CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214755Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 126321

MEETING PRELIMINARY COMMENTS

Flamel Ireland Limited dba Avadel Ireland
Attention: Marla Scarola, M.S.
The Weinberg Group Inc.
1129 Twentieth Street NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:[1]

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate for Extended-Release Oral Suspension (FT218).

We also refer to your May 4, 2020, correspondence, received May 4, 2020, requesting a meeting to discuss the acceptability of your planned New Drug Application.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, contact me at teresa.wheelous@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Wheelous, R. Ph.
Sr. Regulatory Project Manager
Neurology 1
Division of Regulatory Operations Neurology
Office Regulatory Operations Neuroscience
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ENCLOSURE:

- Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY TELECON MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 7, 2020, 3:00 PM
Application Number: IND 126321

Product Name: Sodium Oxybate for Extended-Release Oral Suspension (FT218)
Indication: Treatment of cataplexy and excessive daytime sleepiness in narcolepsy

Sponsor Name: Flamel Ireland Limited dba Avadel Ireland
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

FDA ATTENDEES (tentative)

Eric Bastings, MD – Director (Acting), Division of Neurology 1
Ranjit Mani, MD – Clinical Lead Reviewer, Division of Neurology 1
Sreedharan Sabarinath, PhD – Clinical Pharmacology Team Lead
Gopichand Gottipati, PhD – Clinical Pharmacology Reviewer
Martha Heimann, PhD – CMC Team Lead
Justine Kalonia, PharmD – DMEPA Safety Evaluator
Leah Falade, PhD – Biopharmaceutics Reviewer
Chad Reissig, PhD – Supervisory Pharmacologist, CSS
Cara Alfaro, PharmD – Clinical Analyst, Division of Clinical Compliance Evaluation, OSI

Avadel ATTENDEES

Greg Divis, Chief Executive Officer
Jordan Dubow, MD, Chief Medical Officer
Jason Vaughn, PhD, Senior Vice President, Technical Operations
Courtney Wells, Vice President, Clinical Operations
David Seiden, MD, Medical Director

The Weinberg Group Inc.
Marla Scarola, Vice President, Regulatory Program Management
Robert Roth, MD, PhD, Worldwide Medical Director Emeritus
Nicholas Fleischer, RPh, PhD, Vice President, Clinical Pharmacology and Biopharmaceutics
Carrie Rabe, PhD, Vice President, Nonclinical and Toxicology

Nita U. Patel, PhD, Senior Vice President, Global Regulatory Issues and Head of CMC
(b) (4), Consultant

1. INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 7, 2020, 3PM between Flamel Ireland Limited dba Avadel Ireland and the Neurology 1 Division. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

2. BACKGROUND

This submission contains a briefing package for a Pre-New Drug Application (Pre-NDA) meeting for Sodium Oxybate for Extended-Release Oral Suspension (FT218). The proposed indication for that product is the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. The sponsor plans to submit a New Drug Application seeking the approval of FT218 for the indication above, using the Section 505 (b)(2) pathway and Xyrem® as the reference.

Currently, Xyrem (sodium oxybate oral solution [500 mg/mL]) is the only brand-name product approved for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy. While Xyrem is a liquid, FT218 is a powder for oral suspension. Further, whereas the approved formulation Xyrem® is administered in two separate doses nightly, separated by an interval of 2.5 to 4.0 hours, the sponsor anticipates that FT218 will be administered once nightly. The proposed total nightly dose of FT218 is to be the same as that recommended in the Prescribing Information for Xyrem, as is to be the dose titration regimen for FT218 based on total nightly dose.

The clinical studies of FT218 that have been completed so far or are ongoing in support of the proposed NDA include a Phase 3 efficacy and safety study, and a number of clinical pharmacology studies, all of which are summarized in this meeting package.

The Phase 3 efficacy and safety study (CLFT218-1501) referred to above is complete. That study, which was conducted under a Special Protocol Agreement, was a randomized, double-blind, placebo-controlled, parallel-arm clinical trial of 13 weeks duration in which 212 patients with either Narcolepsy Type 1 or Narcolepsy Type 2 were enrolled and randomized

in equal proportions to treatment with either FT218 (in a final dose of 9.0 gram nightly) or placebo. The primary efficacy measures for evaluating FT218 in the treatment of excessive daytime sleepiness were the Maintenance of Wakefulness Test score and the Clinical Global Impression of Change in sleepiness; the primary efficacy measure for evaluating FT218 in the treatment of cataplexy was the number of cataplexy attacks weekly. A hierarchical statistical analysis comparing the FT218 and placebo groups on these measures and directed at preserving the overall type 1 error was conducted. A number of secondary efficacy measures were also used. Safety outcomes included adverse events vital signs, safety laboratory tests, electrocardiograms, physical examinations, and the Columbia-Suicide Severity Rating Scale. Preliminary data for this study are reported in this package as being indicative of the efficacy of FT218 in the treatment of both cataplexy and excessive daytime sleepiness in narcolepsy.

The several clinical pharmacology studies conducted so far include a bioavailability and bioequivalence study comparing FT218 with Xyrem® approved in the European Union. Summary observed clinical pharmacology from these studies are provided in this submission. Additional clinical pharmacology studies are planned, including a bioavailability and bioequivalence study comparing FT218 with Xyrem® approved in the United States.

A Chemistry, Manufacturing, and Controls summary and other data are also included in this package, along with an outline of the contents and format of the proposed NDA for FT218.

The stated objectives of the Pre-NDA meeting are directed at seeking feedback from the Agency regarding the following: whether previous Agency concerns regarding this development program have been adequately addressed; the adequacy of the proposed data package and clinical information to support a 505(b)(2) pathway NDA; and recommendations regarding the format of the planned NDA.

3. DISCUSSION

REGULATORY

Question 1:
Given the totality of this information, can the Agency comment on FT218's eligibility for orphan exclusivity upon NDA approval?

