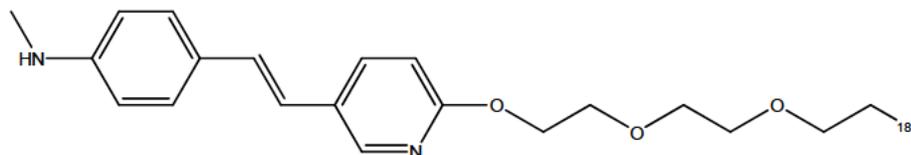
11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 500 – 1900 MBq / ml @ End Of Synthesis (EOS)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(E)-4-(2-(6-(2-(2-(2-[¹⁸F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylanilineChemical Formula: C₂₀H₂₅¹⁸FN₂O₃

Molecular Weight: 359.43

Elemental Analysis: C, 66.83; H, 7.01; F, 5.01; N, 7.79; O, 13.35

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	Adequate	30-Jan-2003 13-Oct-2006	Reviewed for injectable radiopharmaceutical drug product by Leon A. Epps, Ph.D.
	III			3	Adequate	11-Feb-2011	DMF was evaluated for sterility assurance by

Chemistry Review Data Sheet

(b) (4)	V	(b) (4)	4, 6	Adequate	11-Feb-2011	Microbiology Reviewer Sterility assurance of the vials from (b) (4) was evaluated by Microbiology Reviewer and was satisfactory.
	V		1	Adequate	11-Feb-2011	DMF was evaluated for sterility assurance by Microbiology Reviewer
	III		4	N/A	-	(b) (4) validation for sterility was evaluated by Microbiology Reviewer and was satisfactory.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	79,511	Sponsor's IND for the drug.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable.		
EES	Pending	09-Mar-2012	
Pharm/Tox	Approval	11-Feb-2011	Sunday O. Awe, Ph.D.
Biopharm	Not Applicable.		
LNC	Not Applicable.		
Methods Validation	Not Requested		
DMEPA / OSE	Proprietary Name is acceptable.	10-Dec-2011 06-Mar-2012	Kevin Wright
EA	Categorically excluded from the requirement to prepare an Environmental Assessment.	15-Feb-2011	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	02-Mar-2012	Stephen E. Langille, Ph.D.

The Chemistry Review for NDA 202008

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided manufacturing facilities are in acceptable compliance for cGMP and acceptable final package insert and container closure labeling is received.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Florbetapir F 18 Injection is produced as a sterile solution for intravenous injection in a 10 mL, 30 mL or 50 mL multi-dose vial containing 500 mBq/mL (13.5 mCi/mL) to 1900 mBq/mL (51.4 mCi/mL) of Florbetapir F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.5 mg of sodium ascorbate, USP, 0.1 mL dehydrated alcohol, USP and 0.9 mL of 0.9% sodium chloride injection, USP.

The unit dose is prepared by the radio-pharmacy and is 370 MBq (10 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 mL, therefore a maximum of 45mg of sodium ascorbate, USP, 1 mL dehydrated alcohol, USP and 9 mL of 0.9% sodium chloride injection, USP may be present in the human dose. For smaller unit dose volumes (less than 10 mL), the ratios of sodium ascorbate, dehydrated alcohol, and 0.9% Sodium Chloride Injection are maintained. The composition of the drug product is not altered (no dilution) after manufacture of the multi-dose vial of the drug product in preparation of the unit radio-pharmacy doses.

A concentration of (b) (4) is needed to maintain Drug Substance radiochemical purity over the shelf-life of the product. The formulation (b) (4) remains within the physiologically compatible range of pH 5.5 to 7.5. The Drug Substance remains soluble in formulation in this pH range and stability studies have not shown sensitivity of Drug Substance to pH within this range.

The Osmolality of Drug Product formulation was experimentally determined (b) (4). The Osmolality was calculated (b) (4).

The Drug Substance, florbetapir F 18, contains the radioactive isotope fluorine-18 (F-18). F-18 undergoes radioactive decay primarily (96.9% abundance) through emission of a positively charged beta particle (positron; β^+) having maximum and average energies of 634 and 249 keV, respectively. The half-life of F-18 is 109.77 minutes. A positron generated from F-18 decay travels a maximum distance of 2.4 mm (mean linear range = 0.2 mm) in tissue until it collides with an electron and annihilates. The annihilation event produces two 511 keV gamma photons which are emitted 180° to one another. It is the coincidental detection of these two 511 keV gamma photons which forms the basis for positron emission tomographic imaging. F-18 decays to stable O-18 oxygen.

