CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114082

MEETING MINUTES

Braeburn Pharmaceuticals, Inc.
47 Hulfish Street, Suite #441
Princeton, NJ 08542

Attention: Frank E. Young, MD, PhD
EVP, Regulatory and Medical

Dear Dr. Young:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for CAM2038 (buprenorphine) injection.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2017. The purpose of the meeting was to discuss your proposed New Drug Application for CAM2038.

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) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 5180929

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:	March 16, 2017, 3:00 to 4:00 p.m.
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1315 Silver Spring, Maryland 20903
Application Number:	IND 114082
Product Name:	CAM2038 q1w buprenorphine SC injection CAM2038 q4w buprenorphine SC injection
Indication:	Treatment of opioid dependence and as part of a complete treatment plan to include counseling and psychosocial support
Sponsor/Applicant Name:	Braeburn Pharmaceuticals, Inc.
Meeting Chair:	Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Meeting Recorder:	Swati Patwardhan, Regulatory Project Manager, DAAAP

FDA ATTENDEES

- Sharon Hertz, MD, Director, DAAAP (on phone)
- Rigoberto Roca, MD, Deputy Director, DAAAP
- Celia Winchell, MD, Clinical Team Leader, DAAAP
- Emily Deng, MD, Clinical Reviewer, DAAAP
- Gioia Guerrieri, MD, Clinical Reviewer, DAAAP
- Dan Mellon, PhD, Pharmacology/Toxicology Supervisor, DAAAP
- Jay Chang, PhD, Pharmacology/Toxicology Team Leader, DAAAP
- Gary Bond, PhD, Pharmacology/Toxicology Reviewer, DAAAP
- Yun Xu, PhD, Team Leader, Division of Clinical Pharmacology II (DCP-II) (on phone)
- Suresh Naraharisetti, PhD, Clinical Pharmacology Reviewer, DCP-II
- David Petullo MS, Lead Mathematical Statistician, Office of Biostatistics (OB), Division of Biostatistics II (DBII),
- Feng Li, PhD, Statistician, OB, DBII
- Lars Johannesen, PhD, Clinical Pharmacology Reviewer, DCP I
- Selena Ready, PharmD, Risk Management Analyst, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology(OSE)

- Kimberly Lehrfeld, PharmD, Team Leader, DRISK, OSE
- Mathew Davis, PharmD, Safety Regulatory Project Manager, DRISK, OSE (on phone)
- Millie Shah, PharmD, Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA), OSE (on phone)
- Valerie Wilson, PharmD, Safety Evaluator, DMEPA, OSE
- Swati Patwardhan, Regulatory Project Manager, DAAAP

SPONSOR ATTENDEES

- Behshad Sheldon, President and Chief Executive Officer (CEO), Braeburn Pharmaceuticals
- Fredrik Tiberg, PhD, President and CEO, Camurus
- Serena Kim, PharmD, Sr. Vice President, Clinical Development and Medical Affairs, Braeburn Pharmaceuticals
- Frank E. Young, MD, PhD, Executive Vice President, Clinical and Regulatory Affairs, Braeburn Pharmaceuticals
- Sheila A. Mathias, JD, PhD, Sr. Director Regulatory Affairs, Braeburn Pharmaceuticals
- Mathews Adera, MD, PhD, Executive Director, Clinical Development, Braeburn Pharmaceuticals
- (b) (4) Consulting Toxicologist
- (b) (4) Statistical and Database Consultant to Braeburn, (b) (4)
- (b) (4)
- (b) (4)
- Sonia J. Oosman, MS, Director of Clinical Operations, Braeburn Pharmaceuticals
- Reed Brady, Vice President, Quality and Compliance, Braeburn Pharmaceuticals

BACKGROUND

The Sponsor, Braeburn Pharmaceuticals, is developing CAM2038 (buprenorphine) injection depot for the treatment of opioid dependence and as part of a complete treatment plan to include counseling and psychosocial support. A Pre-IND meeting was held in February 2015 to discuss their Phase 3 development program and an IND was submitted in April 2015.