FDA Response to Question 1:
Exclusivity determinations generally are made at the time of approval, and it is therefore premature to opine on whether your application could qualify for exclusivity at this time. Eligibility for orphan-drug exclusivity is based on the facts at the time of marketing approval. The Office of Orphan Products Development (OOPD) will conduct a review for the determination of orphan-drug exclusivity at the time of New Drug Application (NDA) approval. OOPD will notify you by email with the outcome of our review.

Question 2:

As discussed with the Agency on multiple occasions and most recently in the Type C WRO received December 4, 2019, Avadel encountered significant difficulty obtaining U.S.-sourced Xyrem® to use in the pivotal comparative bioavailability study necessary to allow for Avadel to reference the Agency's previous findings of safety and efficacy of sodium oxybate (Xyrem® NDA 021196). Recently, Avadel was able to obtain enough U.S. Xyrem® to conduct the pivotal comparative bioavailability study (PKFT218-1801). The product was accompanied by a Certificate of Authenticity from (b) (4), the product supplier, provided in Appendix 1. Avadel contracted (b) (4) in (b) (4) to analyze the product for sodium oxybate assay, impurities, identity, pH, and appearance, and issued a Certificate of Analysis with these results (an example is provided Appendix 2). Avadel intends to submit this documentation in the NDA which along with the results of the pivotal comparative bioavailability study will establish the bridge between FT218 and NDA 021196.

Does the Agency agree that the U.S. Xyrem® documentation is adequate to establish that the comparator used in the pivotal comparative bioavailability study is the product approved under NDA 021196?

FDA Response to Question 2:

The information and documentation you have described on the lots of the proposed relied-upon listed drug product should be submitted to your planned NDA. It will be considered, as appropriate, during the normal course of review of the application. However, it is not clear from your question whether you have concerns about the authenticity of the U.S. Xyrem provided to you. Please clarify. If you have doubts regarding the authenticity of the relied-upon listed drug material, please describe your concerns and your plans to address them.

Question 3:

As noted in Section 7.4, Avadel is planning to conduct a Human Factors validation study prior to NDA submission. However, given the COVID-19 public health emergency and Avadel's desire to avoid causing unnecessary risk for any patient, the timing, locations, and exact logistics of the study are uncertain.

If the COVID-19 public health emergency remains in effect and impacts Avadel's ability to complete the HF validation study prior to NDA submission, will the Agency allow the NDA to be submitted without the HF validation study report if Avadel commits to filing the study report within two months of the original NDA submission?

FDA Response to Question 3:

After consideration of the information provided, we do not agree with your proposal to proceed with a partial NDA submission containing all required content, with the exception of the Human Factors (HF) Validation Study Report. We recommend the final HF Validation Study Report be submitted at the time of the original NDA submission.

CLINICAL

Question 4:

The CLFT218-1501 study demonstrated statistical significance ($p<0.001$) compared to placebo for the 9 g, 7.5 g, and 6 g dose of FT218 for all three co-primary endpoints: Maintenance of Wakefulness Test, Clinician Global Impression-Improvement, and weekly cataplexy attacks as per the hierarchy outlined in the statistical analysis plan under the SPA agreement. A summary of the primary efficacy analysis of CLFT218-1501 is presented in Section 10.2.2. Per the agreement during the June 12, 2015 Type B (PIND) meeting that a single pivotal efficacy and safety trial will be adequate to support the eventual NDA filing along with reliance on the safety and efficacy of sodium oxybate established by the approval of Xyrem®, Avadel intends to file a 505(b)(2) NDA with CLFT218-1501 as the single pivotal efficacy and safety trial.

Does the Agency agree that CLFT218-1501 can serve as the single pivotal efficacy and safety trial to support the approval of FT218 for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy?

FDA Response to Question 4:

We agree with your proposal, based on the summary data that you have provided in this briefing package and subject to the Agency's review of the full data for that study when it is submitted with your planned NDA.

Question 5:

Avadel will present the results of the single pivotal efficacy and safety trial in Section 2.7.3 Summary of Clinical Efficacy. The efficacy of FT218 will also rely on the efficacy of Xyrem® (NDA 021196). In addition, Avadel intends to conduct a review of the literature published since six months prior to the last Xyrem® safety-related labeling changes (i.e., April 2018) to identify any new and relevant efficacy information. Given that Avadel has conducted only one efficacy study, Avadel does not intend to include an Integrated Summary of Efficacy in Section 5.3.5.3.

Does the Agency agree with the approach to Section 2.7.3 and that an Integrated Summary of Efficacy is not required?

FDA Response to Question 5:

Your proposal is acceptable.

Question 6:

Avadel has conducted eight Phase 1 single-dose studies in healthy volunteers with FT218. Total patient exposures are available from seven of these studies; data are currently pending from the eighth. In the seven complete Phase 1 studies, a total of 152 patients received single doses of FT218 at doses of 4.5 g, 6 g, 7.5 g, and 9 g. Twenty (20) subjects received single doses of FT218 4.5 g, 132 subjects received single doses of FT218 6 g, 54 subjects received two single doses of FT218 6 g separated by at least a three-day washout, 45 subjects received two single doses of FT218 6 g and FT218 6 g + sodium valproate

separated by at least a three-day washout, 20 subjects received single doses of FT218 7.5 g, and 12 patients received single doses of FT218 9 g. In all Phase 1 studies, there was only one Serious Adverse Event (SAE) of somnolence in a subject at the 9 g dose (in PKFT218-1601) and only 2 subjects experienced severe AEs (somnolence). All other adverse events were mild to moderate in severity and most were adverse events known to occur with sodium oxybate (i.e., nausea, vomiting, somnolence, dizziness). A total of 5 subjects discontinued due to adverse event, 4 subjects due to vomiting at 6 g of FT218, and 1 subject from anxiety at 6 g of FT218. Prior to NDA submission, Avadel will conduct two additional Phase 1 Pharmacokinetic (PK) studies in healthy volunteers: a relative bioavailability study of FT218 6 g compared to 6 g of twice-nightly sodium oxybate (U.S. Xyrem®) and a bioequivalence study of FT218 6 g clinical trial material compared to FT218 6 g manufactured at an alternate drug product manufacturer ((b) (4)

