CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209819Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107607

MEETING MINUTES

Indivior Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Clorey Toombs
Director, Regulatory Affairs

Dear Ms. Toombs:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for RBP-6000 (buprenorphine-ATRIGEL one-month depot).

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2016. The purpose of the meeting was to discuss plans for the NDA submission of RBP-6000.

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 Swati Patwardhan at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Selma Kraft, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 14, 2016, 3:00 to 4:00 p.m.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	IND 107607
Product Name:	RBP-6000 (buprenorphine-ATRIGEL one-month depot)
Indication:	For the treatment of opioid use disorder (OUD) as part of a complete treatment plan to include counselling and psychosocial support
Sponsor/Applicant Name:	Indivior Inc.
Meeting Chair:	Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products, DAAAP
Meeting Recorder:	Selma Kraft, PharmD, Regulatory Project Manager, DAAAP

FDA ATTENDEES

- Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Product (DAAAP)
- Rigoberto Roca, MD, Deputy Director, DAAAP
- Celia Winchell, MD, Clinical Team Leader, DAAAP
- Emily Deng, MD, Clinical Reviewer, DAAAP
- Yun Xu, PhD, Team Leader, Division of Clinical Pharmacology II (DCP-II)
- David Lee, PhD, Clinical Pharmacology Reviewer, DCP-II
- Dan Mellon, PhD, Pharmacology/Toxicology Supervisor, DAAAP
- Jay Chang, PhD, Pharmacology/Toxicology Team leader, DAAAP
- Gary Bond, PhD, Pharmacology/Toxicology Reviewer, DAAAP
- Ciby Abraham, PhD, CMC Team Leader, OPQ/DNDP II
- David Petullo, MS, Statistic Team Leader, Division of Biostatistics II, (DB II)
- Yi Ren, Statistical Reviewer, DBII
- Jim Tolliver, PhD, Pharmacologist, Controlled Substance Staff (CSS)/Office of Center Director (OCD)

- Kelly Kitchens, PhD, Team Leader, Biopharmaceutics, Office of Pharmaceutical Quality (OPQ)
- An-Chi Lu, PhD, Biopharmaceutics Reviewer, OPQ
- Lars Johannesen, PhD, Qt-IRT Scientific Co-Lead, OCP

SPONSOR ATTENDEES

- Sue Learned, MD, PharmD, PhD Senior Vice-President, Global Clinical Development
- Barbara Haight, PharmD Senior Director, Medicines Development Leader, Global Clinical Development
- Amanda Garofalo, MSHS Global Clinical Program Lead, Global Clinical Development
- Sunita Shinde, MD Research Fellow, Global Clinical Development
- Paul J. Fudala, PhD, RPh Senior Fellow, Clinical Science, Global Clinical Development
- Richard Norton, PhD Director, Formulation Development
- Brent Coonts, Director, Chemistry, Manufacturing and Controls (CMC) Operations
- Celine Laffont, PhD Director, Quantitative Clinical Pharmacology, Modelling and Simulation, Global Clinical Development
- Dayong Li, PhD Head, Data and Statistical Sciences
- Rosonald Bell,Msc, PhD, DABT Director, Toxicology
- Julie Tripp, MS, CVT Preclinical Toxicologist, Global Clinical Development
- Eddie Li, MD, PhD Senior Vice-President, Global Regulatory Affairs
- Bruce Paolella, MSc Director, Regulatory Affairs North America
- Clorey Toombs, RAC Director, Regulatory Affairs Strategy
- Vanita Dimri, MS, RAC Senior Manager, Regulatory Affairs
- Robert Nelson, Manager, Global Regulatory Affairs CMC

BACKGROUND

Indivior is developing RBP-6000 (buprenorphine-ATRIGEL one-month depot) for the treatment of opioid use disorder as part of a complete treatment plan to include counseling and psychosocial support. The Sponsor plans to submit an application referencing relevant literature and information from previously-approved NDAs which are owned by Indivior. A Pre-NDA meeting was submitted on August 5, 2016, and the meeting request was granted on August 17, 2016. The briefing package was received on November 7, 2016, for the meeting scheduled for December 14, 2016.

FDA sent Preliminary Comments to Indivior Inc., on December 13, 2016.

DISCUSSION

The questions from the November 7, 2016, briefing package are reproduced below in *italics*, and our responses are in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

Chemistry, Manufacturing and Controls Development

Question 1:

In accordance with 21 CFR 4.4(b)(1) and FDA Draft Guidance: "Current Good Manufacturing Practice Requirements for Combination Products" dated January 2015, Indivior intends to pursue a streamlined approach for maintaining CGMP compliance of the RBP-6000 combination drug product. Indivior intends to provide the following list of information in Section 3.2.P.7 (unless indicated otherwise) of the NDA to support the device portion of the application. Indivior believes that this list constitutes a complete set of information necessary for submission in the NDA to support the use of the device with the RBP-6000 drug product.

Does FDA concur that the following information constitutes a complete list of information necessary to support the use of the device with the RBP-6000 drug product, and that the information to be included is provided in the correct Section of the NDA?

- *summary of the container closure/device system;*
- *complete description of the device/primary container;*
- *pictures/engineering drawings of the primary container assembly/subassembly;*
- *list of all standards and guidelines the device conforms to (Section 3.2.P.2.4);*
- *combination product principle of operation (Section 3.2.P.2.4);*
- *biocompatibility information (Section 3.2.P.2.4);*
- *sterilization information and validation methodology (Section 3.2.P.2.4);*
- *shelf-life and associated testing information (Section 3.2.P.2.4);*
- *supplier information;*
- *relevant testing protocols/reports and data, e.g., bench, animal, clinical and human factors*
  (Section 3.2.S.2.4 and Section 5.3.5.4 as applicable);
- *a concise summary of the design control activities for this combination product (Section 3.2.P.2.4), this summary will include:*
  - *an identification of the Risk Analysis method(s) used to evaluate risk of the device selection.*
  - *Identification of mitigations and results.*

FDA Response to Question 1:

The items listed in Question 1 of your meeting package appear generally acceptable to support filing the NDA from device perspective. However, without knowing the content of the submission, the adequacy of the data submitted in the NDA will be a review issue. No needle information was mentioned. You must describe the needle and the packaging information and provide any relevant design verification and validation data. In addition, provide design specification document for the delivery system.

Discussion:

There was no further discussion of this question.

Question 2

On 02 September 2016 (SN0062), Indivior submitted an amendment to IND 107607, to provide the justification for not conducting a Human Factors validation study for RBP-6000. Included in

the amendment was the Use Error Analysis, results for the Human Factor formative study and the detailed justification. Does the Agency agree that a Human Factors validation study for RBP-6000 is not required to be submitted in the NDA based on the information provided in the amendment?

FDA Response to Question 2:
Yes, we agree with your approach.

Discussion:
There was no further discussion of this question.

Question 3:

(b) (4)

Does the Agency concur that this approach is acceptable (b) (4) *? Does the Agency concur that this approach is acceptable for other types of similar/related post-approval changes listed in the FDA guidance requiring a biostudy as well?*

FDA Response to Question 3
No, we do not concur with your approach. (b) (4) **. We recommend that you submit a detailed proposal or study protocol to the Agency for review. The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.**

Discussion:
There was no further discussion of this question.

Nonclinical

Question 4:

Does FDA agree that the proposed nonclinical data summarized from the literature and supporting studies with the ATRIGEL Delivery System allow for the assessment of the risk benefit profile in the use of NMP and PLGH in the formulation?

FDA Response to Question 4

While preliminary review of the data appears to support filing your NDA, the adequacy of the data to support approval continues to be a review issue that may be resolved only with the NDA review.

If the cited literature is needed to support the safety of the drug product formulation, your application may be a 505(b)(2) application.

Discussion:

There was no further discussion of this question.

Question 5:

At the End of Phase II meeting (30 September 2014), the Agency stated that it did not agree with Indivior's rationale (b) (4) *To date, Indivior has conducted or is currently conducting a comprehensive reproductive and developmental study program. Does the Agency agree that the studies have been adequately designed to provide safety information regarding both the ATRIGEL Delivery System and RBP-6000?*

FDA Response to Question 5

As a clarification, we noted at the September 30, 2014, meeting that "At this time, we cannot determine whether additional developmental and reproduction toxicity studies will be required." We agreed that studies with buprenorphine did not appear warranted; however, it was not clear if the components of the ATRIGEL vehicle were adequately qualified so we could not agree at that time that additional studies with PGLH and NMP could be omitted. Based on our preliminary review of the literature submitted to address the potential reproductive and developmental effects of the components of the ATRIGEL vehicle, it appears that this information would be adequate to support filing the NDA, although the adequacy of this information to support approval of your product can only be determined after a full review of all the submitted information and consideration of the benefit:risk profile of your product in the context of the proposed indication.