The Drug Substance (florbetapir F 18) in Florbetapir F 18 Injection is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity

Executive Summary Section

(MBq/ μ g) at the end of synthesis (EOS) is required to be (b) (4) is typically approximately (b) (4) and has ranged from (b) (4) to (b) (4). The specific activity is required to be (b) (4) at expiry. The strength (concentration) of Drug Substance in Drug Product is required to be NLT 500 MBq/mL and NMT 1900 MBq/mL at EOS and is required to be NLT 37 MBq/mL at expiry. The shelf-life (expiry) specifications mean that a 370 MBq maximum human dose of Florbetapir F 18 Injection will contain not more than 50 μ g of florbetapir F 19 and will be contained in not more than 10 mL of a solution that is 10% v/v in ethanol.

Florbetapir F 18 Injection typically contains approximately (b) (4) florbetapir F 19. The solubility of Florbetapir F 19 in Drug Product formulation (10% v/v ethanol, 0.45% sodium ascorbate, and 0.81% sodium chloride aqueous solution) was determined (b) (4)

B. Description of How the Drug Product is Intended to be Used

Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β -amyloid, a defining pathology of Alzheimer's disease (AD).

The recommended single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of \leq 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b) (4) flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. Subsequent to administration the subject is imaged for 10 minutes using a PET camera. A 10 minute scan has been shown to provide good quality PET images.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an approval action, provided manufacturing facilities are found to be acceptable by Office of Compliance and the applicant submits acceptable labeling, for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are adequate to support the product application.
- The microbiology has recommended approval action from product quality microbiology.
- There are no outstanding issues with specifications, methods and impurities.
- The stability of the product has been sufficiently demonstrated to support a 10 hour expiration dating period.

III. Administrative

A. Reviewer's Signature

Ravindra K. Kasliwal, Ph.D.

B. Endorsement Block

Kasliwal / 17-Feb-2011
Leutzinger / 17-Feb-2011
Al-Hakim / See DARRTS

C. CC Block

See DARRTS

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/s/

RAVINDRA K KASLIWAL
03/09/2012

ALI H AL HAKIM
03/10/2012

NDA 202-008

AMYVID™ (Florbetapir F 18) Injection

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Avid Radiopharmaceuticals. Inc.

Applicant: Avid Radiopharmaceuticals. Inc.
3711 Market Street 7th Floor
Philadelphia, PA 19104

Indication: Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain.

Presentation: The drug product is supplied as a multidose vial and administered as a single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b)(4) flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose.

Establishments Evaluation Report (EER) Status: Pending

Consults:	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm Toxicology -	Acceptable

Original Submission: September 17, 2010

Re-submissions: N/A

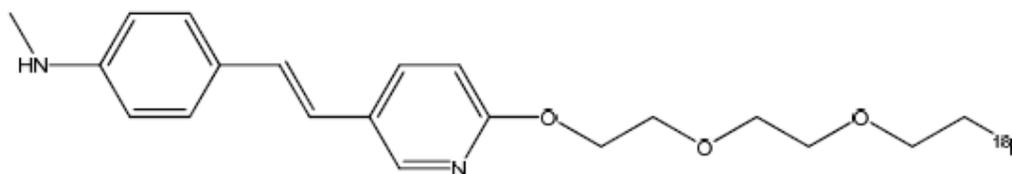
Post-Approval CMC Agreements: None at this time.

Drug Substance:

The Drug Substance, florbetapir F 18, contains the radioactive isotope fluorine-18 (F-18). F-18 undergoes radioactive decay primarily (96.9% abundance) through emission of a positively charged beta particle (positron; β^+) having maximum and average energies of 634 and 249 keV, respectively. The half-life of F-18 is 109.77 minutes. A positron generated from F-18 decay travels a maximum distance of 2.4 mm (mean linear range = 0.2 mm) in tissue until it collides with an electron and annihilates. The annihilation event produces two 511 keV gamma photons which are emitted 180° to one another. It is the coincidental detection of these two 511 keV gamma photons which forms the basis for positron emission tomographic imaging. F-18 decays to stable O-18 oxygen.