In the Phase 3 REST-ON study, 107 patients were dosed with at least one dose of FT218 4.5 g, 97 were dosed with at least one dose of FT218 6 g, 88 were dosed with at least one dose of FT218 7.5 g, and 77 patients were dosed with at least one dose of FT218 9 g. The mean exposure of FT218 was 72.1 days in the REST-ON study. Patients were treated with FT218 g for a mean of 7.0 days, 6 g for a mean of 13.8 days, 7.5 g for a mean of 33.2 days, and 9 g for a mean of 33.6 days. Data from the REST-ON study was of a longer duration than the Phase 1 studies and included many more patients at higher doses of FT218. Conclusions on the safety of FT218 can better be drawn from the REST-ON study while the single dose Phase 1 safety data in healthy volunteers provides only limited information. Integrating the Phase 1 single-dose pharmacokinetic data in healthy volunteers into one dataset will not provide any more useful information than the presentations of individual study data from REST-ON. Therefore, Avadel proposes to summarize the data from the ten Phase 1 studies in the Section 2.7.4 Clinical Summary of Safety and not integrate it into a Phase 1 dataset in Section 5.3.5.3 Integrated Summary of Safety. The safety results of the sole Phase 3 efficacy study will also be presented in Section 2.7.4 Clinical Summary of Safety and will not be presented in Section 5.3.5.3 Integrated Summary of Safety.

Does the Agency agree with this approach?

FDA Response to Question 6:

It is acceptable to summarize the data from the ten Phase 1 studies in Section 2.7.4 (Clinical Summary of Safety) and not integrate it into a Phase 1 dataset in Section 5.3.5.3 (Integrated Summary of Safety). You should provide the individual study reports including case report forms as well as datasets for adverse events and narratives for the serious adverse events and discontinuations. Please provide links from the Clinical Summary of Safety to those documents and datasets and from those documents and datasets back to the Clinical Summary of Safety.

It is acceptable to present the results of the Phase 3 efficacy study in Section 2.7.4 (Clinical Summary of Safety). You should provide the individual study reports including case report forms as well as datasets for adverse events, laboratory and vital signs, and narratives for serious adverse events (SAEs), deaths, and discontinuations. You should also provide links from the Clinical Summary of Safety to those documents and datasets and from those documents back to the Clinical Summary of Safety.

Please refer to the standard safety request document in Attachment 1 that provides our expectations for presentation and inclusion of clinical safety data.

Question 7:
Avadel then proposes that Section 5.3.5.3 Integrated Summary of Safety will include a summary of the sodium oxybate post-marketing data available through FDA's AERS database. Avadel will also conduct a review of the literature published since six months prior to the last Xyrem® safety-related labeling changes (i.e., April 2018) to identify any new and relevant safety information.

Does the Agency agree with the proposed approach to the ISS?

FDA Response to Question 7:
This proposal is acceptable.

Question 8:
In the 120-day safety update, Avadel will provide safety data generated in the open label extension/switch study (CLFT218-1901) which will start to enroll patients approximately June 1, 2020.

Does the Agency agree with this approach for the 120-day safety update?

FDA Response to Question 8:
Your proposal is acceptable.

Question 9:
In Module 5 of the NDA, Avadel intends to provide CDISC-compliant ADaM and SDTM datasets for all completed Phase 1 and Phase 3 clinical studies with the exception of PKFT218-1301. This study was initiated after December 17, 2016 and evaluated three prototype formulations of FT218. A complete study report will be provided; however, no datasets are available due to the exploratory nature of the study.

Does the Agency agree with the proposed format of the dataset submission?

FDA Response to Question 9:
Your proposal not to provide the datasets for Study PKFT218-1301 is acceptable. The proposed format in which other datasets are to be submitted is also acceptable.

Question 10:
Avadel intends to propose that FT218 be controlled in the same manner as other FDA-approved formulations of sodium oxybate (i.e., Schedule III for the drug product formulation). Avadel will present the proposal for scheduling in Section 5.6 of Section 2.7.4 Summary of Clinical Safety that will include data/narratives of reports of abuse, overuse, or overdose, instances of lost, stolen, missing, or unaccounted for drug; drop-outs for protocol violation, lack of efficacy, lost to follow up, noncompliance to study medication or procedures, over compliance, or other, and reports of use by anyone other than study subjects from the Phase 3 REST-ON study.

The section will also include an evaluation of the abusability of the FT218 dosage form in comparison to other FDA-approved formulations of sodium oxybate. The proposed language for Section 9, Drug Abuse and Dependence, will rely on the approved language in the Xyrem® label with revisions for FT218-specific characteristics or relevant data gathered in the Phase 3 study.

Does the Agency agree with this approach to the abuse potential assessment and location of the proposal for scheduling?

FDA Response to Question 10:
In your NDA submission, you should include any data that may help to determine whether or not the product's extended-release property can be overcome intentionally, e.g., from product manipulation, or as an accidental exposure, e.g., from co-ingestion with alcohol or other conditions.