Your proposed reproductive and developmental study program testing the final drug product formulation does not appear to be adequate to characterize the safety of NMP in Atrigel because, as designed, NMP exposures would not be adequate over the course of the standard dosing interval for these studies. If you choose to conduct new reproductive and developmental toxicology studies with the ATRIGEL vehicle and/or with its individual components, we recommend that the studies be designed such that adequate systemic exposures to the individual components are achieved throughout the critical exposure periods as appropriate for the specific study protocols. For example, embryofetal development studies with NMP should employ daily dosing by an appropriate route (e.g.,

subcutaneous) throughout the period of organogenesis. High dose selection must be based on appropriate justification (e.g., maternal toxicity, maximum feasible dose, multiples of clinical exposure) per the ICH guidance for industry: *S5A Detection of Toxicity to Reproduction for Medicinal Products*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074950.pdf.

Discussion:
The Division requested clarification regarding the status of the reproductive and developmental toxicity studies. The Sponsor stated that they have completed three dose-range finding studies and three GLP studies in rats and rabbits with the RBP-6000 drug product and the ATRIGEL vehicle. In these studies, three doses of RBP-6000 and three doses of the ATRIGEL vehicle were tested. The Division inquired how frequently the test articles were administered in these studies and whether they were designed to address the potential reproductive and developmental effects of NMP. The Sponsor clarified that they were not administered daily, but rather intermittently. The Sponsor acknowledged that systemic exposure to NMP would likely be of limited duration since it dissociates from the depot product rapidly following injection. However, the Sponsor contended that the doses were given at the most critical time points of reproduction and development in these studies and no effects were seen on male or female fertility and any other endpoints examined.

The Division stated that even if the doses were given during the most critical time points, the length of exposure may not be sufficient to adequately characterize NMP's potential effects as the standard nonclinical dosing frequency to fully assess potential toxicity is daily during the relevant reproductive and developmental periods (e.g., daily during gestation in an embryo-fetal study). For example, a single RBP-6000 dose on Gestational Day 7 to assess potential embryo-fetal effects would only provide embryo/fetus exposure for 1-2 days as the NMP exits the dosing site as the drug depot is formed. This is the issue that was noted in the formal FDA response to Question 5.

The Division reiterated that the information submitted to date from literature will support the filing of the NDA application, but the adequacy of the data, which will include literature and new toxicology studies, to support the safe use of NMP for approval can only be determined after review of the data. Additional literature references may be needed to supplement the data. The Division also stated that if reliance on literature is required to support the safety of NMP or any other aspect of the product for approval, it will make the NDA a 505(b)(2) application unless the Sponsor owns or has right of reference to the data in the literature. The Sponsor agreed to submit the ongoing studies along with literature references with the NDA submission.

Question 6:
Does FDA agree that the proposed nonclinical data are sufficient to support review of the NDA?

FDA Response to Question 6
The proposed nonclinical data described in your briefing package appear sufficient to support filing and review of the NDA. The adequacy of these data to support the approval of your product will be a review issue.

Discussion:
There was no further discussion of this question.

Clinical

Question 7:

a) *Integrated Summary of Efficacy*
The ISE will be fulfilled by the content of m2.7.3 (Clinical Summary of Efficacy) which will include a complete analysis of efficacy as required for the ISE. For the Clinical Summary of Efficacy, the presentation of efficacy data will focus primarily on the Phase III, double-blind, placebo-controlled efficacy, safety and tolerability trial for RBP-6000 (RB-US-13-0001). Therefore, Indivior proposes not including an integrated analysis of efficacy data (i.e., integration of data, because there is only 1 pivotal, double-blind, randomised trial). A summary of findings from the Phase II OB study (RB-US-13-0002) will also be included in the Clinical Summary of Efficacy, because this study provides confirmatory evidence as described in the Type C meeting minutes dated 13 June 2013). Additional supportive data from other studies will also be included, but not integrated.

Subgroup analyses will be performed to assess the consistency of the treatment effect for the following subgroups:

- *gender (male, female)*
- *race (black, white, other)*
- *ethnicity (Hispanic or Latino, not Hispanic or Latino)*

Descriptive statistics will be presented without statistical testing.

Does the agency agree with the proposed content of the Clinical Summary of Efficacy?

FDA Response to Question 7a
No, we do not agree. Although you do not need to perform a pooled efficacy data analysis from these two studies, you must submit an integrated summary of efficacy from these two studies to demonstrate that the provided evidence is substantial for supporting the efficacy of RBP-6000 for the proposed indication. Assuming that there are no review issues, the proposed content of the Clinical Summary of Efficacy by presenting the Phase 3 study (RB-US-13-0001) as the pivotal study and a summary of findings from the Phase 2 opioid blockade study (RB-US-13-0002) as the confirmatory evidence appears to be appropriate. Ensure that the full RB-US-13-0002 report is included in the NDA submission.

Additionally, we have the following recommendations regarding efficacy data analysis:

1. **Subgroup analysis for the treatment effects should also include: age, BMI, geographic region (if indicated), disease severity (moderate vs severe), primary opioid of abuse (heroin vs prescription drugs; short-acting vs long-acting), time since first opioid abuse, achieved daily dose of Suboxone prior to randomization.**

2. **A graphical display of subject-level urine toxicology data where urine test are indicated as negative, positive, or missing will be needed to demonstrate the quality of urine toxicology assessments.**

b) *Integrated Summary of Safety*

As with the ISE, the ISS will be fulfilled by the content of m2.7.4 (Clinical Summary of Safety) which will include a complete analysis of safety as required for the ISS. For the Clinical Summary of Safety, safety data will be provided from all of the completed clinical studies as of the data cut-off date for the NDA (12 August 2016) and for an interim analysis of the ongoing, long-term, open-label safety and tolerability study.

The Phase III studies (RB-US-13-0001 and RB-US-13-0003) had different designs. One is double-blind, placebo controlled efficacy and safety study; the other is open-label, long-term safety study (Table 5). Safety analyses will be presented separately for each study. However, additional analyses including subgroup analyses will be performed for pooled data for:

- *demographics and baseline characteristics;*
- *exposure to study treatment (RBP-6000 or Placebo);*
- *injection site tolerability [including injection site pain visual analog scale (VAS), burning and stinging].*

For all other studies, safety data will be presented separately for each study, and no data pooling will be performed.

Does the agency agree with the proposed content and pooling strategy for the Clinical Summary of Safety?

FDA Response to Question 7b

No, we do not agree. In addition to displays by individual studies, display the safety data in the following pools:

1. **Phase 1 studies**
2. **Phase 3 studies (pooled)**
3. **Double-blind study**
4. **Open-label studies**

Include the data from all studies in analyses of SAEs, laboratory effects, and EKG effects. For the analysis of injection site reactions, include the number of injections. For the purpose of calculating exposure time, we do not agree that a year is defined as twelve 28-day periods. In order to produce a clear and accurate tabulation of the extent of exposure to your product, provide tabulations of dose by duration in weeks, rather than months.

The tabulation should break out the cumulative exposure in four-week intervals (e.g., at least 4 weeks, at least 8 weeks, etc).

Refer to the Guidance for Industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf

and *Integrated Summary of Effectiveness Guidance for Industry*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf

Discussion:
The Sponsor stated that, due to design differences in the various studies, it may be uninformative to pool data from these studies and asked the Division to clarify the format for the safety data submission. While the Division acknowledged the differing study designs, there are certain types of events that would be useful to evaluate the overall safety of the product. It would be advantageous for the Sponsor to integrate the data for the NDA submission. The Sponsor asked which specific events the Division wants to see integrated. The Division suggested adverse reactions, such as injection site reaction, signs and symptoms of CNS depression, and labs of special interest such as liver function tests.

The Sponsor sought clarification regarding the studies used for each pool of data (see Appendix A). The Sponsor asked that if they should pool safety data from Phase 1studies including single dose and multiple studies together. The Division suggested that the Sponsor should pool Phase 1 single dose studies and multiple dose studies separately. Refer to the following regarding the agreed upon pooling of the safety data to be submitted:

1. Pool 1: Phase 1 single ascending dose studies
2. Pool 2: Phase 1 multiple ascending dose studies
3. Pool 3: Phase 2 opioid blockade study
4. Pool 4: Phase 3 double blind study
5. Pool 5: Phase 3 open label study
6. Pool 6: Both phase 3 studies

The Sponsor asked if the ECG related data can be presented as a separated QTc evaluation. The Division agreed.