The Drug Substance (florbetapir F 18) in Florbetapir F 18 Injection is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity approximately (b) (4) and has ranged from (b) (4) to (b) (4). The specific activity is required to be (b) (4) at expiry. The strength (concentration) of Drug Substance in Drug Product is required to be NLT 500 MBq/mL and NMT 1900 MBq/mL at EOS and is required to be NLT 37 MBq/mL at expiry. The shelf-life (expiry) specifications mean that a 370 MBq maximum human dose of Florbetapir F 18 Injection will contain not more than 50 µg of florbetapir F 19 and will be contained in not more than 10 mL of a solution that is 10% v/v in ethanol.

Chemical structure, molecular weight and molecular weight are provided below:



Chemical Formula: $C_{20}H_{25}^{18}FN_2O_3$

Molecular Weight: 359.43

Elemental Analysis: C, 66.83; H, 7.01; F, 5.01; N, 7.79; O, 13.35

Chemical Name: (*E*)-2-(2-(2-(5-(4-(*tert*-butoxycarbonyl(methyl)amino)styryl)pyridin-2-yloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate

Note:

The Drug Substance is (b) (4) during the manufacturing process. The Drug Substance and the Drug Product are manufactured (b) (4).

Conclusion: Drug substance is adequate.

Drug Product:

Florbetapir F 18 Injection is produced as a sterile solution for intravenous injection in a 10 ml, 30 ml or 50 mL multi-dose vial containing 500 mBq/mL (13.5 mCi/mL) to 1900 mBq/mL (51.4 mCi/mL) of Florbetapir F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.5 mg of sodium ascorbate, USP, 0.1 mL dehydrated alcohol, USP and 0.9 ml of 0.9% sodium chloride injection, USP.

Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β -amyloid, a defining pathology of Alzheimer's disease (AD).

The unit dose is prepared by the radio-pharmacy and is 370 MBq (10 mCi) at time of calibration (time of patient injection). The unit dose is contained in a maximum volume of 10 ml, therefore a maximum of 45mg of sodium ascorbate, USP, 1 mL dehydrated alcohol, USP and 9 ml of 0.9% sodium chloride injection, USP may be present in the human dose. For smaller unit dose volumes (less than 10 mL), the ratios of sodium ascorbate, dehydrated alcohol, and 0.9% Sodium Chloride Injection are maintained. The composition of the drug product is not altered (no dilution) after manufacture of the multi-dose vial of the drug product in preparation of the unit radio-pharmacy doses. A concentration of (b) (4) is needed to maintain Drug Substance radiochemical purity over the shelf-life of the product. The formulation (b) (4) remains within the physiologically compatible range of pH 5.5 to 7.5. The Drug Substance remains soluble in formulation in this pH range and stability studies have not shown sensitivity of Drug Substance to pH within this range. The Osmolality of Drug Product formulation was experimentally determined (b) (4). The Osmolality was calculated (b) (4).

The recommended single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of ≤ 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b) (4) flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. Subsequent to administration, the subject is imaged for 10 minutes using a PET camera. A 10 minute scan has been shown to provide good quality PET images.

The proposed expiration dating period of 10 hours after EOS, or when either the shelf-life specific activity or strength specification is reached, whichever is soonest is acceptable.

Conclusion: Drug product is adequate.

Overall Conclusion: From CMC point of view, the NDA is recommended for approval pending satisfactory overall cGRMP recommendation.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

Proposed label for the drug product.



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/s/

ALI H AL HAKIM
02/22/2011

NDA 202008

AMYVIDTM
(Florbetapir F 18) Injection

Avid Radiopharmaceuticals, Inc.
3711 Market Street 7th Floor
Philadelphia, PA 19104

Ravindra K. Kasliwal, Ph.D.
Division of New Drug Quality Assessment-III
Office of New Drug Quality Assessment
Division of Medical Imaging Products

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Chemistry Review Data Sheet

1. NDA **202008**
2. REVIEW #: 1
3. REVIEW DATE: 18-Feb-2011
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	17-Sep-2010
Amendment	09-Nov-2010
Amendment	07-Jan-2011
Amendment (QR, CC)	31-Jan-2011
Amendment (EG)	17-Jan-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Avid Radiopharmaceuticals, Inc.
Address: 3711 Market Street, 7th Floor
Philadelphia PA 19104
Representative: Alan P. Carpenter, Ph.D.
Vice President, Legal and Regulatory Affairs
Telephone: 215-298-0707
E-Mail: carpenter@avidrp.com