The Sponsor submitted a Pre-NDA meeting request on October 12, 2016, which was granted and scheduled for March 16, 2017. A briefing package was received on February 15, 2017. The objective for the Pre-NDA meeting was to discuss the proposed NDA submission and resolve any remaining questions necessary for the NDA submission.

FDA sent Preliminary Comments to Braeburn on March 13, 2017.

DISCUSSION

The questions from the February 16, 2017, briefing package are reproduced below in *italic font,* the Division's responses are in bold font, and the meeting discussion is in normal font.

Prior to the meeting, the Sponsor communicated that they would like to focus on the preliminary responses to Questions 4, 5, 6, 7, and 8, as well as the additional statistical comment 14. Handouts were provided on March 16, 2017, to facilitate the discussion, which are included at the end of the minutes.

Question 1:

Context: Following the Nonclinical Hold issues raised by the Division (IND 114082, Clinical Hold Letter, July 9, 2015), the Sponsor has conducted a chronic (9-month) subcutaneous repeat- dose toxicology study in the dog with the CAM2038 q1w and CAM2038 q4w product, and included the relevant vehicles for each drug product. The study provides adequate clinical coverage for the CAM2038 products, as well as of the excipient glycerol dioleate (GDO) and (b) (4) *N-2-methyl pyrrolidone (NMP). The chronic study also includes characterization of the local injection site reactions, including assessments of multiple injections into the same injection site.*

The Sponsor submits that the toxicity and local tolerability data for the CAM2038 products from this pivotal 9-month study in dogs recommended by the Agency, in addition to the substantial toxicity and local tolerability data from 8-week and 18-week toxicity studies in dogs, supported by studies in rodents provide adequate characterization of the toxicity and the local injection site tolerability for the CAM2038 drug products to bridge to the data for buprenorphine are sufficient to support the market registration of the CAM2038 product.

Question: Does the Agency concur that the Sponsor has addressed the concerns raised by the Division?

FDA Response:

Your nonclinical program appears to lack a chronic 6-month repeat-dose toxicity study in rodents as noted in our Clinical Hold letter dated July 9, 2015, and the longest repeat-dose general toxicity studies described in the submitted literature-based toxicological risk assessment for NMP appear to be only 90 days in duration. However, we acknowledge that the risk assessment did include references to long-term carcinogenicity studies with NMP in rats and mice, which represent reviewable entities that may adequately address the potential toxic effects of repeated exposure to NMP in a rodent model. Therefore, based on the studies described in your meeting package and our preliminary review of the literature-based toxicological risk assessments for the excipients GDO and NMP, it appears that your nonclinical program would be adequate to support submission of your NDA. It is important to note that published literature to support the safety of excipients rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation. Importantly, the adequacy of all 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.

Meeting Discussion:

There was no discussion at the meeting.

Question 2:

Context: The Sponsor has presented data generated for the excipient glycerol dioleate (GDO) by toxicokinetic assessments of subcutaneous administration of GDO in rat; short-term and chronic (6-months) subcutaneous toxicity in rat; in vitro and in vivo genotoxicity data; pre- and post- natal developmental (PPND) data in rat. In Addition the Sponsor will rely on extensive published literature data to address the carcinogenicity potential of GDO to support the clinical use of GDO in the CAM2038 products. Finally a PPND study was conducted in response to the Division's concern about on reproductive toxicity of GDO in the Nonclinical Hold (IND 114082, Clinical Hold Letter, July 9, 2015). A thorough and comprehensive risk assessment report has been compiled to address the use of GDO in the CAM2038 drug products based on these available data.

Question: Does the Agency concur that the Sponsor has addressed the concerns raised by the Division?

FDA Response:

As noted in our response to Question 1, it appears that the nonclinical studies and literature on GDO described in your meeting package would be adequate to support submission of the NDA. However, 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.