Question 8:
With respect to electronic datasets and Case Report Tabulations, Indivior plans to submit the study tabulation data in the CDISC-SDTM (most current version) format and the analysis datasets, programmed from the SDTM domains, in the CDISC ADaM format for each of the completed studies and the interim analysis of the ongoing, long-term, open-label safety and tolerability study.

Is the Agency in agreement with the proposed plan for submitting study-level datasets in the NDA?

FDA Response to Question 8
Yes, we agree. The proposed plan appears to be appropriate.

Discussion:
The sponsor stated that ADaM datasets are not available for two of the legacy studies, RB-US-10-0011 and RB-US-11-0020 and proposed to submit complete datasets, SDTM datasets, and analysis datasets. The Division agreed with the proposed submission.

Question 9:
Does the Agency agree that the data to be provided from the 6 completed clinical studies and the interim analysis of the ongoing, long-term, open-label safety and tolerability study support the review of this application for the indication stated?

FDA Response to Question 9
See our response to Questions 7a and 7b.

Assuming that there are no review issues, with additional analyses, the pivotal Phase 3 Study RB-US-13-0001 and confirmatory Phase 2 Study RB-US-13-0002 will provide sufficient data to support the review of efficacy of RBP-6000 for the proposed indication.

In regard to the safety database, you have not provided the tabulations of dose by duration in weeks. Therefore, we could not determine whether the exposure data is sufficient to support the review of safety of RBP-6000 for the proposed indication at this time.

Discussion:
There was no further discussion of this question.

Question 10:
Complete data from the double-blind efficacy study RB-US-13-0001 and interim data from the ongoing long-term safety and tolerability study RB-US-13-0003 together provide a minimum of 500 subjects with 6 months of dosing and 100 subjects with 1 year of dosing, where one month is defined as 28 days. Does the Agency agree that the data to be provided for 500 subjects with 6 months of dosing and 100 subjects with 1 year of dosing from these Phase 3 studies where one month is defined as 28 days supports the review of this application for the indication stated?

FDA Response to Question 10
We do not agree that a month is defined as 28 days or that a year is defined as 12 x 28 days. We are unable to determine how many subjects were treated for 6 months (26 weeks) and how many for one year (52 weeks) based on your submission. However, we are able to exercise some flexibility if you have provided sufficient exposures with 48 weeks of duration.

Discussion:
The Sponsor sought clarification on the duration of the long-term study to meet the minimum safety standards for NDA submission (see Appendix A). The Division clarified that one year is 365 days. If the Sponsor does not have data for 100 patients who have been treated for 365 days, the NDA submission may still be considered fileable if the patients were exposed for 48 weeks. However, these patients do not represent a year of exposure as 52 weeks is considered a year. The Sponsor stated that patients receive an injection every 28 days for 12 injections, which is exposure for 48 weeks. However, some patients may receive an injection a few days later, which will extend the exposure beyond 48 weeks. The Sponsor stated they will indicate which subjects were exposed beyond 48 weeks. In the Appendix A, the Sponsor summarized that they had data of approximately 173 subjects who have received 12 injections over approximately 48 weeks period. The Division asked if the Sponsor had data for 173 subjects exposed at 300 mg for 12 injections. The Sponsor responded that as of November 2016, a combination of patients have received 12 doses of 100 mg or 300 mg of RBP-6000. The Division suggested that the majority of the data should be from patients who received the 300 mg dose of RBP-6000 for the longest duration as safety data is currently lacking for that high exposure and long duration of exposure.

Question 11:
The PK data presented in the application will consist of descriptive analyses from Phase I and Phase II studies along with the combined population PK analysis of the Ph3DB and MAD study data. Exploratory modelling work based on individual SAD and MAD studies will be presented only in the form of peer-reviewed publications. Exposure-response models for illicit opioid use and opioid withdrawal signs/symptoms will be developed from the Ph3DB study data. The population PK/PD modeling report will be included in the submission. Is this approach acceptable to the Agency?

FDA Response to Question 11:
No, we do not agree. If you plan to use any modeling work or analysis to support approval of your NDA or labeling statements, provide the modeling work (exploratory, final and validated models, etc.) with full reports and supporting files such as dataset, control stream, analysis output, etc., in the NDA submission, so we can reproduce the results and conduct additional analysis if necessary.

Discussion:
There was no further discussion of this question.

Question 12:
Is the FDA in agreement with the plan for submission of narratives and Case Report Forms (CRFs) in the NDA?

FDA Response to Question 12
No, we do not agree. Submit both individual subjective narratives and CRFs for all subjects with a pregnancy, a fatal event, a serious adverse event, or an AE leading to premature discontinuation.

Discussion:
There was no further discussion of this question.

Question 13:
Subjects were enrolled in Study INDV-6000-301 (an extension of Study RB-US-13-0003) after the 12 August 2016 NDA data cut-off date. It is proposed that no data from ongoing Study INDV-6000-301 be included in the Clinical Summary of Safety. Does the agency agree with this proposal?

FDA Response to Question 13
If the subjects in INDV-6000-301 are considered part of the safety database to meet the required number and duration of exposures, the data must be included in the initial NDA submission. If the safety database is adequate without these subjects, the data from this study can be provided in the 120-day safety update along with new integrated analyses including these subjects.

Discussion:
(b) (4)
The Division stated that the data from the long-term study should be submitted at the time of the NDA submission as part of the complete safety database. It is not helpful to have new safety data halfway through a review cycle as there may not be enough time to review it completely. Depending on the nature of data, the submission of additional data can extend the review period by three months, even if it is under priority review or can result in a complete response during the first cycle of review. If the application warrants discussion by an advisory committee (AC), a delay in submission of data could result in cancellation of the AC and a complete response during the first review cycle. It is the Sponsor's responsibility to submit a complete application that includes all relevant and additional information beyond the minimum standards for a safety database at the time of the NDA submission for review.

Question 14:
Indivior and the FDA have had numerous communications regarding the requirement of a QT assessment during the RBP-6000 development program and concur that a comprehensive QT evaluation for RBP-6000 will be provided in the NDA submission.

Does the Agency agree that the proposed approach will provide sufficient information to enable submission and review of the NDA?

FDA Response to Question 14
The proposed approach appears reasonable, but the provided description does not permit extensive comments at this point in time.

Consider the following general comments when submitting the results of this analysis:

1. **When using exposure-response as the primary analysis we recommend that the modeling methods and assumptions, criteria for model selection, rationale for model components and the plan for pooling of data are specified prior to analysis to limit bias.**

2. **We also recommend the inclusion of an evaluation of the model assumptions, hysteresis (a plot of data by-time point and a hysteresis loop plot), and assessment of goodness of fit. The recommended model for this analysis is a linear mixed effects model including the following terms: drug concentration (placebo concentrations set to 0), treatment (active or placebo), nominal time postdose (categorical) and baseline QTc as well as a random effect on the intercept and slope.**

3. **When submitting analysis of your drug on the QTc interval, include the following for all studies in your analysis:**
   a. **Electronic copy of study report**
   b. **Electronic copy of clinical protocol**
   c. **Electronic copy of the Investigator's Brochure**
   d. **Annotated CRF**
   e. **A data definition file which describes the contents of the electronic data sets**
   f. **Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).**
   g. **Data set whose QT/QTc values are the average of the above replicates at each nominal timepoint.**
   h. **Narrative summaries and case report forms for any**
      i. **Deaths**
      ii. **Serious adverse events**
      iii. **Episodes of ventricular tachycardia or fibrillation**
      iv. **Episodes of syncope**
      v. **Episodes of seizure**
      vi. **Adverse events resulting in the subject discontinuing from the study**

Discussion:
The Sponsor stated that none of the subjects in the QT study were on a naltrexone blockade.

Question 15:
Indivior received an Advice/Information request letter on September 19, 2016. As described in the company position, we plan to use literature data in conjunction with safety/exposure analyses to support appropriate dosing recommendations for co-administration of CYP3A4 inhibitors/inducers with RBP-6000.

Does the Agency agree that the proposed approach will provide sufficient information to enable submission and review of the NDA?

FDA Response to Question 15
You propose to use data from multiple sources to address the potential of drug interaction with 3A4 inhibitors. Without reviewing these data, we cannot make a final conclusion on whether this approach is acceptable or not.

