

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212123Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 119863

MEETING MINUTES

Avid Radiopharmaceuticals, Inc.
Attention: Stephen Truocchio, M.S., RAC
Senior Director, Regulatory Affairs and Project Management
3711 Market St., 7th Floor
Philadelphia, PA 19104

Dear Mr. Truocchio:

Please refer to your Investigational New Drug Application (IND submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 18F-AV-1451.

We also refer to the meeting between representatives of your firm and the FDA on November 15, 2018. The purpose for this Type B meeting is to present the proposed contents of a New Drug Application (NDA) for flortaucipir F 18 injection. The primary meeting objective is to ensure the acceptability of the proposed NDA contents as they intend to support the draft indication statements.

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

If you have any questions, call Lisa Skarupa, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 15, 2018 from 1pm to 2:30pm
Meeting Location: Face to Face White Oak Bldg. 22, Conference Room 1417

Application Number: IND 119863
Product Name: Flortaucipir F 18
Indication: Flortaucipir F 18 is a radioactive diagnostic agent for PET imaging of the brain to estimate the density and pattern of the aggregated tau ^{(b) (4)} in adult patients who are being evaluated for AD ^{(b) (4)}

Sponsor: Avid Radiopharmaceuticals, Inc.

Meeting Chair: Libero Marzella, M.D., Ph.D.
Meeting Recorder: Lisa Skarupa, SRPM

FDA ATTENDEES

Libero Marzella, M.D., Ph.D., Director, Division of Medical Imaging Products (DMIP)
Alex Gorovets, M.D., Deputy Division Director, DMIP
Anthony Fotenos, M.D., Clinical Team Leader, DMIP
Alex Hofling, M.D., Clinical Reviewer, DMIP
Eldon Leutzinger, Ph.D., CMC Team Leader
Jonathan Cohen, Ph.D., Pharmacology-Toxicology Reviewer, DMIP
Sue-Jane Wang, Ph.D., Acting Deputy Director, OB/ DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer
Tristan Massie, Ph.D., Neurology Statistical Reviewer
Martin Haber, Ph.D., Product Reviewer
Valerie Huse, Ph.D., Microbiology Reviewer
Ranjit Mani, MD, Neurology Reviewer, DNP

Lisa Skarupa, SRPM, DMIP

SPONSOR ATTENDEES

Anupa Arora, MD, Associate Medical Director
Tyler Benedum, PhD, Vice President, CMC Development
Emily Collins, PhD, Vice President, Imaging R&D
Kelly Conway, PhD, Director, Biology, Imaging R&D
Michael Devous, Sr., PhD, Vice President, Imaging
Adam Fleisher, MD, Chief Medical Officer
Carey Horchler, PhD, Director, Chemistry, Imaging R&D
John-Lister James, PhD, Senior VP, Chemical Development and Manufacturing
Ming Lu, PhD, Lead Statistician
Mark Mintun, MD, President
Caitlin Pearson, PhD, Director, CMC Regulatory and Technology Transfer
Michael Pontecorvo, PhD, Vice President, Clinical Development
Stephen Trucchio, Senior Director, Regulatory Affairs and Project Management

1.0 BACKGROUND

The sponsor submitted a pre-NDA meeting request dated September 14, 2018 and their meeting package, dated October 16, 2018. The purpose for this Type B meeting is to present the proposed contents of a New Drug Application (NDA) for flortaucipir F 18 injection. The primary meeting objective is to ensure the acceptability of the proposed NDA contents as they intend to support the draft indication statements. Avid is currently targeting a flortaucipir NDA in late Q4 2018 or Q1 2019. The preliminary FDA comments were sent to the sponsor December 13, 2018. The sponsor chose to discuss specific topics. The following meeting minutes reflect the sponsor-led discussions on Questions 1.1, 1.6 and 8. Additional follow-up communication was made for the CMC Question 18. In addition, the sponsor suggested that at the time of their NDA submission, to support their NDA review, the sponsor would bring a laptop with scans used in the pivotal trials, and scans used in training, similar to that provided for florbetapir.