Meeting Discussion:

There was no discussion at the meeting.

Question 3:

Context: The Sponsor has assembled the short-term toxicity and toxicokinetic studies of subcutaneous administration of (b) (4) *N-methyl-2-pyrrolidone (NMP) in rat and rabbits, as well pharmacokinetic data for NMP for human administration of CAM2038 q4w to provide an adequate data to bridge to available literature safety data for NMP to support the clinical use of the CAM2038 products.*

Question: Does the Agency concur?

FDA Response:

We agree that generation of nonclinical subcutaneous (SC) exposure data in order to provide a scientific bridge to referenced nonclinical toxicology data from the literature (that is not by the SC route) may be useful. As noted previously, final determination of the value of the literature data to support approval of your NDA review can only be accomplished following review of your NDA submission.

Meeting Discussion:

There was no discussion at the meeting.

Question 4:

Context: The Sponsor submitted on August 16, 2016 two inter-related questions about the ISS to the Division. The Table presented in the briefing package presents an overview of the studies conducted during the clinical development of CAM2038.

Background:

- *Studies HS-11-426 and HS-13-487 are Phase 1 studies conducted in normal healthy volunteers under naltrexone blockade.*
- *HS-07-307 and HS-13-478 are short term studies (1 & 2 wk. exposure, respectively) in adults with opioid use disorder*
- *Studies HS-11-421, HS-14-499 and HS-15-549 are long-term outpatient studies (6 months, 12 months, and 4 months exposure, respectively), in opioid dependent subjects.*

Question: To simplify the coding and the analysis of the ISS, the Sponsor proposes to submit the ISS using the following pooling strategy. Healthy volunteer studies (HS-11-426 and HS-13-487) would be pooled. Short-term studies in opioid dependent subjects (HS-07-307 and HS-13-478) would be pooled. Study HS-15-549 includes subjects with chronic non-cancer pain with history of opioid dependence, which the Sponsor believes is similar enough with the two long-term studies, therefore should be pooled with these long-term studies. Lastly, long-term studies (HS-11-421, HS-14-499, and HS-15-549) would be pooled. Does the Agency concur?

Additionally, the Sponsor plans to use SDTM v 3.1.3 for the NDA. Does the Agency concur?

FDA Response:

Your plan to use SDTM v3.1.3 for your NDA submission appears to be appropriate. However, we do not agree with your data pooling strategy.

1. **Ensure that the ISS includes analyses and discussion of the q1w and q4w injections both separately and pooled together.**
2. **Integrate the safety data in the following pools:**

- **Phase I naltrexone blockade studies (HS-11-426 and HS-13-487)**
- **Single dose escalation study (HS-07-307)**
- **Phase II multiple dose opioid challenge study (HS-13-478)**
- **Phase II multiple dose open label study (HS-15-549)**
- **Phase III studies (HS-11-421 and HS-14-499)**
- **Multiple dose open label studies (HS-15-549 and HS-14-499)**
- **Phase III double blind study (HS-11-421)**
- **Phase III open label study (HS-14-499)**

3. **Studies on subjects with opioid dependence should be pooled in analyses of SAEs, non-serious severe adverse events, adverse events leading to drop outs, laboratory effects, and EKG effects.**
4. **For analysis of injection site reactions, studies in healthy volunteers should be integrated into the analysis and the analysis should take into consideration the number of injections, doses used, and anatomical locations.**

Additional comments for safety datasets:

1. **Your NDA submission must include an adequate number of patients who have been exposed at the dose (or dose range) believed to be efficacious to characterize the safety. The predicted systemic exposure (steady state C_{max} and $C_{average}$) of CAM2038 160 mg is higher than the highest labeled dose of your intended reference product (Subutex). Therefore, your safety database must include adequate exposure to characterize the safety of CAM2038 160 mg for at least one year. Additionally, you must include an adequate number of patients who have been exposed to CAM2038 weekly injections at the maximum dose (32 mg) and maximum labeled duration to characterize the tolerability of local injection toxicity.**

   Because it appears that the number of patients exposed to the maximum doses may be quite limited, your submission should include a discussion of how the safety of the maximum doses may be supported by information about the systemic safety of buprenorphine at comparable exposures, and by the local safety experience with lower doses of your depot products.