We acknowledge that RBP-6000 may be less affected by inhibition of 3A4 activity than transmucosal buprenorphine products, due to the lack of a first pass effect. We are also aware of the ketoconazole drug interaction study with a transdermal buprenorphine product showing that drug-drug interaction effects with buprenorphine may differ based on route of administration. However, RBP-6000 is a subcutaneous injection depot, so the results of a study involving the transdermal route may not apply. Also note that this literature source used a specific, named commercial product (i.e., Butrans). To rely on any findings from this publication, you must have the right to refer to this literature or you must list that drug product as a reference drug product and provide adequate patent certification via the 505(b)(2) pathway.

You also propose to use data from your Phase 3 study. It is not clear whether the collected data will be sufficient to draw conclusions regarding the effects of concomitant medications on the PK of your product. Unless buprenorphine exposure data is available from before and after administration of various 3A4 inhibitors and inducers, it will be difficult to draw a definitive conclusion. Provide additional information on the data collected from the Phase 3 study to date (e.g., lists of 3A4 inducers and inhibitors with identification of weak, moderate and strong induction/inhibition, number patients on each of the inducer/inhibitor, dosing regimen and treatment duration of the 3A4 inhibitor/inducer, availability of blood samples from the patients) to aid in further deliberation on this matter.

If there are patients on RBP-6000 treatment now, we strongly recommend that you collect PK data in the patients who will start or discontinue 3A4 inhibitor/inducer treatment. These data will be very helpful to address this question or confirm the findings.

Discussion:
The Division stated that without thoroughly reviewing all data, it was not possible to confirm whether currently available data will be sufficient to draw conclusions regarding the drug-drug interactions of CYP3A4 inducers or inhibitors with RBP-6000 exposure. Additionally, in the

pre-NDA meeting package, there are insufficient data from the Phase 3 study to understand the number of patients on each inhibitor/inducer, types of inducer/inhibitor used, e.g., strong, moderate, weak inducers/inhibitors, doses and dosing regimens, to characterize the PK (pharmacokinetics) effect of inducers/inhibitors on RBP-6000, especially at the higher proposed doses of RBP-6000. The Division strongly recommended conducting an additional open-label study in patients dosed to steady-state with RBP-6000, with drug levels obtained before and after initiation of strong CYP3A4 inhibitors or inducers.

The Sponsor stated that they have PK data in patients who were concurrently on CYP3A4 inhibitors/inducers in the Phase 3 study and have not found any changes in plasma concentration. Additionally the Sponsor will utilize population PK modeling to further assess drug interactions. The Division stated that data were necessary from the worst-case drug interaction scenario, e.g., strong inducer/inhibitor interactions at steady state concentrations, and would need to review the data in its entirety. If the 3A4 inhibitors/inducers used in the Phase 3 study were not strong inhibitors/inducers, or PK steady-state was not reached, then the data will not be informative. Utilizing population PK modeling may be useful; however, without looking at the overall population PK data, it is difficult to assess the validity. The adequacy of the DDI and population PK data for approval will be determined after review of the data. The Division reiterated that to conduct an additional open label study in patients who are concurrently on strong CYP3A4 inhibitors or inducers is highly recommended.

The Division recommended the Sponsor write a draft label to determine which required sections are still missing critical data, especially the clinical pharmacology section of the label. The Sponsor may use the Probuphine label as an example of the information needed in a modern product label. The Division reiterated that if any part of the label uses literature that references an approved drug, the Sponsor will need to either obtain the right to reference the product or use it as a listed drug product via the 505(b)(2) pathway with adequate patent certifications.

Regulatory

Question 16:

(b) (4) *Does the agency agree with this approach?*

FDA Response to Question 16

If you plan to use literature (e.g., published study involving drug-drug interactions using Butrans) or findings from other NDAs which do not belong to you, your application may become a 505(b)(2). If you plan to utilize information from literature (e.g., Butrans) or approved NDA products and if you have any intention 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). 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 is scientifically appropriate.

Refer to the additional 505(b)(2) information below for more information.

Discussion:

(b) (4)

The Division stated that if the Sponsor is relying on any literature to support the product's NDA, including inactive ingredients (i.e., NMP), excipients, routes of administration, etc., it may be deemed to be a 505(b)(2) application. The Sponsor has to own all the data for the studies conducted and/or obtain the right of reference to the literature used to qualify as a 505(b)(1) application.

The Division also stated that if the Sponsor mentions a brand named product (i.e., Butrans) or a product by its generic name (i.e., buprenorphine) that is not owned by the Sponsor, it may be deemed to be a 505(b)(2) application. The Sponsor will have to patent certify if the literature used refers to a brand named product. A relative bioavailability study is needed to establish a scientific "bridge" between RBP-6000 and the referenced drug used.

Question 17:
Indivior requests clarification on whether this NDA will fall under "The Program" under PDUFA, i.e., is a standard 10-month review to be expected rather than a 12-month "Program" review cycle?

FDA Response to Question 17
"The Program" under PDUFA is for NME NDAs and Original BLAs. Your product is neither. Therefore, "The Program" does not apply to your product.

Discussion:
There was no further discussion of this question.

Question 18:
In the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) published in May 2013, the disease state language is described as Opioid Use Disorder (OUD) as opposed to opioid dependence or addiction.

Subjects were inducted (and briefly maintained) on a buprenorphine sublingual product prior to being transitioned to RBP-6000 in the Phase III double blind study (RB-US-13-0001). Currently marketed buprenorphine products for SL and/or buccal administration are indicated for the treatment or maintenance treatment of opioid dependence. Additionally, some of the newer class labelling language such as the Neonatal Opioid Withdrawal Syndrome (NOWS) related language discusses "addiction" treatment.

In communications regarding the product, understanding that an audience can include patients, healthcare providers and/or formulary representatives, does FDA agree that using terms such as dependence, addiction and OUD are relevant to these communications as appropriate?

FDA Response to Question 18
Because only patients with moderate to severe opioid use disorder based on DSM-5 criteria were studied, when the term "opioid use disorder" is used in communicating about the product, the qualifier "moderate to severe" should be used.

Discussion:
There was no further discussion of this question.

Question 19:
Is the Agency planning to convene an Advisory Committee meeting for this product?

FDA Response to Question 19
We will determine at the time of NDA filing whether there are issues requiring discussion at an Advisory Committee meeting.

Discussion:
There was no further discussion of this question.

ADDITIONAL COMMENTS

CMC:

We suggest you refer to the following guidance documents and regulations for your NDA.

1. **ICH guidance for industry, *"ICH Q3A (R) Impurities in New Drug Substances,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf.**

2. **ICH guidance for industry, *"Q3B (R2) Impurities in New Drug Products,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf**

3. **ICH guidance for industry, *"Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,"* available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm134966.htm**

4. ***"Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070551.pdf**

5. **ICH guidance for industry, *"Q2A Text on Validation of Analytical Procedures,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf.**

6. **ICH guidance for industry, *"Q2B Validation of Analytical Procedures: Methodology,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf.**

7. ***"Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf.**

8. ***"Guidance for Industry Q1A (R2) Stability Testing for New Drug Substances and Products,"* available at** http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf.

9. **Guidance on Elemental Impurities Q3D http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm371025.pdf**

Clinical Pharmacology:

Ensure that you discuss or address the following in the NDA submission:

10. **Because RBP-6000 is a one-month depot product, its dosing regimen may not be easily adjusted between doses, a point which has safety implications in some patient populations, e.g., patients with hepatic and renal impairment. Buprenorphine is highly metabolized and, thus, plasma levels may be higher in patients with moderate to severe impairment. As mentioned in PIND meeting, provide relevant relative bioavailability (as well as safety and efficacy, as appropriate) information for RBP-6000 in hepatic and renally impaired patients and propose dosing recommendations in these patients or a rationale for how proper dosing recommendations can be made in the absence of these data.**

11. **At the May 14, 2013, Type C meeting we alerted you about our concerns regarding** (b) (4)

(b) (4)

12. **With respect to Study RB-US-12-0005, a MAD study, for Cohort 6, it is not clear how may subjects received various Subutex run-in doses, e.g., 8 – 24 mg Subutex run-in doses followed by 300 mg RBP-6000 administration. In the study report, provide information regarding the different Subutex run-in phase doses, number of subjects for each run-in dose, and any other related information. Provide buprenorphine C_{max} and AUC_{0-24} comparisons on Day 1 and Day 2 (a "second peak" was observed from RBP-6000), and, at steady-state, for RBP-6000 and Subutex run-in phases.**

Nonclinical:

13. **If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your NDA that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.**

14. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds must be adequately justified for safety from a toxicological perspective.**

15. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

    a) **You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b) **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90 days should be completed.**

Refer to
Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

c) **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.**

16. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

17. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. The choice of solvents and conditions for the extraction studies should be justified. The**

results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, you should still evaluate at least three batches of your drug product over the course of your stability studies and base the final safety assessment on the levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these leachables may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, refer to the FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf
and the FDA guidance for industry: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070575.pdf.

Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 1.5 mcg/day total daily exposure for a chronic indication or 120 mcg/day for an acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

18. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks adequate safety justification for extractables and leachables.**

19. **Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product in Module 2 of the NDA submission. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.**

20. We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.

21. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.

Controlled Substance Staff

22. In your pre-NDA meeting request letter dated August 5, 2016, you included a question (numbered Question 14) that pertained to a possible (b) (4) claim. Although the question was not ultimately included in your meeting package, we provide the following response for your reference.

Provide a detailed explanation of your intentions with regard to pursuing (b) (4) claims for RBP-6000, including the path forward for obtaining such claims.

Question 14
The FDA guidance – (b) (4)

(b) (4)

(b) (4)

Does the Agency agree?

FDA Response to Question No. (b) (4) **. Any consideration of** (b) (4) **RBP-6000 must await a complete review of all relevant studies included in an NDA submission.**

As noted during the September 30, 2014, End-of-Phase 2 meeting, we encouraged you to provide detailed protocols for review and comment for the category 1 (Tier 1) studies that you proposed to conduct on RBP-6000. It does not appear, however, that these protocols were ever submitted. In addition, it does not appear that results of category 1 testing conducted on the RBP-6000 formulation or simulated depot samples were submitted. If performed, both the methodology and the findings of these studies will have to await review under an NDA submission.

Discussion:
The Division obtained clarification on the Sponsor's intentions regarding the

(b) (4)

ACTION ITEMS

1) The Sponsor will submit integrated safety data as outlined in the discussion section for Question 7b.

2) The Sponsor will look at the drug-drug interaction data regarding CYP 3A4 inhibitors and inducers and submit the data as part of the NDA submission. The adequacy of the data will be determined after review of the data.

3) The Division recommends the Sponsor submit data from the Sponsor's compassionate use/expanded access study as part of the safety database for the NDA submission and not as an amendment.

4) The Sponsor will submit complete datasets, SDTM datasets and analysis datasets for the two legacy studies: RB-US-10-0011 and RB-US-11-0020.

GENERAL COMMENTS

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 Fpediatric patients unless this requirement is waived, deferred, or inapplicable. If 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.

PRESCRIBING INFORMATION

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

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your

pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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.

NARRATIVE SUMMARIES

Narratives summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation/forms, as this adds little value. A valuable narrative summary is written like a discharge summary with a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and sex
- 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
- Pertinent test results (e.g., lab data, ECG data, biopsy data)
- 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

MANUFACTURING FACILITIES

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

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

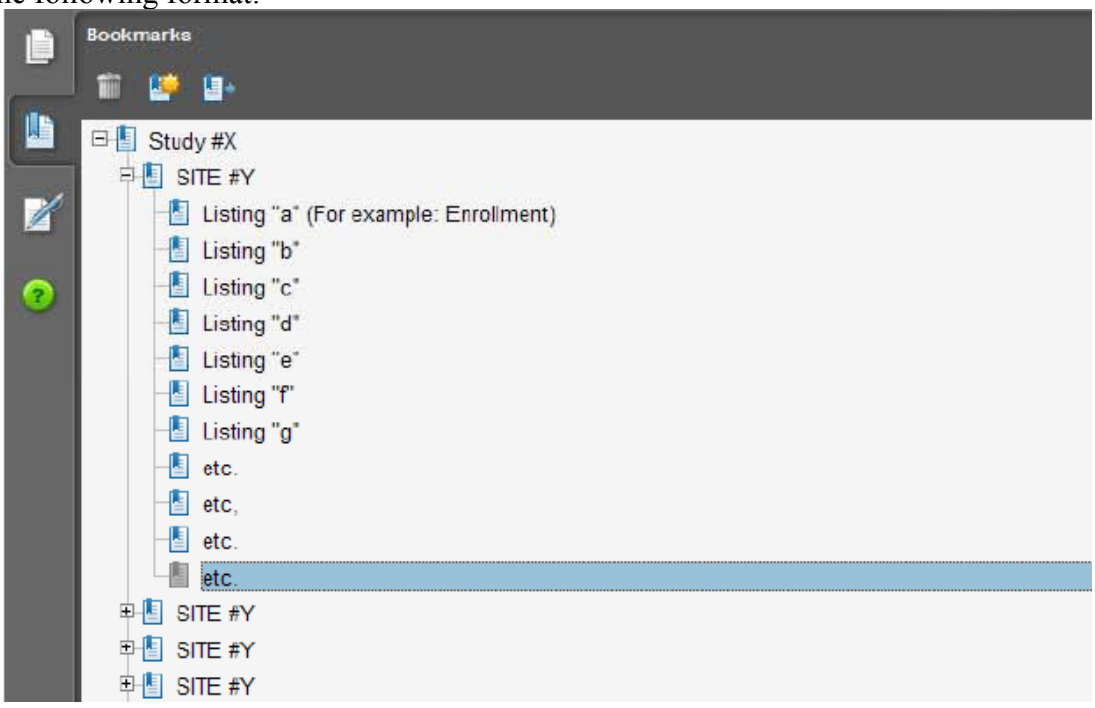
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ATTACHMENTS AND HANDOUTS

Appendix A: Pre-meeting comments from Indivior Inc.

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

/s/

SELMA S KRAFT
01/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107607

MEETING MINUTES

Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Clorey Toombs
Senior Manager, Regulatory Affairs

Dear Ms. Toombs:

Please refer to your Investigational New Drug Application (IND) submitted September 17, 2010, received September 17, 2010, under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for RBP-6000 (buprenorphine ATRIGEL).

We also refer to the meeting between representatives of your firm and the FDA on September 30, 2014. The purpose of the meeting was to discuss your Phase 3 development program for RBP-6000.

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 me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
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:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	Tuesday, September 30, 2014, 12 noon to 1pm
Meeting Location:	White Oak Bldg 22, Room 1313
Application Number:	IND 107607
Product Name:	RBP-6000 (buprenorphine ATRIGEL)
Indication:	Treatment of opioid use disorder
Sponsor/Applicant Name:	Reckitt Benckiser Pharmaceuticals (RBP)
Meeting Chair:	Celia Winchell, MD, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder:	Matthew Sullivan, Supervisory Regulatory Health Project Manager, DAAAP

Sponsor Attendees:	**Title**
Mark Greenwald, PhD	Clinical Consultant
Paul J. Fudala, PhD, RPh	Senior Fellow, Clinical Science
Azmi Nasser, PhD	Global Director, Clinical Development
Emarjola Bako, MD	Medical Advisor
Alex Kouassi, PhD	Director, Biostatistics and Statistical Programming
Celine Laffont, PhD	Senior Manager, Clinical Pharmacology and Translational Medicine
Clorey Toombs, RAC	Senior Manager, Regulatory Affairs
Zacharoula Konsoula, PhD	Nonclinical Scientist
Ju Yang, PhD	Global Director, Regulatory Affairs
Rick Norton, PhD	Director, Formulation Development
Division Attendees:	**Title**
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Rachel Skeete, MD, MHS	Clinical Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
David Lee, PhD	Clinical Pharmacology Reviewer, OCP
Janice Derr, PhD	Biometrics Team Leader, Office of Biostatistics
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Jay Chang, PhD	Acting Pharmacology/Toxicology Team Leader, DAAAP

Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Alan Trachtenberg, MD, MPH	Medical Officer, Controlled Substance Staff (CSS)
Julia Pinto, PhD	Acting Branch Chief, Office of New Drug Quality Assessment
Lisa Skarupa	Regulatory Health Project Manager, Office of Surveillance and Epidemiology
Sarah Arnold, MD, MPH	Medical Officer, DAAAP
Matthew Sullivan, MS	Supervisory Regulatory Health Project Manager, DAAAP

BACKGROUND

On July 8, 2014, Reckitt Benckiser Pharmaceuticals requested an End-of-Phase 2 meeting to discuss their Phase 3 development program for RBP-6000.

The Division granted this meeting, and the Sponsor submitted a meeting package in support of the meeting, on July 30, 2014. The responses to the questions in this meeting package are presented below. Preliminary comments were sent to the Sponsor on September 26, 2014, and they responded on September 29, 2014, with brief written clarifications to a number of questions. These clarifications are included below the question to which they pertain.