Overall, your approach to the abuse potential assessment and scheduling appears reasonable. In addition to the abuse potential assessment outlined above, you should monitor and report all central nervous system- or abuse-related adverse events (AEs) from clinical studies (in Phases 1, 2, and 3) and provide detailed narratives for any abuse-related AEs in accordance with recommendations in Section V.B. of the Agency's Guidance for Industry entitled "*Abuse Potential of Drugs*" (January 2017) which is available at the link below.

https://www.fda.gov/media/116739/download

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 11:
At the PIND meeting, the Agency requested that Avadel explore the impact of beverages whose pH is neutral or basic, and the potential impact of antacids on the integrity of the release- controlling coating of the proposed modified-release product. The results would then be used to determine whether a formulation interaction clinical study of FT218 co-administered with antacids is warranted. Avadel conducted two studies to address this concern:

1. A study of the impact of the beverage (neutral or basic drinking water, soft drinks, hot beverages) used for reconstitution on the dissolution profile of FT218 (ETD 218-005)

2. An in vitro study to simulate the effect of antacid or proton pump inhibitor intake on gastric pH and its impact on the dissolution profile of FT218 (ETD 218-006)

ETD 218-005 evaluated the dissolution profile of FT218 when reconstituted in a naturally alkaline water with high pH (8.5), mineral water with high bicarbonate ion concentration

(4263 mg/L) with pH 6.4, mineral water with comparatively moderate bicarbonate ion concentration (1250-1410 mg/L) with pH 5.8, and tap water as a reference (initial pH 7.6).

Dissolution profiles of 9 g FT218 were evaluated in 0.1 N HCl and were found to be similar in all but the water with the highest bicarbonate ion concentration. Although the dissolution was slightly faster in the high bicarbonate ion water, the similarity factor (f2) was equal to 58. Comparable results were observed using a 3 g FT218 dose. The dissolution profiles were unchanged by the time interval between reconstitution to dissolution (measured at 5, 15, and 30 minutes). Dissolution profiles after reconstitution in Coca-Cola (pH 3.1) and Crystal Light (pH 5.1 when dissolved in tap water) and warm (50°C) and hot (90°C) water was also evaluated. The only significant difference observed was in-vitro dose dumping when hot water was used linked to the (b) (4).

ETD 218-006 was performed to simulate the effect of antacid or proton pump inhibitor (PPI) on gastric pH and its impact on the dissolution profile of FT218. The presence of antacid increased pH resulting in a slight increase in the amount of API released by the formulation but without dose dumping. An in-vitro test was conducted that was developed to mimic the increase of pH that my occur in the stomach after taking PPIs followed by an increase of the dissolution medium to pH 6.8 to simulate intestinal pH. No evidence of dose dumping was observed.

The study reports are provided as Appendix 3 and Appendix 4.

Does the Agency agree that these studies adequately address the Agency's concern and that a formulation interaction clinical study is not required?

FDA Response to Question 11:
The results of the *in vitro* studies of FT218 in various beverages as reported in this meeting package appear to indicate a lack of dose-dumping potential *in vitro* in the selected beverages and in warm water, and an interaction study in humans is not needed Please note that the acceptability of these *in vitro* studies and the related labeling text that you propose will be a matter of review after submission of your planned NDA.

Question 12:
The proposed Drug Substance and Drug Product release/stability specifications are provided in the Section 11.3.5.1.

Does the Agency agree that both the Drug Substance and Drug Product release/stability specifications are acceptable for NDA filing?

FDA Response to Question 12:
The adequacy of the proposed specifications will be determined during the review of the NDA based on the data provided. We also have the following comments.

Drug Substance
The drug substance specification appears acceptable to support the NDA filing. You should provide a Letter of Reference to the Drug Master File (DMF) when the NDA application is

filed. For ease of review, you should provide in the NDA the following drug substance information: general information, physico-chemical properties, specifications and a Certificate of Analysis of the drug substance.

Drug Product
You should provide a risk assessment for elemental impurities in the drug product per ICH Q3D Elemental Impurities and USP Chapter <232> and establish appropriate controls.

Biopharmaceutics
The acceptability of your proposed dissolution acceptance criteria will be a matter of review after the submission of your NDA. Please refer to the Biopharmaceutics comments in the minutes of the End-of-Phase 2 meeting that was held on May 16, 2018, regarding dissolution method development and setting of the acceptance criteria.

Question 13:
Avadel intends to include (b) (4) in the FT218 NDA as the primary drug product manufacturing site with (b) (4) listed as an alternate drug product manufacturing site. To support the (b) (4) site, the NDA will include data on registration batches manufactured using three batches of IR beads and three batches of CR beads which are blended to form the final drug product. The following packaging configurations will have 36 months of long-term, 24 months of intermediate, and six months of accelerated stability data.

Table 1 Proposed (b) (4) Drug Product Registration Batches

Strength	4.5 g	6.0 g	7.5 g	9.0 g
Batch	P171029	P171033	P171034	P171030
	P171032	--	--	P171035
	P171037	--	--	P171038

To support the alternate (b) (4) manufacturing site, Avadel will provide three months of long- term and three months of accelerated stability data for the same number of batches for each strength as described for (b) (4) i.e., three batches of the lowest (4.5 g) and highest (9.0 g) strengths and one batch for each of the intermediate strengths (6.0 g and 7.5 g). Please see Section 11.3.6 for further details.

Does the Agency agree that:

a) the proposed stability data that will be provided on the (b) (4) registration batches will be adequate for NDA filing and that

b) the stability data that will be provided on the (b) (4) batches will be adequate and acceptable for filing (b) (4) as an alternate drug product manufacturing site?

FDA Response to Question 13:

The proposed stability data package appears adequate to support the filing of the planned NDA with (b) (4) as an alternate manufacturing site. The adequacy of the data to support shelf life assignment will be a matter for review.

LABELING

Question 14:

(b) (4)

Does the Agency agree that this is acceptable?

FDA Response to Question 14:

(b) (4)

However, as further discussed below, we are unable to concur with your present proposal for the reasons outlined below.

(b) (4)

(b) (4)

Question 15:
Avadel intends to propose the following indication for FT218:

- Treatment of cataplexy in adults with narcolepsy
- Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy

Does the Agency agree with the scope and population of the indication?

FDA Response to Question 15:
Your proposal appears acceptable, subject to our review of the data contained in your planned NDA.

Question 16:
Avadel intends to rely on Section 8.1 and Section 8.2 of the approved Xyrem® label to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and does not intend to include a PLLR white paper in the FT218 NDA submission.