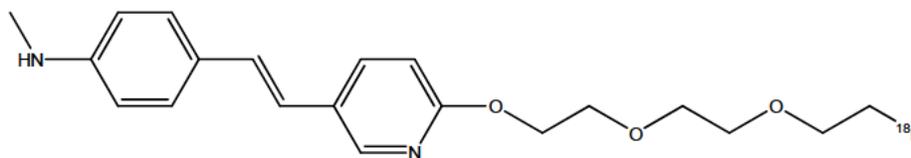
8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: AMYVID
- b) Non-Proprietary Name (USAN/INN): Florbetapir F 18
- c) Code Name/# (ONDC only): ¹⁹F-AV-45
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

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

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Radiopharmaceutical (PET drug)
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 500 – 1900 MBq / ml @ EOS
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 (E)-4-(2-(6-(2-(2-(2-[¹⁸F]fluoroethoxy)ethoxy)ethoxy)pyridin-3-yl)vinyl)-N-methylaniline

Chemical Formula: C₂₀H₂₅¹⁸FN₂O₃

Molecular Weight: 359.43

Elemental Analysis: C, 66.83; H, 7.01; F, 5.01; N, 7.79; O, 13.35

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	30-Jan-2003 13-Oct-2006	Reviewed for injectable radiopharmaceutical drug product by Leon A. Epps, Ph.D.
	III			3	Adequate	11-Feb-2011	DMF was evaluated for sterility assurance by Microbiology Reviewer
	V			4, 6	Adequate	11-Feb-2011	Sterility assurance of the vials From (b) (4) was evaluated by Microbiology Reviewer and was

Chemistry Review Data Sheet

(b) (4)	V	(b) (4)	1	Adequate	11-Feb-2011	satisfactory. DMF was evaluated for sterility assurance by Microbiology Reviewer
	III		4	N/A	-	(b) (4) validation for sterility was evaluated by Microbiology Reviewer and was satisfactory.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	79,511	Sponsor's IND for the drug.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable.		
EES	Pending	15-Feb-2011	
Pharm/Tox	Approval	11-Feb-2011	Sunday O. Awe, Ph.D.
Biopharm	Not Applicable.		
LNC	Not Applicable.		
Methods Validation	Not Requested		
DMEPA / OSE	Proprietary Name is acceptable.	10-Dec-2011	Ravindra K. Kasliwal, Ph.D.
EA	Categorically excluded from the requirement to prepare an Environmental Assessment.	15-Feb-2011	Ravindra K. Kasliwal, Ph.D.
Microbiology	Approval	11-Feb-2011	Stephen E. Langille, Ph.D.

The Chemistry Review for NDA 202008

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act, provided an acceptable form of office of compliance for manufacturing facility inspections is received, and acceptable final package insert and container closure labeling is received.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Florbetapir F 18 Injection is produced as a sterile solution for intravenous injection in a 10 mL, 30 mL or 50 mL multi-dose vial containing 500 mBq/mL (13.5 mCi/mL) to 1900 mBq/mL (51.4 mCi/mL) of Florbetapir F 18 at End of Synthesis (EOS). Each mL of the solution contains 4.5 mg of sodium ascorbate, USP, 0.1 mL dehydrated alcohol, USP and 0.9 mL of 0.9% sodium chloride injection, USP.

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A concentration of (b) (4) is needed to maintain Drug Substance radiochemical purity over the shelf-life of the product. The formulation (b) (4) remains within the physiologically compatible range of pH 5.5 to 7.5. The Drug Substance remains soluble in formulation in this pH range and stability studies have not shown sensitivity of Drug Substance to pH within this range.

The Osmolality of Drug Product formulation was experimentally determined (b) (4). The Osmolality was calculated (b) (4).

The Drug Substance, florbetapir F 18, contains the radioactive isotope fluorine-18 (F-18). F-18 undergoes radioactive decay primarily (96.9% abundance) through emission of a positively charged beta particle (positron; β^+) having maximum and average energies of 634 and 249 keV, respectively. The half-life of F-18 is 109.77 minutes. A positron generated from F-18 decay travels a maximum distance of 2.4 mm (mean linear range = 0.2 mm) in tissue until it collides with an electron and annihilates. The annihilation event produces two 511 keV gamma photons which are emitted 180° to one another. It is the coincidental detection of these two 511 keV gamma photons which forms the basis for positron emission tomographic imaging. F-18 decays to stable O-18 oxygen.