The questions from the Sponsor and September 29, 2014, clarifications are in italics, and the Division responses are in bold font. Meeting discussion is in normal font.

DISCUSSION

Question 1 *In the single and repeated dose toxicity studies, apoptosis of pancreatic acinar cells was observed following treatment with RBP-6000. RBP assessed the findings and conducted a literature search related to the cause of the pancreatic cell apoptosis. RBP added additional tests to the clinical studies to monitor pancreatic function. Does FDA agree with the proposed strategy to address the apoptosis of pancreatic acinar cells?*

FDA Response:
As previously discussed, your proposed strategy to address the potential for increased apoptosis of pancreatic acinar cells after treatment with RBP-6000 via clinical monitoring of pancreatic function is acceptable for this stage of your drug development program; however, additional information is required to support your NDA. Based on the existing chronic toxicology study results, it is still not clear whether the increased severity of pancreatic acinar cell degeneration is a spontaneous event or treatment-related. Submit historical control data from the laboratory that conducted the study to put these findings into perspective. In addition, provide data to support your position that these effects may be secondary to stress.

We note that in your chronic rat toxicology study, there was also an apparent increased incidence of alveolar macrophage infiltrates in the lung in treatment groups compared to the vehicle control group. This is perplexing given the route of administration of the drug product used in the study. Provide historical control data for these finding from the conducting laboratory and submit your rationale as to why you feel these findings do not represent safety concerns.

Final determination of the adequacy of these nonclinical general toxicology data to support your NDA can only be provided upon review of the complete NDA submission.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 2 *During the development of RBP-6000, previous findings for buprenorphine and established ATRIGEL products were used in conjunction to determine the toxicology study program. Based on that information, a saline control was omitted from the studies and an ATRIGEL vehicle control was used instead. It is RBP's belief that, based on this information and on the complete findings from the toxicology program, no further studies are warranted. Does the FDA agree?*

FDA Response:
Omission of the recommended saline control arm complicates the interpretation of the pivotal chronic toxicology studies, particularly given the lung and pancreatic findings noted above, and the fact that the levels of N-methyl-2-pyrrolidone (NMP) in your drug product are novel with respect to the dose and different balance of risk and benefit for the indication in the currently FDA-approved drug products. Your NDA must include a detailed toxicological risk assessment to justify the safety of the NMP that addresses all of the standard toxicological endpoints outlined in the FDA guidance to industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. Reliance upon the Agency's previous finding of safety for the Eligard drug product alone will not be adequate as this drug product was approved for advanced prostate cancer and the development programs for such indications are generally limited and may not be complete for this indication.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 3 *RBP has conducted single and repeated dose toxicity studies with RBP-6000 in accordance with the proposed SC route of administration, to confirm the systemic toxicological profile of ATRIGEL delivery system and assess local tolerance. The pharmacological profile of buprenorphine is well established,* (b) (4) *Does FDA agree?*

FDA Response:
As we agreed upon previously, a dedicated carcinogenicity study of RBP-6000 is not required, in part, because there were no preneoplastic lesions observed in chronic rat and dog studies with RBP-6000 and an Atrigel control. However, your NDA must still include a detailed toxicological risk assessment for the components in the Atrigel vehicle to support the safety of the vehicle components as per the FDA guidance to industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf.

At this time, we cannot determine whether additional developmental and reproduction toxicity studies will be required. (b) (4) **At the pre-IND meeting, you expressed plans to submit data or a rationale explaining your position, but this has not yet been submitted. You must address this issue.**

Discussion:
There was no discussion beyond the Division's initial written response.

Question 4 *RBP plans to submit data regarding the evaluation of RBP-6000 in single-dose, repeated-dose and genetic toxicity studies in the NDA filing. RBP was granted a carcinogenicity waiver for RBP-6000 in July 2013. In addition it is planned to reference previous preclinical studies assessing the toxico-pharmacologic profile of buprenorphine which has been well established and is supported by substantial data within the FDA database and in the published literature. Does FDA agree that these data are sufficient to support the approval of RBP-6000 from a preclinical safety perspective?*

FDA Response:
We cannot provide a recommendation that your NDA may be approved from a nonclinical perspective until we review the entire NDA submission. Although your reliance upon the previously completed studies for the buprenorphine drug substance and your completed chronic toxicology studies with the drug product may be adequate to address these aspects of your NDA, as noted in our previous responses, there appear to be

outstanding issues that will have to be addressed in your NDA. The following items must be specifically addressed:

1. **Provide the historical control data for the findings of increased apoptosis of pancreatic acinar cells and incidence of alveolar macrophage infiltrates in the lung of the rat and your justification for why these findings are not treatment-related and adverse. Likewise, provide the data to support your conclusion that the pancreatic findings can be attributed to stress.**

2. **Provide a toxicological risk assessment for the novel use of the excipient NMP in your formulation. In the risk assessment, address what is known regarding the impact of the compound on general toxicity, genetic toxicity, reproductive and developmental toxicity, and carcinogenicity, as per the FDA guidance document referenced above.**

3. **Provide a toxicological risk assessment for the use of the excipient PLGH in your formulation. In the risk assessment, address what is known regarding the impact of the compound on general toxicity, genetic toxicity, reproductive and developmental toxicity, and carcinogenicity, as per the FDA guidance document referenced above.**

4. **Reliance upon a specific FDA-approved drug product to support the safety of these excipients will require adequate patent certification and the product must be listed as a referenced product as part of a 505(b)(2) application. See our additional comments regarding submission of an NDA under section 505(b)(2) at the end of this document.**

5. **The NDA must address the fate of the Atrigel vehicle. Specifically, you must characterize the biostability of the drug product vehicle in vivo via determination of the length of time the material remains in the body, the distribution of the material in the body and the ultimate elimination of the breakdown products of the vehicle.**

6. **In your NDA, include a table that specifically compares the purity profile of the nonclinical batches used in the pivotal toxicology studies to that of the final clinical formulation. If the levels of impurities in the nonclinical batches are lower than the specifications requested, include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed specifications in the clinical batches, and do not represent a safety concern.**

7. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within**

the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:

a. You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90-days duration should be completed.

8. The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.

9. Include a detailed discussion of the nonclinical information in the published literature in your NDA and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Copies of all referenced citations must be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 5 *Does the FDA agree that the following clinical development plan will generate sufficient data to support the approval of, and the proposed indication for, RBP-6000 in the targeted patient population?*

FDA Response:
Your proposed clinical development plan may represent sufficient clinical data to support filing an NDA submission for RBP-6000. Determination of the adequacy of the data for demonstrating safety and efficacy of your product to support approval is a matter for review and will be assessed during NDA review.

It is premature to comment on the proposed indication. However, we note that patients in the Phase 3 trial will undergo induction and titration to a target dose of buprenorphine sublingual (SL) film prior to injection. As such, an indication of maintenance treatment of opioid use disorder may be more appropriate.

RBP Clarification: During the discussion at the RBP-6000 Guidance Meeting held on May 14, 2013, the FDA indicated to RBP that a two-week induction and "stabilization" period is not sufficient to establish responsiveness to and stabilization on the conventional (i.e., sublingual) formulation, and that FDA would not consider that population as "stabilized".

We agree with the FDA and chose the "treatment of opioid use disorder" indication since new entrants to treatment will continue to be stabilized after receiving RBP-6000 as they proceed to "maintenance" treatment. Thus, new entrants to treatment will be receiving more than simply maintenance treatment.

Discussion:
The Division informed the Sponsor that the "treatment of opioid use disorder" indication may imply that RBP-6000 may be used as initial treatment for new entrants to treatment, as with the buprenorphine/naloxone sublingual film product, which now is indicated for "treatment of opioid use disorder." However, prior to the initial RBP-6000 injection, patients are to undergo induction with, and titration to a target dose of, sublingual buprenorphine/naloxone before receiving an RBP-6000 injection. (b) (4) [redacted].
The Division responded the specific wording of how to convey that patients should receive sublingual buprenorphine prior to initiating RBP-6000 therapy, and the location of such wording in labeling, would be discussed as development continues.

Question 6 *Based on FDA feedback, RBP has conducted an opioid blockade study to determine the Phase 3/commercial doses of RBP-6000 and proposes to conduct an adequate and well-controlled Phase 3 efficacy/safety study and a long-term safety study (as described above). RBP believes that the design of the Phase 3 safety and efficacy study will generate sufficient data to assess the efficacy and safety of RBP-6000. Does the FDA agree? With regard to the Phase 3 safety and efficacy study:*

FDA Response:
We recommend some modifications to the design of the Phase 3 safety and efficacy trial. See below for specific recommendations.