2. DISCUSSION

Clinical

Question 1: *Does the Division agree that the data from the clinical development program are supportive of a submission for the proposed indication?*

1.1. An important aspect of the indication statement is that the flortaucipir PET signal represents

 (b) (4)

(see summary in Section 4.2). We would appreciate the Division's suggestions on our proposed claim, and what additional information or analyses might be provided in support.

FDA Response: Your provided Study A16 results best support a labeled indication for detection of NFT B3 pathology rather than (b) (4) (b) (4)

MEETING DISCUSSION:

The sponsor confirmed their understanding that that the labeled indication should reflect the truth standard used in the pivotal study (NFT pathology) and the utility statement would provide information on the level of pathology detected (B3). (b) (4)

1.2. Another key statement in the indication is that flortaucipir characterizes not only the density, but also the pattern, of the aggregated tau of AD in the brain. The A16 primary outcome 1 shows that a particular pattern on a flortaucipir scan (i.e., a τ AD pattern) is associated with a pattern and density of tau at autopsy that corresponds to advanced Braak stage (V/VI; B3 NFT score). We also intend to present in the NDA analyses from the A16 autopsy study showing high regional correspondence between visual read results vs. pathology. Additionally, support will come from the histelide analyses performed on the front-runners of A16, which shows a correlation between quantitative immunohistochemistry at autopsy and flortaucipir PET quantitation (SUV_r) in the same regions. Does the Division concur that the analyses planned appear sufficient to support a claim regarding the pattern of aggregated tau? If not, we would appreciate suggestions of how such a claim might be supported based on the clinical development studies to be presented in the NDA.

FDA Response: The results of the planned analyses you describe could support a pattern characterization claim.

(b) (4)

FDA Response: [REDACTED] (b) (4)

FDA Response: [REDACTED] (b) (4)

1.5. We would welcome any feedback from the Division on the draft USPI (Appendix 3). We are specifically interested in feedback on the approach to the Image Display and Analysis section. Does the Division have any comments on the approach, including how to choose an appropriate color scale and set the upper contrast values for clinical interpretation?

FDA Response: The draft Image Display and Analysis section appears reasonable.

1.6. [REDACTED] (b) (4)

[REDACTED]

MEETING DISCUSSION:

[REDACTED] (b) (4)

Question 2: *Is the Division aligned with the proposal to present the Integrated Analyses of Efficacy and Safety in CTD Modules 2.7.3 and 2.7.4, respectively?*

FDA Response to Question 2: Yes, as long as ICH-specified page limits are met.

Question 3: *Does the Division have any comments on the efficacy presentations proposed for the Integrated Summary of Efficacy (Appendix 4)?*

FDA Response to Question 3: See response to Clinical Question 1.4.

Question 4: *Does the Division have any comments on the safety presentations proposed for the Integrated Summary of Safety (Appendix 5)?*

FDA Response to Question 4: As previously agreed upon, summaries of available safety data from independent investigator studies should be included. Such data can be separated from the proposed ISS pooled analysis.

Question 5: *We are planning a fully compliant CDISC data package (see Section 8.6). Does the Division have any comments on the proposed SAS data package to be provided in the planned NDA?*

FDA Response to Question 5: The proposed SAS data package appears acceptable.

Question 6: *Does the Division agree with the narratives and CRF submission proposal in Section 8.3?*

FDA Response to Question 6: Yes.

Question 7: Does the Division have any comments on the priority review justification provided in Section 9.1?

FDA Response to Question 7: A decision regarding priority review designation can only be made at the time of NDA filing of a submission that includes a priority review request.

Question 8: Does the Division note any deficiencies in the clinical sections that would impair the review of the NDA?