The Drug Substance (florbetapir F 18) in Florbetapir F 18 Injection is characterized by radiochemical identity, radiochemical purity, specific activity, strength, radionuclidic identity and radionuclidic purity. The specific activity

Executive Summary Section

(MBq/ μ g) at the end of synthesis (EOS) is required to be (b) (4) is typically approximately (b) (4) and has ranged from (b) (4) to (b) (4). The specific activity is required to be (b) (4) at expiry. The strength (concentration) of Drug Substance in Drug Product is required to be NLT 500 MBq/mL and NMT 1900 MBq/mL at EOS and is required to be NLT 37 MBq/mL at expiry. The shelf-life (expiry) specifications mean that a 370 MBq maximum human dose of Florbetapir F 18 Injection will contain not more than 50 μ g of florbetapir F 19 and will be contained in not more than 10 mL of a solution that is 10% v/v in ethanol.

Florbetapir F 18 Injection typically contains approximately (b) (4) florbetapir F 19. The solubility of Florbetapir F 19 in Drug Product formulation (10% v/v ethanol, 0.45% sodium ascorbate, and 0.81% sodium chloride aqueous solution) was determined (b) (4)

B. Description of How the Drug Product is Intended to be Used

Amyvid (Florbetapir F 18 Injection) is a diagnostic radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β -amyloid aggregates in the brain. A negative florbetapir-PET scan is clinically useful in ruling out the presence of β -amyloid, a defining pathology of Alzheimer's disease (AD).

The recommended single intravenous dose for Amyvid is 370 MBq (10 mCi) of florbetapir F18 in a dose volume of \leq 10 mL. The Amyvid dose is administered by intravenous injection followed by a (b) (4) flush of 0.9% Sodium Chloride Injection to ensure full delivery of the dose. Subsequent to administration the subject is imaged for 10 minutes using a PET camera. A 10 minute scan has been shown to provide good quality PET images.

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for an approval action (provided manufacturing facilities are found to be acceptable by Office of Compliance and the applicant submits acceptable labeling that addresses our comments) for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are adequate to support the product application.
- The microbiology has recommended approval action from product quality microbiology.
- There are no outstanding issues with specifications, method and impurities.
- The stability of the product has been sufficiently demonstrated to support a 10 hour expiration dating period.
- The company should be told that until acceptable 36 month data on 3 batches become available, a retest period of (b) (4) should be used for AV-105.

III. Administrative

A. Reviewer's Signature

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Kasliwal / 17-Feb-2011
Leutzinger / 17-Feb-2011
Al-Hakim / See DARRTS

C. CC Block

See DARRTS

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/s/

RAVINDRA K KASLIWAL
02/18/2011

ALI H AL HAKIM
02/18/2011

FILEABILITY ASSESSMENT
Branch VII

Division of New Drug Quality Assessment-III
Office of New Drug Quality Assessment

OND Division: DMIP

NDA: 202-008

Applicant: AVID Radiopharmaceuticals, Philadelphia, PA 19104-6283

Stamp Date: September 17, 2010

PDUFA: TBD

Trademark: AMYVID

Established: Florbetapir F 18 Injection

Dosage Form: Sterile solution

Route of Administration: IV

FILEABILITY SUMMARY

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		There are 19 drug product manufacturing facilities, all of which have been entered into EES.
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		This was also confirmed with the company at 07-Oct-2010 meeting.
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		
13.	Has the applicant provided a method	X		

	validation package?			
14.	Is a separate microbiological section included?	X		Microbiology information is provided in module 3 of the NDA.

Consults To Be Initiated:	
Item	Consult To
1. Trademark: AMYVID	DMEPA
2. Microbiology	OPS Microbiology Staff

ONDQA Fileability: YES

Fileability Review By: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer

Date: 14-Oct-2010

Branch Chief: Ali Al-Hakim, Branch Chief
Division of New Drug Quality Assessment

Date: 14-Oct-2010

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/s/

RAVINDRA K KASLIWAL
10/29/2010

ALI H AL HAKIM
10/29/2010