RBP Clarification: Does the FDA agree that the subject population is appropriate for the proposed indication?

Discussion:
See discussion under Question 6.a.

a. Does the FDA agree that the subject population is appropriate for the proposed indication?

FDA Response:
You have chosen to enroll new entrants to treatment into the Phase 3 trial which appears appropriate. (b) (4) **The protocol-specified criteria must describe a population that requires such treatment.**

RBP Clarification: Prior to being randomized to receive RBP-6000 or placebo, subjects must meet all of the protocol inclusionary and exclusionary criteria. Additionally, prior to being inducted with sublingual buprenorphine, potential subjects must demonstrate opioid withdrawal as evidenced by a COWS score greater than 12. (b) (4)

Discussion:
(b) (4)

The Division stated (b) (4) that the Sponsor should discuss the proposed protocol with experts in the addiction treatment community to ensure that the inclusion and exclusion criteria will ensure enrollment of only those subjects for whom pharmacologic therapy is warranted. The Division acknowledged that the new DSM-5 criteria are intended to capture a broader population of patients with SUD to facilitate early identification of problem use and early intervention, and therefore, not all those with an SUD diagnosis will be candidates for pharmacologic treatment. The Division granted that the opioid dependence diagnosis in previous DSM iterations that was used to define a population for whom pharmacologic treatment may be appropriate is no longer used, and this change may present some challenges in defining the appropriate

population. The Division advises sponsors to define a population for whom pharmacologic treatment is appropriate, and suggests that the DSM-5 criteria for OUD could be a resource and basis for establishing these criteria. The Division emphasized the need to specify objective eligibility criteria, (b) (4) to ensure that an appropriate population is enrolled, and to define the population for whom RBP-6000 would be appropriate in the clinical setting.

b. Does the FDA agree that the dosages and dosing regimens, including the design and duration of the run-in phase with SUBOXONE sublingual film, are appropriate?

FDA Response:
Based on the available data presented to date, the dosages and dosing regimens, including the design and duration of the run-in phase with buprenorphine sublingual film appear appropriate for evaluation.

Discussion:
There was no discussion beyond the Division's initial written response.

c. Does the FDA agree that the study design and planned statistical methods are appropriate to adequately assess the benefit risk for RBP-6000 for the proposed indication?

FDA Response:
We have some concerns about your proposal to evaluate the CDF of the percentage of urine samples negative for opioids combined with self-reports of illicit opioid use collected from Weeks 1 through 24 across the 3 treatment groups. Although the approach is generally reasonable, it is important that the difference between the treatment groups and placebo be clinically relevant. That is to say, the results should show separation of curves at the right-hand side of the x-axis, where the proportion of negative urine tests is the largest (i.e., subjects are abstinent or near-abstinent). Because of the difficulties inherent in interpretation of this type of analysis, we recommend that you establish a definition for treatment response and treatment failure based on urine toxicology findings and self-report of opioid use. Definitions of "treatment failure" might be based on criteria that would warrant use of rescue medication or transfer to more intensive treatment. Definitions of "treatment success" could be based on drug use patterns towards the end of the study, to give patients time to engage in treatment and attain abstinence.

RBP Clarification: In order to address the concern for a clinically relevant analysis, we agree to replace the key secondary endpoint with a clinically meaningful parameter of treatment success. This will be defined as four consecutive weeks of abstinence between weeks five and twenty-four as measured by urine samples negative for opioids. The

percent rate of success will be compared between the active and placebo groups by a chi-square test.

A difference of at least 15% found between active and placebo would be considered clinically meaningful.

Discussion:
The Sponsor stated that they would adopt the key secondary endpoint of 4-week treatment success. The Division inquired if there was any specific justification for using 4 weeks as a clinically meaningful measure, to which the Sponsor replied that they were not aware of any. The Division also asked if any four-week consecutive period of abstinence would be considered treatment success, to which the Sponsor replied that it would. The Division voiced concerns with defining any four-week period between Week 5 and Week 24 as success, given that the timing of the four-week period within the ascertainment window has implications for defining treatment success. For example, a subject demonstrating four weeks of "transitory abstinence" early on during a 24-week trial, but who subsequently goes on to have a number of weeks of illicit opioid use should not be considered a treatment success. The Division stated that the final four weeks of the study make a more compelling window during which abstinence should be measured, but acknowledged that it may be difficult to demonstrate.

The Sponsor noted that they were basing the proposed one-month sustained abstinence endpoint, in part, on a published study. The Division requested that the Sponsor submit their protocol with supportive justification of the clinical benefit of this endpoint. The Division also noted that a "treatment failure" may be more easily defined, and that the Sponsor may wish to consider using that endpoint instead.

The Sponsor clarified that their primary endpoint would remain unchanged. The Division responded that a responder curve is acceptable on a conceptual level, but can be problematic to interpret. As is the case for the proposed key secondary endpoint, the same applies for the primary endpoint, in that abstinence demonstrated toward the end of the ascertainment window, rather than only early in treatment, is considered more compelling. For example, a subject demonstrating, for example, five weeks of "transitory abstinence" early on during a 24-week trial, but who later has a number of weeks of illicit opioid use should not be considered a "win."

A suitable, clinically- and pharmacologically- justified "grace period" to engage patients in treatment would be allowed to be incorporated in the analysis. Data from the "grace period" are not included in the analysis.

RBP Clarification: The grace period will be the four weeks after the first injection of RBP-6000.

(b) (4)

We do not agree with the proposal (b) (4) **Our concern is with the validity of the statistical comparisons between the active and control arms, in the event that all patients are not allocated at random to the study arms. We recommend that subjects who withdraw from the study during the double-blind period be classified as "failures" for purposes of the primary efficacy analysis.**

RBP Clarification: (b) (4) *This will be further clarified in the protocol.*

We advise you to consider whether decreasing the frequency of urine testing (potentially collecting urine samples weekly rather than thrice weekly, particularly during any part of the study considered a "grace period") might improve study retention and, thereby, minimize missing data and the need for replacement of subjects.

RBP Clarification: We plan to collect urine samples once weekly. This will be consistently reflected in the protocol.

We agree with the proposed analysis for the primary and key secondary efficacy endpoints, including the approach to missing urine samples and self-reports. However, if the primary efficacy endpoint and/or the key secondary efficacy endpoints will be modified, then the analysis methods will also need to be modified accordingly.

We agree with the proposed approach to multiplicity in the hypothesis tests for the primary and key secondary efficacy endpoints.

See also the response below regarding proposed outcome measures.

d. *Does the FDA agree that the proposed outcome measures are adequate to assess the efficacy and safety of RBP-6000?*

FDA Response:
See our response to Question 6.c. above regarding the proposed primary outcome measure.

You propose " [redacted] (b) (4) **as the key secondary endpoint. However, we are not aware of an evidence base that establishes** [redacted] (b) (4) **, and, in turn, would permit appropriate interpretation of these data. In order to use this endpoint, you must provide appropriate validation.**

Note that the literature on "craving" in addiction suggests that the term "craving" is not a well-defined concept, having different meanings to different patients, as well as different meanings to clinicians as compared to patients. As such, we are not confident that the term "craving" is sufficiently well-defined to serve as, or support, any medical product claim.

Finally, it is unlikely that the other proposed secondary or exploratory endpoints will be appropriate to support medical claims. Instead, these will provide supportive data.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 7 *RBP proposes that all eligible subjects who completed the Phase 3 double-blind study will be given the option to participate in a long-term safety study, in which they will receive the highest tested dose of RBP-6000 (300 mg). Dose adjustments will be allowed during the safety study. RBP believes that the safety data collected from these 2 studies are adequate to demonstrate the long-term safety of RBP-6000. Does the FDA agree?*

FDA Response:
You will need to ensure that your safety database contains a sufficient number of exposures to adequately characterize the local tolerability of your product and systemic safety of buprenorphine in this new formulation. We recommend a safety database of at least 500 patients treated with RBP-6000 for at least six months, and approximately 100 patients treated for at least one year.

Given that RBP-6000 is expected to be used chronically, provide data on long-term use with respect to rotation of sites and the effect of returning to previously-used sites. Specifically, evaluate the impact that any scarring that may develop in the context of repeated injections may have on safety and efficacy (due to changes in plasma exposure as a result of scarring) of your product.