Does the Agency agree that this approach is acceptable?

FDA Response to Question 16:
It is acceptable to rely on the approved Xyrem® label to comply with PLLR. In addition, you should include a summary and presentation of events of pregnancy in the clinical trials for FT218 in the NDA.

Question 17:
As described in Section 11.3.3.3.5 , the product will be packaged into (b) (4) packs and printed with lot number and expiration at the time of packaging. (b) (4)

(b) (4)

(b) (4)

Does the Agency agree that this approach is acceptable for NDA filing and for the eventual launch post approval.?

FDA Response to Question 17:
We do not agree that the proposed approach to (b) (4)

(b) (4)

4. OTHER IMPORTANT MEETING LANGUAGE SECTIONS:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION
At this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

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*.[3] 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 FDA.gov.[4]

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[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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*.

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

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single*

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

development.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[9] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[10]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this

[9] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[10] http://www.regulations.gov

regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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,* and the associated conformance guide, *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*.[11]

[11] https://www.fda.gov/media/85061/download

Attachment 1

DNP Pre-NDA/Pre-BLA Meetings
General Clinical Safety Requests

General Submission Contents:

1. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
2. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
3. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
4. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
5. Include active hyperlinks from the lists of references to the referenced article.
6. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
7. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
8. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
9. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
10. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each

adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.

3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed "drug-related."
5. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies including the reasons for termination if this occurred. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
   - Patient age and gender
   - Adverse event onset and stop dates (presented as relative Study Day number)
   - Signs and symptoms related to the adverse event being discussed
   - An assessment of the relationship of exposure duration to the development of the adverse event
   - Pertinent medical history

- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   - Age
   - Sex
   - Dates of screening, randomization and starting therapy
   - Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   - Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   - Prior medications and concomitant medications with dates of start and end
   - Vital signs and laboratories, sorted by date, with reference ranges *
   - Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *
   - Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

   * Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.

   For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to IND 106533.
   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

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/

TERESA A WHEELOUS
07/02/2020 09:45:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126321

MEETING MINUTES

Avadel Ireland
Attention: Marla Scarola, MS
Vice President, The Weinberg Group
1129 Twentieth St NW, Suite 600
Washington, DC 20036

Dear Ms. Scarola:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sodium Oxybate for Extended-Release Oral Suspension (FT218).

We also refer to the meeting between representatives of your firm and the FDA on May 16, 2018. The purpose of the meeting was to discuss the ongoing development program for FT218.

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 Susan Daugherty, Regulatory Project Manager at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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:	End-of-Phase 2
Meeting Date and Time:	May 16, 2018; 3-4 pm EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1315 Silver Spring, Maryland 20903.
Application Number:	IND 126321
Product Name:	Sodium Oxybate for Extended-Release Oral Suspension (FT218).
Indication:	Cataplexy and excessive daytime sleepiness in narcolepsy
Sponsor/Applicant Name:	Avadel
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Susan Daugherty

FDA ATTENDEES

Billy Dunn, MD, Director
Nicholas Kozauer, MD, Associate Director
Ranjit B Mani, MD, Senior Medical Officer
Martha R Heimann, PhD, OPQ Lead
Ta-Chen Wu, PhD, Acting Biopharmaceutics Team Lead
Parnali Chatterjee, PhD, Biopharmaceutics Reviewer
Angela Men, PhD, Clinical Pharmacology Team Lead
Dawei Li, PhD, Clinical Pharmacology Reviewer
Kun Jin, PhD, Biometrics Team Lead
Alan Trachtenberg, MD, Controlled Substance Staff
Jamie Wilkins Parker, PharmD, DRISK
Laura Zendel, PharmD, DRISK
Donella Fitzgerald, Pharm D, Team Leader, DRISK
Henry Startzman, MD, Medical Officer, Office of Orphan Product Development
Gumei Liu, Reviewer, Office of Orphan Product Development
Carolyn Yancey, MD, Medical Officer, DPMH
Natalie Branagan, MD, Clinical Reviewer
Susan Daugherty, Project Manager

SPONSOR ATTENDEES
Avadel Pharmaceuticals
Sandra Hatten, Senior Vice President, Quality and Regulatory Affairs
Lisa McNeil, Senior Director, Regulatory Affairs
Philip Matson, Director of Regulatory Affairs Europe
Cendrine Grangeon, Pharmaceutical Development Project Leader
David Monteith, PhD, Vice President, Research and Development
(b) (4)

The Weinberg Group Inc.
Nicholas Fleischer, RPh, PhD, Vice President, Clinical Pharmacology and Biopharmaceutics
Bob Roth, MD, PhD, Medical Director
Marla Scarola, MS, Vice President, Regulatory Program Managment
(b) (4), Consultant

1.0 BACKGROUND

This submission contains a briefing package for an End-of-Phase 2 meeting to discuss the further development of an extended-release formulation of sodium oxybate, Sodium Oxybate for Extended-Release Oral Suspension (FT218). FT218 is to be indicated for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

The FT218 formulation proposed for marketing is to consist of a powder for reconstitution and will be supplied in dosage units (b) (4) packs) having the following strengths: 4.5 g, 6.0 kg, 7.5 g, and 9.0 g. The formulation is to be suspended in water immediately prior to administration.

Currently, Xyrem (sodium oxybate oral solution [500 mg/mL]) is the only drug product marketed in the US for the treatment of both cataplexy and excessive daytime sleepiness in narcolepsy. Whereas Xyrem is administered in two separate doses nightly, separated by an interval of 2.5 to 4.0 hours, the sponsor anticipates that FT218 will be administered once nightly. The total nightly dose of FT218 is expected to be the same as that recommended for Xyrem.

Several clinical pharmacology trials of FT218 have been completed, and others are planned. A Phase 3 efficacy study of FT218 (Study CLFT218-1501) is currently ongoing under a Special Protocol Agreement.