FDA Response to Question 8:

- As discussed in the response to Clinical Question 1.4, (b) (4)
a (b) (4)

- For additional analysis of Study A16 results, your NDA submission should include subject numbers in the following table for each of the five readers:

	Autopsy NFT score B2/B3	Autopsy NFT score B0/B1
tAD+/tAD++ PET		
tAD- PET		

- Given potential interest in the community for off-label use, your evidence of the limited utility of flortaucipir for detection of non-AD tauopathies such as CTE and PSP may need to be reflected in labeling. We anticipate that this might also be an important topic for FDA advisory committee discussion.

MEETING DISCUSSION:

The Division clarified that the (b) (4)

The sponsor was encouraged to consult the labels of other products approved by the Division for examples of how such information might appear in labeling. (b) (4)

The Division expressed their preference for prospectively-collected, independent datasets to test hypotheses. Pooled analyses would be considered useful for exploratory purposes.

For the following questions, the Sponsor requested “WRITTEN ONLY” responses.

NonClinical

Question 9: *Does the Division note any deficiencies in the nonclinical sections that would impair the review of the NDA?*

FDA Response to Question 9:

We do not note any deficiencies in the nonclinical sections that would impair the review of the NDA.

Please ensure that the final study report for the pharmacokinetic drug interactions study (Section 4.2.2.6) is included in the submitted NDA.

CMC

Question 10: *Is the proposed organization of Module 3 suitable for review?*

FDA Response to Question 10: **Yes, the proposed organization of Module 3, which has been provided as a draft Table of Contents, is suitable for review.**

Question 11: *Because the Drug Substance and Drug Product are manufactured* ^{(b) (4)}


Is this proposal reasonable?

FDA Response to Question 11: **Yes, this proposal is reasonable.**

Question 12: *Is the proposed stability data package for precursor reasonable?*

FDA Response to Question 12: **Yes, the proposed stability data package (as illustrated in Table 6.2 AV-1622 Stability Data to be Submitted in NDA) is reasonable. Evaluation of a proposed retest period will be done during the review.**

Question 13: *Is the proposed content of manufacturing facility and equipment information reasonable?*

FDA Response to Question 13: **Yes, the proposed content of manufacturing facility and equipment as described in Section 6.5 is reasonable.**

Microbiology: The proposed content of manufacturing facility and equipment information is reasonable; however, the Agency recommends that a written process be established for the cleaning of equipment used in the manufacture of the drug product at the proposed manufacturing facilities.

Question 14: *Is the proposed strategy for Drug Substance / Drug Product process validation reasonable?*

FDA Response to Question 14: No. In addition to three process validation batches, you will need to submit the executed batch records for these process validation batches. The adequacy of the proposed strategy for the Drug Substance / Drug Product process validation will be determined during review of the NDA.

Microbiology: Based on the information provided, the strategy for process validation is not reasonable. As per the 2009 Guidance on PET Drugs – Current Good Manufacturing Practice (CGMP), (b) (4)



Question 15: *Are the proposed release specifications and PQITs for Drug Substance / Drug Product reasonable?*

FDA Response to Question 15: The proposed release specifications and PQITs for Drug Substance and Drug Product tentatively appear to be reasonable. However, without batch data and other information as necessary we cannot comment on their adequacy. This will be determined during review of the NDA.

Microbiology: The proposed maximum injectable volume of 10 mL would equate to a possible endotoxin load of (b) (4) EU/volume which follows the USP <85> recommendations. Based on the nature of PET drug products, the release specifications are acceptable in relation to the information provided.

Question 16: *Are the proposed test methods for Drug Substance / Drug Product and validation reasonable?*

FDA Response to Question 16: Yes, the test methods as shown in Table 6.9 are reasonable. **Microbiology:** The proposed test methods and validation are reasonable.

Question 17: *Is the proposed microbiological information (procedures, testing and validation) reasonable?*

FDA Response to Question 17: The procedures, testing and validation are reasonable as provided in the Pre-NDA briefing document.