RBP Clarification: RBP plans to characterize the safety profile of RBP-6000 based on the studies performed throughout the development program. As part of the Phase 3 study,

we plan to roll patients from the double-blind efficacy study into the long term safety study. For this reason, we plan to randomize approximately 470 subjects to have 6 months safety data for at least 300 patients on active treatment. Since the safety profile of buprenorphine has been extensively characterized, and based on the available safety data of RBP-6000 to date, we believe this cumulative data will be enough to allow for the risk benefit assessment at the time of submission. Does the FDA agree?

Discussion:
The Sponsor stated that they intend to include 470 patients who have had any RBP-6000 exposure, 300 patients treated with RBP-6000 for at least six months, and approximately 100 patients treated for at least one year in their safety database. The Division noted that the recommended size for the safety database, namely 500 patients treated with RBP-6000 for at least six months, and approximately 100 patients treated for at least one year, is a guideline for the safety database. Because the safety profile of buprenorphine, the active ingredient, is considered to be well-characterized, the safety database proposed by the Sponsor could potentially provide sufficient information to allow for a risk-benefit assessment. However, Atrigel, the RBP-6000 vehicle, has only been used in approved dental products and for palliative treatment for prostate cancer. Accordingly, an Agency finding of safety for a product indicated for advanced prostate cancer cannot be extrapolated to this drug product due to the very different risk:benefit profile.

The Division inquired about the studies noted by the Sponsor comparing the vehicle to saline, and the Sponsor replied that studies of four weeks and three months duration have been completed. The Division also inquired if the nonclinical studies comparing saline to the Atrigel vehicle have been submitted to the IND file. The Sponsor responded that they had not, and that they were only intending to submit them with the NDA. The Division recommended that the Sponsor submit them to the IND for evaluation so that a determination as to their adequacy can be made in advance of the NDA submission.

The Division stated that the 300 patients represented a minimum number, and that safety issues may arise which would necessitate an increase in the safety database. The Division noted that there are concerns about pancreatic apoptosis, and although pancreatic enzymes are being evaluated, pancreatic enzyme levels were not evaluated in the animal studies to determine if there is any correlation between the observed apoptosis and pancreatic enzyme levels. Additionally, there are concerns about alveolar macrophage infiltration. In order to ensure that the safety database is appropriately sized, the Division recommends that the Sponsor include 500 patients treated with RBP-6000 for at least six months.

Question 8 *RBP believes that the PK studies being conducted, in addition to the PK modeling and simulation data, will provide adequate data to support an NDA for RBP-6000. RBP also believes that the data are adequate to address the PK-related questions raised by the FDA. Does the FDA agree?*

FDA Response:
Your proposed PK studies and modeling/simulation data may be sufficient to support a complete clinical pharmacology package for RBP-6000 NDA submission. Determination of the adequacy of the data to support approval is a matter for review and will be assessed during NDA review.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 9 *In the MD PK and PD study referenced above, subjects were transitioned from 8 mg sublingual buprenorphine to 50 mg RBP-6000, from 12 mg sublingual buprenorphine to 100 mg RBP-6000, from 8 mg sublingual buprenorphine to 100 mg RBP-6000, from 14 mg sublingual buprenorphine to 200 mg RBP-6000, from 24 mg sublingual buprenorphine to 200 mg RBP-6000, and from 8-24 mg sublingual buprenorphine to 300 mg RBP-6000.* (b) (4) .
Does the FDA agree?

FDA Response:
You can utilize PK, modeling, and simulation information to support dose selection as well as the transition from sublingual buprenorphine in your Phase 3 trials and overall RBP-6000 drug development. However, the information in the label describing transition of patients from sublingual buprenorphine to RBP-6000 should mainly come from the efficacy and safety data in your Phase 3 trials.

Provide a thorough summary of screen failure based on initial eligibility requirements, and randomization screen failure.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 10 *RBP has previously agreed to conduct a thorough QTC prolongation assessment study with buprenorphine as part of a postmarketing commitment for SUBOXONE sublingual film, and RBP intends to request a Type C meeting with the FDA to discuss appropriate designs for this study. RBP believes that data from this buprenorphine QTC prolongation assessment study, in combination with ECG monitoring in the Phase 3 clinical study, will be adequate to assess the potential risk of QTC prolongation associated with RBP-6000. Does the FDA agree?*

FDA Response:
A thorough QT assessment with Suboxone sublingual film may provide potential data for risk evaluation of QTc prolongation with your new RBP-6000 formulation. A thorough QT (tQT) study with the RBP-6000 formulation may not be needed if you can provide adequate justification why the results from Suboxone sublingual film can be applied to RBP-6000 formulation, taking into consideration factors such as the final approved dosing regimen of RBP-6000, the final study design and results of the tQT study of Suboxone sublingual film, etc. You can submit the 'revised' tQT study for Suboxone sublingual film and seek the Agency's feedback. As there is evidence that buprenorphine may cause QT prolongation, you must propose adequate ECG monitoring in the Phase 3 clinical study.

Discussion:
There was no discussion beyond the Division's initial written response.

Question 11 *In accordance with the FDA draft guidance document* [redacted] (b) (4) *Does the FDA agree that the data that will be collected from the in vitro and in vivo studies will support a claim that RBP-6000* [redacted] (b) (4) *?*

FDA Response:
The product delivery system involves a depot injectable formulation. To [redacted] (b) (4) [redacted] (b) (4) **The adequacy of the information, including methodology and final results, will be determined during the NDA review.**

Discussion:
There was no discussion beyond the Division's initial written response.

Additional Clinical Comments:

1. **Establish a mechanism by which to ensure that there is no unmasking of treatment assignment for patients based on the volume of injection / size of syringe, specifically during months 3–6 of the Phase 3 trial when patients randomized to the 300 mg x 2 & 100 mg x 4 arm or corresponding placebo arm, receive the 100 mg dose from the syringe specific to that dose.**
2. **Separate induration from swelling on the injection site grading scale.**
3. **Withdrawal signs and symptoms must be fully characterized throughout the duration of all studies.**
4. **A human factors usability evaluation may be required for this drug-device combination.**

RBP Clarification: We believe the collection of SOWS and COWS throughout the duration of the study will sufficiently characterize the profile of withdrawal signs and symptoms.

Discussion:
The Sponsor stated that they will collect both COWS and SOWS throughout the study, from before induction to study completion. The Division concurred with this approach.

Action Items:

1. The Sponsor agreed that the labeling for RBP-6000 will describe that it is to be used after induction on sublingual buprenorphine.
2. The Division encouraged the Sponsor to seek expert opinion in crafting their inclusion and exclusion criteria to ensure that all enrolled subjects are appropriate for pharmacologic therapy. OUD in the DSM-5 is a general and broad term, with a low threshold for meeting diagnostic criteria, intended to catch early-phase problem use. RBP-6000 will not be appropriate for all patients meeting DSM-5 criteria for OUD. The Sponsor will need to make sure the label reflects the appropriate population for RBP-6000 treatment.
3. The Sponsor will modify their key secondary endpoint, likely to be 4-week treatment success. They will submit a justification supporting the clinical benefit of the selected endpoint. For the primary endpoint, it may be more prudent to define treatment failure rather than treatment success. The Sponsor should provide justification for the proposed definition of treatment failure and/or treatment success. Sustained four-week periods of abstinence are more compelling at the end of the ascertainment window.
4. The Sponsor will submit the 4-week and 3-month toxicology studies comparing saline to the drug product vehicle. The Sponsor understands that a previous finding of safety for the

drug product vehicle Atrigel for use in a drug product approved for advance prostate cancer is not adequate to support the safety of the novel excipient for their drug product. They will provide a complete toxicological risk assessment for the components of this novel excipient.

5. The Division will endeavor to review nonclinical studies submitted to the IND, and provide comments to the Sponsor as applicable. The nonclinical data have implications for the size of the safety database. The buprenorphine safety profile has been well-characterized, but although Atrigel is a component of approved products, none of these products have been used in a similar fashion to its proposed use in OUD, and the safety of Atrigel may need to be further evaluated. As such, for the clinical safety database, 300 is the absolute minimum for six months, and the Sponsor was encouraged to increase the size of the safety database to 500.
6. The Sponsor will assess the COWS and SOWS scores throughout the study.
7. The Sponsor informed the Division of plans to submit a draft REMS in mid-year 2015, and request comment to receive feedback on the proposed REMS prior to NDA submission.
8. The Sponsor will provide full in vitro protocols to get feedback and determine if the protocols will provide sufficient data to support (b) (4).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 this drug product for this indication has an orphan drug designation, you are exempt from these requirements. 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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.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, in part, 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, in part, 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. trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X*

3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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/

MATTHEW W SULLIVAN
10/23/2014