Avadel plans to submit a New Drug Application (NDA) for FT218 under the 505(b)(2) regulatory pathway, using Xyrem as the reference listed drug.

The objectives of this End-of-Phase 2 Meeting are the following:

- To obtain guidance regarding the design of a proposed summative human factors study of FT218.
- To confirm that FT218 is exempt from the requirements of the Pediatric Research Equity Act (PREA).

- To discuss the data required to obtain orphan exclusivity for FT218 upon NDA approval.
- To obtain guidance on utilizing the Shared System Risk Evaluation and Mitigation Strategy (REMS) for sodium oxybate.
- To obtain guidance on the adequacy of a proposed approach to pharmacokinetic data bridging to permit reliance on data in NDA 21196 for Xyrem to support the approval of FT218 under the under the 505(b)(2) regulatory pathway, using Xyrem as the reference listed drug.
- To discuss the labeling implications of the predicted results of a planned clinical study of the drug-drug interaction between FT218 and sodium valproate.
- To discuss the possibility of amending Protocol CLFT218-1501 to permit the inclusion of patients with limited previous exposure to Xyrem (currently, patients enrolled in that study are required to be Xyrem-naïve).
- To obtain guidance on the adequacy of the proposed overall clinical development program for FT218 to support a future NDA for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy.

FDA sent Preliminary Comments to Avadel on May 10, 2014. Avadel responded on May 13, 2018, and indicated that they want to discuss the responses to Questions 5, 3, 8, and 6, in that order. The sponsor's responses follow *FDA Response*.

2. DISCUSSION

Question 1:
Does the FDA agree that the summative human factors protocol is sufficient to validate FT218's use-related risk mitigation strategies?

FDA Response to Question 1:
Please refer to the Agency's Information Request, dated April 3, 2018. We note that you submitted your Human Factor validation study protocol on April 11, 2018. We will need 90 days from the receipt of that submission to review and provide comments about that protocol. Written comments will be provided to you at the completion of that review.

Discussion at Meeting
Both the Agency and sponsor observed that the Human Factor validation study protocol remained under review and that an information request from the Agency was being addressed by the sponsor.

In the sponsor's pre-meeting response to the Agency's preliminary response communication, the sponsor had not listed this question as an item for further discussion. Thus, no representatives of the Division of Medical Error Prevention and Analysis (DMEPA) were present at the meeting. Agency staff present at the meeting did not immediately know of any other information that the sponsor could provide the Agency in support of the above Human Factor validation study protocol.

Question 2:
According to the Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act (September 2005), PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526." FDA has not issued regulations applying PREA to orphan designated indications. Thus, it is Avadel's understanding that submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. Avadel was granted orphan designation on January 8, 2018 for narcolepsy (Orphan Designation No. 16-5302). Therefore, Avadel does not intend to submit a Pediatric Study Plan or waiver request.
Does the Agency agree that this is acceptable?

FDA Response to Question 2:
We agree with your proposal. Sodium Oxybate for Extended-Release Oral Suspension (FT218) was granted orphan drug designation for the treatment of narcolepsy (DRU-2016-5302). The indication that you intend to seek, the treatment of cataplexy and excessive daytime sleepiness in narcolepsy, is covered by orphan drug designation DRU-2016-5302. Therefore, PREA does not apply and the submission of an Initial Pediatric Study Plan (iPSP) for FT218 is not required.

Discussion at Meeting
None.

Question 3:
Avadel intends to compile all available information supporting the superiority of FT218 and will include it in the request for exclusivity in the eventual NDA submission. In addition to the information already presented in the orphan designation request, Avadel is proposing the following to support orphan exclusivity:

- Demonstration that, based on the overall PK package, FT218 will be a more predictable product in terms of consistency of blood levels experienced by patients and resultant efficacy and safety. Because patients do not have to measure the drug (as it comes in single dose units), there is less room for dosing inconsistency. Also, patients only need to take one dose before bedtime thereby eliminating the variability in the timing of the middle-of-the-night dose, which is a known challenge for patients on the twice nightly regimen. Further, from the FT218 dose proportionality study at 4.5, 7.5 and 9 g, the kinetics are close to linear which is not the case with Xyrem, and from the recently completed food effect study, it has been demonstrated that timing of food intake is less impactful than seen with Xyrem. Please see Appendix 9 for a summary of supportive PK arguments.
- A comparison of side effects from the FT218 Phase 3 trial versus the publicly available data from the Xyrem clinical trials. We intend to investigate whether the expected improvements in administration compliance and blood levels experienced result in a lower incidence of adverse events such as accidents in the middle of the night and residual sleepiness.
- A survey of Xyrem users measuring compliance with the second dose in terms of both timing and omission and the frequency of adverse events and incidents associated with the taking of the second nightly dose. Avadel will develop a survey to be distributed to current Xyrem users to obtain data on compliance and the impact the second dose has on patients. The

objective will be to provide the Agency with additional data supporting that FT218 and the once-nightly dosing regimen provide a MC-to-PC over Xyrem.

- A user testing study comparing Xyrem and FT218: The Xyrem Instructions for Use (IFU) involve drawing two half-doses with a syringe, emptying both half-doses into two separate pharmacy containers and diluting them with water; one to be taken at bedtime and the second to be taken 2.5-4 hours later. Avadel anticipates that the comparative user testing study will demonstrate that FT218 is more user friendly, easier to prepare correctly, and will reduce the potential risk of dosing errors as each dose of FT218 is contained within a single separate drug packet. Through this study we would aim to show:

    - Reduction in the uFMEA Risk Priority Number and error frequency rates for critical dosing errors in FT218 compared to Xyrem,
    - Reduction in the rate of critical dosing errors for FT218 compared to Xyrem, and
    - Preference for FT218 vs Xyrem based upon user experience.

A proposed protocol synopsis is provided in Appendix 10.

a) Does the Agency have specific guidance on any of the approaches described above?
b) Does the Agency agree the above proposals are appropriate and adequate as the basis for demonstrating clinical superiority for the purposes of obtaining orphan exclusivity?