Question 18: *Is the proposed stability data package for Drug Substance / Drug Product reasonable?*

FDA Response to Question 18: No. The testing interval used in a stability protocol in support of a product's shelf-life should include a sufficient number of time points appropriately spaced. For example, in support of a 10-hour shelf-life, we recommend that for all attributes and all container closure systems the stability testing interval contain time points 0, 4, 6, and 10 hours post end of synthesis (EOS).

Question 19: *Is the proposal for Environmental Assessment exemption reasonable?*

FDA Response to Question 19: Yes, the proposal for Environmental Assessment exemption is reasonable.

Question 20: *Does the Division note any deficiencies in the Quality sections that would impair the review of the NDA?*

FDA Response to Question 20

Based on the CMC information provided for Flortaucipir F 18 Injection, the Division of Microbiology Assessment does not have further comments on the summary of the quality sections provided. However, we recommend that the 2009 Guidance on PET Drugs – Current Good Manufacturing Practice (CGMP) be referenced for the future NDA submission content in addition to relevant sections of the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

POST MEETING Communication for CMC Question 18:

Avid Response:

The stability program for Flortaucipir F 18 Injection was designed to assess the stability of Drug Product over the proposed shelf-life, confirm compatibility of Drug Product with the proposed container closure systems, and confirm the stability of Drug Product manufactured at the contract manufacturing organization, (b) (4)

Flortaucipir F 18 Injection is stored as bulk Drug Product in 30 mL or 50 mL Type (b) (4) glass (b) (4) vials crimp-sealed with 20 mm (b) (4) gray (b) (4) closures. The composition of the glass containers and (b) (4) stoppers and the sizes of the vial necks and closures are identical for both vial sizes (30 mL and 50 mL). Therefore, it is

expected that the stability of Drug Product would not be significantly different when stored in either of the vial sizes. Therefore, the stability study program for bulk Drug Product was evaluated in 50 mL Bulk Product Vials (BPV) over the intended shelf-life of 10 hours. Refer to Table 1 below for a summary of the stability studies conducted for Drug Product stored in the BPV Container Closure System.

Table 1: Drug Product Stability Studies in the Bulk Product Vial Container Closure System

Study	Container Closure	Configuration	Conditions	Time Points	Testing	Discussion
1	Sterile, apyrogenic 50 mL Type (b) (4) vial/20 mm (b) (4) closure/20 mm Al crimp seal	Inverted	CRT	0, 6 and 10 h	Limited Release Testing ¹ , Stability Indicating Testing ²	Intended to demonstrate stability of the Drug Product and its compatibility with the container closure system
			40 ± 2 °C	0, 4 h		
		Upright	CRT	0, 6 and 10 h		
			40 ± 2 °C	0, 4 h		
2	Sterile, apyrogenic 50 mL Type (b) (4) vial/20 mm (b) (4) closure/20 mm Al crimp seal	Upright	CRT	0 and 10 h	Full Release Testing ³ , Stability Indicating Testing, Microbiological Quality Testing ⁴	Intended to confirm the stability of Drug Product manufactured at (b) (4)

¹Limited Release Testing = appearance, pH, radiochemical purity (RCP), radiochemical impurities, chemical impurities, radiochemical identity, radionuclidic identity, Flortaucipir F 19 concentration, strength, assay of ethanol, (b) (4) analysis

²Stability Indicating Testing = appearance, pH, radiochemical purity (RCP), radiochemical impurities, chemical impurities, Flortaucipir F 19 concentration, strength, and assay of ethanol

³Full Release Testing = appearance, pH, radiochemical purity (RCP), radiochemical impurities, chemical impurities, radiochemical purity, radionuclidic purity, Flortaucipir F 19 concentration, strength, assay of ethanol, (b) (4) analysis, bacterial endotoxins, (b) (4) integrity, and sterility