2. **In your ISS, provide overall number of exposures, overall duration of exposure, number of exposures by dose, and number of exposures by dose and duration. For CAM 2038 q1w products, provide your tabulations of number of cumulative exposure doses by duration in weeks. For CAM 2038 q4w products, tabulation should break out the cumulative exposure in four-week intervals (e.g., at least 4 weeks, at least 8 weeks, etc.). Note that exposure times should be expressed in weeks, not months or years. If terms such as "one year" or "six months" are used, these should correspond to the commonly-understood definitions of these time frames, i.e., "one year" = 52 weeks.**

3. **For the pivotal safety and efficacy study HS-11-421, subgroup safety data analysis should be conducted by comparing the corresponding doses of CAM2038 and SL BPN using the conversion table to be provided in your labeling.**

4. **Provide case report forms (CRFs) and narrative summaries for deaths, serious adverse reactions, severe adverse events and dropouts due to adverse events ("adverse dropouts"). Guidelines for narrative summary content is provided in the FDA guidance for industry: *Premarket Risk Assessment* available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126958.pdf Narratives should provide enough detail to permit an adequate understanding of the AE.**

5. **All non-serious adverse events (e.g., symptoms, injection site reactions, vital signs, EKG parameters, lab values) need to be graded properly. Provide the toxicity grading scale that describes how you define mild, moderate and severe adverse events.**

6. **The adverse event datasets must contain verbatim terms and lower level terms (LLTs) as well as preferred terms (PTs).**

7. **Provide clear documentation of patient disposition including patients who discontinued for reasons such as "withdrawal by subjects" and "investigator judgment" to provide insight into the underlying reasons these subjects were withdrawn.**

8. **Provide information on the timing of discontinuations, focusing on discontinuations during the first week (treatment initiation). Also provide tabulations differentiating between discontinuations during Phase 1 and Phase 2 of the study.**

Meeting Discussion:

The Sponsor agreed to pool the safety data as recommended by the Division.

Regarding Additional Comment 1, the Sponsor stated that the drug exposure for the weekly product at the 32 mg dose is comparable to the exposure with the sublingual (SL) reference product at 24 mg. However, the exposure with the monthly product dosed at 160 mg exceeds that level of exposure, so additional information will be provided to support it. The Sponsor clarified that a total of only 47 patients were exposed to the 160 mg monthly dose, and this included subjects in the PK study. (b) (4)

To provide support for the local tolerability of the 32 mg weekly and 160 mg monthly doses, the Sponsor plans to provide a comparison of injection site reactions at these doses with those at lower doses. The Sponsor stated (b) (4) The Division did not agree with the Sponsor's rationale (b) (4) The local injection tolerability is also be dependent on the concentration of the API and other excipients.

The Sponsor also plans to submit safety and local tolerability data from the healthy volunteer study, which used doses up to 192 mg weekly, as well as from Phase 3 studies with flexible dosing. Additionally, the Sponsor intends to rely on nonclinical data from the 9-month repeat-dose subcutaneous dog study to support the safety of the clinical doses of 32 mg weekly and 160 mg monthly.

The Division cautioned that if the human PK studies show that systemic exposure levels from the CAM2038 products exceed the reference product, then toxicity data of adequate duration in 2 species will be required to support the systemic safety of the product. The Sponsor noted that they have (b) (4) study data (b) (4) and inquired if this would be acceptable to fulfill the second species requirement if needed.

The Division responded that the (b) (4) data would need to be reviewed to determine if it would provide support for the systemic safety of buprenorphine with respect to the highest doses of the CAM2038 products.