FDA Response to Question 3:

Response to Question 3a:

For the purpose of obtaining exclusivity, a significant and clinically meaningful reduction of adverse events (such as accidents attributable to having to take a second nightly dose of Xyrem) could support the clinical superiority of FT218 over Xyrem by demonstrating the greater safety of FT218 (while maintaining similar efficacy). While in most instances, the demonstration that one product is safer than another product in the same context would require direct ("head-to-head") comparisons of the two products in the same clinical trial, a direct comparison of the safety of FT218 and Xyrem in the same clinical trial may not be required for obtaining exclusivity for FT218, based on the information currently available.

In unusual cases, where neither greater safety nor greater effectiveness of a drug has been demonstrated, the demonstration that the same drug otherwise makes a major contribution to patient care (MCTPC) can be accepted as a means of demonstrating clinical superiority for the purpose of obtaining exclusivity. Whether MCTPC has been demonstrated for drugs intended for serious and life-threatening conditions is determined by the Agency on a case-by-case basis and in the context of the disease or condition that the same drugs are to be indicated for. When greater safety and/or effectiveness of such drugs is not evident, improved compliance or reduced medication errors alone would not be sufficient to demonstrate MCTPC. In demonstrating MCTPC, patient preference for one drug over the other is considered in the context of the underlying cause and functional impact of that preference.

Whether the clinical superiority of a drug has been demonstrated for the purpose of obtaining exclusivity can only be determined, and will depend on the data available, at the time of approval of that drug for marketing.

Response to Question 3b:
Please see our response to Question 3a.

Sponsor's Pre-Meeting Response
We appreciate the Agency's guidance on this issue. We intend to gather as much useful information as possible to demonstrate that FT218 is superior to Xyrem either on the basis of safety, efficacy, or MCTPC.

We understand that we may be able to argue greater safety based on comparison of adverse event data collected in the FT218 Phase 3 study with publicly available Xyrem data. We anticipate there being a demonstrable difference in those adverse events associated with the middle-of-the-night Xyrem dose, such as falls in the night, nighttime amnesia, inability to be awakened, and nighttime nausea. Are we limited to the Xyrem clinical trial experience or would data from the Xyrem postmarket experience documenting the adverse impact of the middle-of-the-night dose also be considered useful? We realize there will likely be a large body of postmarketing data for Xyrem and would want to take an appropriate approach in order to make a "fair" comparison.

As described in the meeting package, we had intended to conduct a survey of Xyrem users as well as a user testing study. In addition to information on compliance and dosing errors, both would assess user preference. We understand from your response that improved compliance or reduced medication errors alone would not be sufficient to demonstrate MCTPC; however, the response included a statement that "patient preference for one drug over the other is considered in the context of the underlying cause and functional impact of that preference." Would you please clarify what that means?

Our first proposed approach was an argument for greater safety and efficacy based on a comparison of the overall PK package of FT218 and Xyrem. Based on the single nightly dosing regimen, the single dose unit presentation, near linear kinetics, and lessened impact of food, Avadel is arguing that FT218 is more predictable in terms of consistency of blood levels experienced by patients. We would be interested in receiving the Agency's feedback on the utility of this approach.

Discussion at Meeting
This item was discussed in detail. The Agency indicated that all the approaches described above could potentially support an application for exclusivity. The Agency further suggested that safety data regarding adverse reactions associated with the second nightly of Xyrem would more likely exist in the post-marketing experience, rather than in the clinical trial experience, for Xyrem. The statement that "patient preference for one drug over the other is considered in the context of the underlying cause and functional impact of that preference" refers to the reasons for patient preference for one drug over the other.

(b) (4)

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Question 5:
Does the FDA agree that a two-way, comparative bioavailability study with non-U.S.-approved drug product (EU Xyrem) and the proposed drug product (FT218), along with publicly available pharmacokinetic data of U.S. Xyrem, as well as a discussion of the properties of U.S. Xyrem and EU Xyrem would be acceptable to establish a bridge to U.S. Xyrem considering difficulties in acquiring U.S. Xyrem?

FDA Response to Question 5:
The response to this question requires further review and discussion within the Agency. We will provide a final response as soon as possible and appreciate your patience while we further consider this matter.

Sponsor's Pre-Meeting Response
(b) (4), (b) (5)

To establish a basis for using EMA-approved Xyrem as a comparator, we provided a bridging rationale in the briefing package. The rationale presented a formulation comparison of EMA- and FDA-approved Xyrem demonstrating that the two products are essentially identical. This argument was accepted by FDA's Office of Generic Drugs in the case of Roxane's generic Xyrem which was approved without any dissolution or BE studies. We also provided a pharmacokinetic comparison of EMA- and FDA-approved Xyrem based on data obtained from Avadel's clinical studies and publicly available sources. Is the Agency able to provide any feedback on this bridging rationale? Is there any additional information that Avadel can provide that will be helpful to the decision-making process?

Are you able to provide us with an anticipated timeline for a response?

Discussion at Meeting
The Agency confirmed its understanding of the scientific rationale presented by the sponsor for using EMA-approved Xyrem as a substitute for FDA-approved Xyrem in the two-way comparative bioavailability study. Internal discussions about the regulatory implications of that approach are continuing at the Agency. The Agency further stated that every effort would be made for a response to be included in the final minutes of this meeting.

Addendum to Discussion at Meeting
The Agency is still evaluating the adequacy of the sponsor's proposal and will provide a response as soon as possible.

Question 6:

[redacted], does the Agency agree that we can use this as the basis for a contraindication?

FDA Response to Question 6:

Our determination [redacted] will be a matter of review when the results of your planned dedicated drug-drug interaction study of FT218 [redacted] are submitted under the planned NDA for that drug. We are not able to respond to this question more definitively at this time.