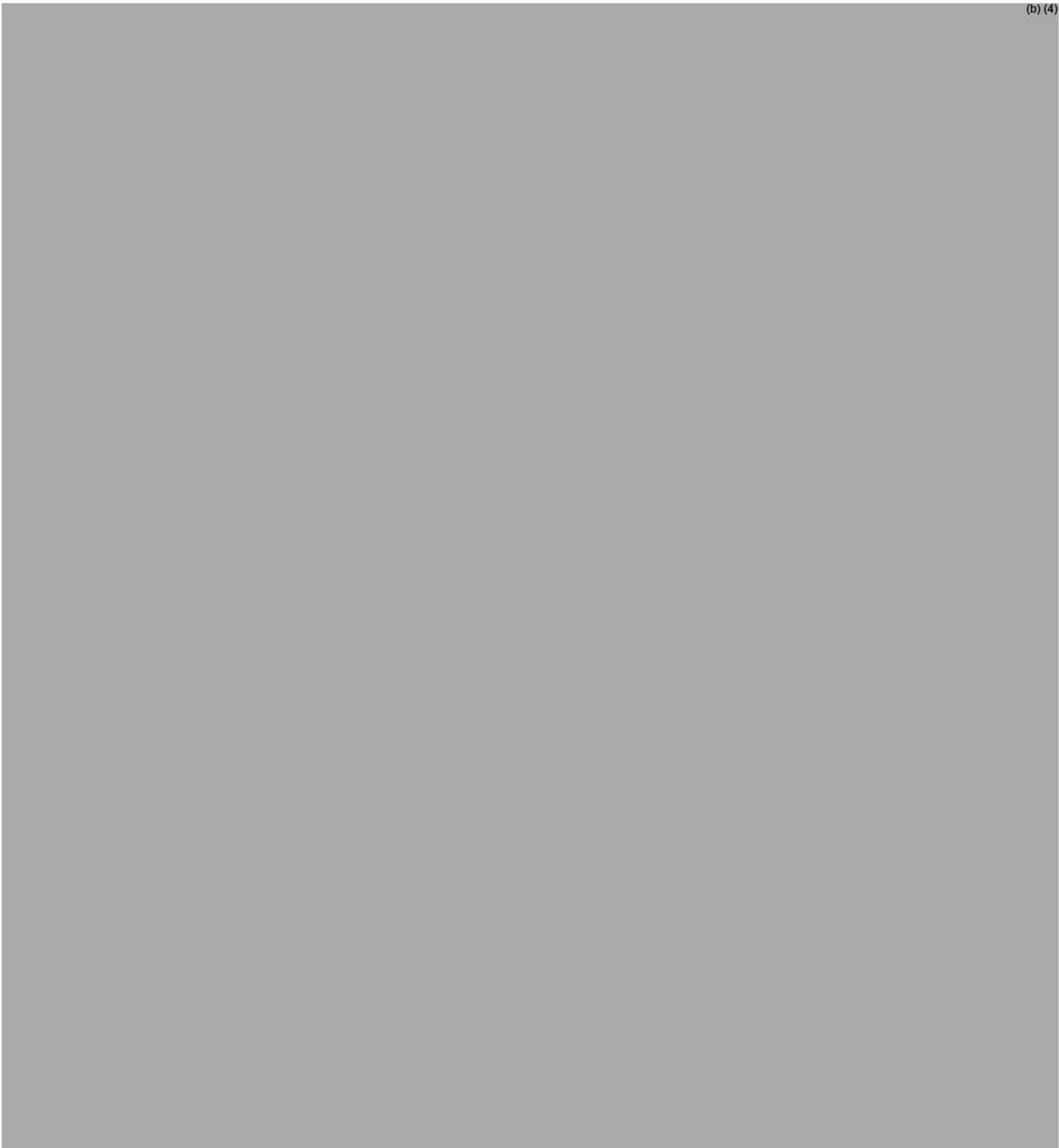
⁴Microbiological Quality Testing = bacterial endotoxins and sterility