The Sponsor was informed that they need to provide a rationale for how re-injection would affect the PK profile if the drug product is injected into the same exact site. The Sponsor responded that they have 8-week human PK data and that they have conducted similar studies in animals. They envision providing diagrams to assist practitioners in avoiding previously-injected sites. The Division noted that animal data may be supportive but felt that clinical data would be needed. The Sponsor explained that it is difficult to mimic re-injection into the same exact site in humans since the dose volumes are so small. The Division told the Sponsor to provide rationale on how and why these studies could not be conducted in humans.

Regarding the Division's request that the Sponsor provide information on the timing of discontinuations (Additional Comment 8), the Sponsor provided a sample table of study retention (Slide 5, attachment), illustrating the proportion of patients retained through the end of Week 1, the end of Phase 1, and the end of Phase 2 and asked for comments. The Division responded that although the tabulation was, in general, what we were interested in, we would like to see it broken down by doses for both the products, as we seek to discern any patterns with respect to time of dropout across the different doses. For example, early (Week 1) dropout in patients on higher doses of the depots could relate to precipitated withdrawal; dropout in later phases in patients on lower doses might relate to inadequate dosing. Tabulations in the NDA

should allow for comparison of low as well as high dose of sublingual buprenorphine with corresponding low and high dose of CAM2038.

Post-meeting note:
With respect to Additional Comment 4, narratives and CRFs are not required for severe AEs that do not meet criteria for seriousness. However, the Division may request additional information on individual cases during the course of the review.

Question 5:

Context: Reference is made to the Sponsor's response submissions Sequence 0047 (Sept 22nd), Sequence 0059 (Oct 25), Sequence 0068 (Dec 14), and Sequence 0077 (Feb8) in regards to the QT-prolonging effects of buprenorphine and CAM2038. The Sponsor notes that the lack of QT- prolonging effect across all the studies including short and long term studies in patients with opioid use disorder suggest that the QT-associated risk for CAM2038 at the doses and regimens studied is likely to be low to very low. Additionally, there is no indication from the clinical data that the risk of QT prolongation is likely to be significantly different or higher than that posed by the reference listed drug. During the Agency-Sponsor TC on February 06, 2017, the Agency indicated that the results of the HS-15-549 study could be used to support the sponsor's request for a TQT waiver.

In view of the overall cardiac safety profile and the lack of a QT-prolongation signal from the CAM2038 clinical development program, and consistent with the requirements for other *buprenorphine approved products, the sponsor believes it is reasonable to request a waiver from the requirement to perform a TQT study and submit existing robust data from HS-15-549. As such the sponsor does not plan to conduct a TQT study prior to marketing approval.*

Question: Does the Agency concur?

FDA Response:

While Study HS-15-549 appears to provide an opportunity for the assessment of the exposure-response relationship for QTc at clinically relevant concentrations, we have some concerns about the quality of the data collected. Whether or not the study will be interpretable will be a review issue. In addition, we want to encourage you to generate more complete in vitro ion channel data on the major cardiac ionic currents (e.g., hERG, L-type calcium, sodium [peak and late], and I_{ks}) for buprenorphine (as well as any major metabolites) and naltrexone. This information could help with the interpretation of the study results from HS-15-549.

Meeting Discussion:

The Sponsor agreed to provide additional in vitro data as suggested and asked for clarification from the Division about whether or not it would be necessary to perform central reading of the paper ECGs from the HS-15-549 study. The Division stated that they did not anticipate that a central reading of the paper ECGs from Study HS-15-549 would be informative.

Post-meeting note:

Concerning our recommendation for the generation of more complete in vitro data, we intended to communicate that this should include the assessment on multiple cardiac ion currents (e.g., hERG, sodium [peak and late], L-type calcium and I_{ks}). An assessment of just one current, e.g. the hERG potassium current, is likely to be of limited utility and we encourage a more complete assessment on multiple cardiac ionic currents to help with the interpretation of your study results. As stated above, this assessment should include buprenorphine, any major metabolites and naltrexone.