Sponsor's Pre-Meeting Response

[redacted] Are you able to provide any insight into the factors that are taken into consideration when deciding whether a contraindication or dosage adjustment is appropriate?

Discussion at Meeting

The Agency stated that in determining whether the concomitant use of FT218 [redacted] both the results of the aforementioned drug-drug interaction study and the feasibility of dose adjustment given the proposed fixed-dose strengths of FT218 would be taken into consideration.

Question 7:

Would the Agency please reconfirm that the described clinical program is adequate for eventual NDA submission and approval?

FDA Response to Question 7:

Please see our response to Questions 5 and 8. Apart from the caveats noted in our response to both questions, the clinical development program for FT218 that you have outlined in this submission appears sufficient in form to support a future NDA for that drug. A final determination of the adequacy of your clinical development program for FT218 will be a matter of review when your planned NDA is submitted.

Discussion at Meeting

None.

Question 8:
Does the Agency agree that an amendment to the existing CLFT218-1501 protocol may be made to include subjects with limited prior Xyrem use without impacting the current SPA agreement with FDA and the associated Statistical Analysis Plan?

FDA Response to Question 8:
Your proposal to amend Special Protocol CLFT218-1501 to allow for the inclusion of patients with limited prior Xyrem exposure (as defined by the criteria specified in that proposal) is acceptable in form, subject to our review of that protocol amendment when it is formally submitted to IND 126321. When you formally submit that amendment to IND 126321, you should specify that you are seeking written confirmation from the Agency, in response, that the proposal will not compromise the existing Special Protocol Agreement for that study.

Sponsor's Pre-Meeting Response
We would like to confirm that we plan to submit a protocol amendment to include subjects with limited prior Xyrem use at a subtherapeutic dose. To ensure that the SPA is not compromised, we will wait to implement any change until we receive written confirmation from the Agency. Are you able to provide us with an anticipated timeline for the review?

Discussion at Meeting
The sponsor confirmed that, when formally submitted to IND 126321, the proposed amendment to Study CLFT218-1501 described above, would not differ in substance from that described in the meeting package. Based on that confirmation, the Agency stated that a letter indicating that the same amendment was acceptable and would not compromise the existing Special Protocol Agreement for that study would be issued within 1 to 2 weeks of its formal submission.

Additional FDA comments

Biopharmaceutics

The current submission does not contain information about the *in vitro* drug release/dissolution method for FT218 that the Agency can provide comments on. As a reminder, details of the development of the *in vitro* dissolution test and setting of the *in vitro* dissolution acceptance criteria for your proposed FT218 drug product should be provided in the planned NDA. Please refer to the Agency's minutes of the Pre-IND meeting held on June 12, 2015, for further details regarding the development of a suitable dissolution method and the setting of acceptance criteria for your proposed extended-release sodium oxybate product. If you wish to receive Agency feedback before the submission of your planned NDA regarding the adequacy of the proposed dissolution method for FT218, please submit the full *in vitro* dissolution method development (test media, apparatus, temperature, agitation speed, etc.) and validation report, with complete data, as an amendment to IND 126321, clearly stating in the cover letter for that amendment that a review of that report by the Division of Biopharmaceutics is requested. Please note that while the acceptability of the dissolution method can be determined at the IND or NDA stage of development, the evaluation of the dissolution acceptance criteria will be performed during review of the NDA. Until the dissolution acceptance criteria for FT218 are accepted by the

Agency, we recommend that you collect complete dissolution profiles for the proposed product during the stability study of the clinical/exhibit batches.

Discussion at Meeting
None.

Controlled Substances Staff Comments:

1. Drugs that affect the central nervous system (CNS), are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., sedation, euphoria, hallucinations) need to be evaluated for their abuse potential. Sodium oxybate is currently controlled under Schedule III of the Controlled Substances Act (CSA) when present in FDA-approved drug product formulations, but the drug substance generally is listed in Schedule I of the CSA. Your NDA submission should address whether your new dosage form should be controlled in the same manner as other FDA-approved formulations of sodium oxybate and should include appropriate product labeling for Section 9 ("*Drug Abuse and Dependence*"). You should provide in your NDA submission any data, information, or references that are supportive of your proposals. A proposal for scheduling of the product under the CSA will be required for your NDA submission [see 21 CFR 314.50(d)(5)(vii)]. Please also see the Agency's Guidance for Industry document entitled "Assessment of Abuse Potential of Drugs," published in January 2017, and available at:

   https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

2. For the studies proposed in your development plan, you should monitor for possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as a "high" or euphoria) and for any occurrence of study drug accountability discrepancies and the reason(s) reported for them. Investigators should obtain more information and explanations from study subjects or others involved when there are drug accountability discrepancies. Towards that end, you should:

   a. Train investigators to capture cases of abuse, misuse, and addiction before starting trials and provide definitions for such cases.
   b. Provide data in tabular form for all reports of abuse, overuse, and lost/stolen/missing or unaccounted product that occurred in clinical trials. Those data should include study number and type of study, subject ID number, narratives, case description, and other details.
   c. Provide narratives for cases where patients drop out from studies for reasons that might be coded as "protocol violation," "lack of efficacy" (to capture aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), "lost to follow up," "non-compliance to study medication or procedures," "over compliance," or "other." Case reports should be provided separately.

d. Report any use of the investigational formulation by individuals other than the subjects (family member, health care practitioner, etc.)

Discussion at Meeting
None.

3.0 ISSUES REQUIRING FURTHER DISCUSSION
Question 5 has not been answered and may require further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
A response to Question 5 is to be provided.	FDA	As soon as possible.

5.0 ATTACHMENTS AND HANDOUTS
The sponsor's responses to the FDA preliminary comments are incorporated under section 2 *Discussion.*

6.0 ADDITIONAL INFORMATION

Prospective Assessments of Suicidal Ideation and Behavior in Clinical Protocols

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 (cder-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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

505(b)(2) Regulatory Pathway

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/s/

ERIC P BASTINGS
06/14/2018