For study 1, limited release testing (includes all release testing except (b) (4) integrity and microbiological (bacterial endotoxins and sterility) testing) was performed at EOS for the stability studies. The tests that are stability indicating (including appearance, pH, radiochemical purity (RCP), radiochemical impurities, chemical impurities, Flortaucipir F 19 concentration, strength, and assay of ethanol) were evaluated at t₆ and t₁₀ (end of shelf-life) when stored at controlled room temperature. Identity tests and impurity tests such as radiochemical identity, radionuclidic identity, (b) (4) were not evaluated at the stability timepoints since these attributes would not change over the shelf-life.

There was very little change observed in results between EOS and each time point. There was no notable difference in results observed for vials stored in the upright or inverted configuration. Notably, the RCP changed a maximum of 2% (b) (4) across all conditions and all configurations.

Based on the limited changes observed in the study above, the stability testing performed at (b) (4) (study 2) was only evaluated at the end of the intended shelf-life. This study included full release testing at the initial timepoint

and the stability indicating tests as well as tests confirming microbiological quality (including bacterial endotoxins and sterility) at t_{10} . The results observed at (b) (4) at t_{10} confirmed the results observed in Study 1.



(b) (4)

CMC post-meeting comments:

The stability protocol for testing the 50 mL container closure system as described in Table 6.10 in the meeting package appears reasonable, but its adequacy will be determined during review of the NDA.

3.0**PREA REQUIREMENTS**

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

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

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

development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

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

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LIBERO L MARZELLA
12/20/2018



IND 119863

MEETING MINUTES

Avid Radiopharmaceuticals, Inc.
Attention: Stephen Truocchio, M.S., RAC
Senior Director, Regulatory Affairs
3711 Market St.
7th Floor
Philadelphia, PA 19104

Dear Mr. Truocchio:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 18F-AV-1451.

We also refer to your July 13, 2017, correspondence, received July 14, 2017, requesting a meeting to discuss:

- the revision of the analysis plans for the proposed pivotal trial Study A16: A Clinico-Pathological Study of the Correspondence Between ¹⁸F-AV-1451 PET Imaging and Post-Mortem Assessment of Tau Pathology.
 - Discuss the choice of truth standard as supportive of proposed indication for (b) (4)/characterization
- the proposed analysis plans for the confirmatory cohort of Study A05: An open label, multicenter study, evaluating the safety and imaging characteristics of ¹⁸F-AV-1451 in cognitively healthy volunteers, subjects with Mild Cognitive Impairment, and subjects with Alzheimer's disease.
 - Discuss the choice of endpoints and study populations as supportive of proposed indication
 - Discuss the choice of statistical methods and hypothesis testing
- the proposed clinically-applicable read method to illustrate relevance to the chosen endpoints for the studies.

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

If you have any questions, call Lisa Skarupa, Regulatory Project Manager at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Guidance

Meeting Date and Time: August 15, 2017 at 1:00pm to 2:00pm
Meeting Location: White Oak Campus, Bldg. 22 Conference Room 1311

Application Number: IND 119863
Product Name: ^{18}F -AV-1451
Indication: Flortaucipir F 18 is a radioactive diagnostic agent for PET imaging of the brain to estimate the density and pattern of aggregated tau in adult patients who are being evaluated for Alzheimer's disease (AD) (b) (4)

(b) (4)

Sponsor Name: Avid Radiopharmaceuticals Inc.

Meeting Chair: Anthony Fotenos, M.D.
Meeting Recorder: Lisa Skarupa, RPM Senior Regulatory Project Manager

FDA ATTENDEES

Libero Marzella, M.D., Ph.D., Division Director, DMIP
Alex Gorovets, M.D., Deputy Division Director, DMIP
Anthony Fotenos, M.D., Clinical Team Leader, DMIP
August Hofling, M.D., Clinical Reviewer, DMIP
Sue-Jane Wang, Ph.D., Acting Division Director, OTS/OB/DBI
Jyoti Zalkikar, Ph.D., Secondary Statistical Reviewer, OTS/OB/DBI
Anthony Mucci, Ph.D., Primary Statistical Reviewer, OTS/OB/DBI
Tristan Massie, Ph.D., Neurology Statistical Reviewer, OTS/OB/DBI
Ranjit Mani, M.D., Clinical Team Leader, DNP
Teresa Buracchio, M.D., Clinical Reviewer, DNP
Lisa Skarupa, Senior Regulatory Project Manager, DMIP

- **Given the Division's response, the Sponsor is conceptualizing a plan that meets both**

(b) (4)

Question 4 A draft Statistical Analysis Plan for Study A05 is provided in Appendix 7. Does the Division have any comments on the proposed statistical methods and hypothesis testing as outlined in the Statistical Analysis Plan for the A05 confirmatory cohort?

FDA Response to Question 4:

Referring to our response to Question 3, the Statistical Analysis Plan (SAP) for the A05 confirmatory cohort (for e.g. sample-size considerations, statistical methods and hypothesis testing, missing-data plan) would have to be revised. Once you make changes according to our recommendations for Question 3, please submit the revised SAP to FDA for review.

Meeting Minutes:

The Sponsor appreciated the request to review A05 SAP; would like clarifications of timing and logistics for receipt of comments.

The Sponsor asked that if they change the SAP of Study A05 and/or A16, can they get a response in 30 days or will another meeting request be necessary. The FDA answered affirmatively to 30 days timeline and said that the additional meeting request might not be necessary.

Question 5 We believe it is possible to robustly assess reader performance within our two pivotal Phase 3 studies and a separate reader study is not required to support NDA submission. Both studies will use readers trained with the same read method and images will be interpreted with identical methods and image review case report forms (CRFs). Does the Division agree with the proposed approach to evaluate reader training as part of the reads done in the two pivotal studies A05 and A16? We value any comments from the Division that would support our proposed approach to include reader evaluation as part of the pivotal studies.

FDA Response to Question 5:

As long as the reading method and training used for protocols A05 and A16 are the

same as those intended for clinical use, we agree that a separate inter-reader reproducibility study is not required beyond your proposed analysis in these protocols. Protocol A05, in particular, should allow adequate analysis of inter-reader reproducibility in a clinically relevant population similar to that of intended use.

Meeting Minutes: The Sponsor needed no further clarification.

Question 6 In previous interactions, FDA has commented on the reader and neuropathology CRFs and requested submission for review. The proposed final CRFs incorporating these edits are provided in Appendix 8 and Appendix 9. Does the Division have any further comments?

FDA Response to Question 6:

The neuropathology CRF appears acceptable. The PET CRF should be modified to require designation of laterality of visualized brain activity by incorporation of “right hemisphere” and “left hemisphere” columns for the anatomy listed in CRF item 3.

Addition of the mesial temporal region to the list of anatomy in item 3 is also suggested.

Meeting Minutes: The Sponsor needed no further clarification.

Additional Post-Meeting FDA Comments:

We acknowledge your difficulties with recruitment for autopsy study A16, and we have the following recommendations as potential solutions. We reference other INDs for which you are providing ¹⁸F-AV-1451. Please explore the feasibility of obtaining autopsy data from those studies. If this is a viable option, please provide a prospective protocol amendment for the collection and incorporation of these data into study A16.

We also recommend that you consider allowing a longer amount of elapsed time between ¹⁸F-AV-1451 PET and autopsy, for example, 12 months rather than 9 months. If this option seems reasonable and could allow more data to be collected, a corresponding protocol amendment reflecting this change should be submitted.

Please keep us informed regarding potential implementation of these recommendations for improving data collection in study A16.

3.0

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cd er-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation

of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

none

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor slides

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIBERO L MARZELLA
09/15/2017