If you plan on conducting non-GLP study(ies) we recommend that you delineate in your study report(s) how the study does not meet GLP standards and that you retain good documentation for study and data verification if FDA were to inspect the facility. In addition, we recommend that you include a positive control in each experiment at a concentration near its anticipated IC_{50}.

Question 6:

Context: Buprenorphine is metabolized to norbuprenorphine primarily by CYP3A4. The Sponsor acknowledges the potential for interaction with CYP3A4 inhibitors and CYP3A4 inducers which could lead, respectively, to increased Buprenorphine concentrations, or decreased plasma concentrations and a lack of efficacy. The effects of co-administered inducers or inhibitors have been established in studies using trans-mucosal buprenorphine products. It is conceivable that the effects may be dependent on the route of administration. The Sponsor believes that the route of administration of CAM2038 which bypasses the First Pass Effect is likely to mitigate the effect of Drug-Drug interactions with CYP3A4 inducers and inhibitors.
Physiologically based pharmacokinetic modeling reports have been utilized for FDA submissions, including for new drug applications. Therefore, in lieu of a DDI study, the Sponsor proposes to utilize physiologically based pharmacokinetic modeling and simulations as described by Zhou et. al (Clinical pharmacology & Therapeutics vol. 92, pages 17-20, 2012) and using guidance from the FDA (Physiologically Based Pharmacokinetic Analyses – Format and Content, 2016) to provide information and data on the impact of CYP3A4 inhibitors and inducers to guide appropriate labeling for CAM2038.

Question: Does the Agency concur with this strategy?

FDA Response:

1. **You may submit PBPK modeling to predict un-tested DDI effects between CAM2038 and a CYP3A modulator. However, whether the results can be used to address the concern of CYP3A4 DDI and the need to conduct a clinical study using a CYP3A modulator will be a review issue.**

2. **If data from any publication are used to support your PB-PK model, to rely on any findings from the publication, you must have the right to use this literature via the 505(b) (2) pathway. For example, if a proprietary drug (e.g., Butrans) was used in the literature, then you need to provide adequate evidence to demonstrate that you have the right to rely on the findings associated with the proprietary drug. Also see our additional comments regarding the 505(b)(2) regulatory pathway.**

3. **When submitting your PBPK report:**
    a. **Verify your PBPK models of buprenorphine with buprenorphine PK data collected in various dosing routes (including IV, SL, and SC).**
    b. **Verify your PBPK models using results of clinical DDI studies with CYP modulators you mentioned under Q6.**
    c. **In your NDA submission, include model files used to generate final PBPK simulations (e.g. drug model files, population files, and output files).**

4. **We acknowledge that CAM2038 may be less affected by inhibition of 3A4 activity than transmucosal buprenorphine products, due to the lack of a first pass effect of swallowed drug. We are also aware of the ketoconazole drug interaction study with a transdermal buprenorphine product (e.g., Butrans) showing that drug-drug interaction effects with buprenorphine may differ based on route of administration. However, CAM2038 is a subcutaneous injection depot, so the results of a study involving the transdermal route may not apply.**

5. **If there are patients on CAM2038 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.**

Meeting Discussion:

The Sponsor asked for further clarification on Item 2. The Sponsor stated (b) (4) the Sponsor asked whether it was necessary submit documentation related to right of reference for these types of publications. The Division clarified that for 505(b)(2) applications, if a referenced published journal article is necessary to support approval of the drug product (including labeling), and if that article includes reference to a brand name drug product, the Sponsor must include that brand named drug as a listed drug product and submit appropriate patent certification. The Sponsor acknowledged and agreed to provide appropriate patent certification in the NDA.

The Sponsor asked whether the Division agreed with the approach (b) (4) The Division noted that it was not possible to comment until the data submitted in the NDA and the

adequacy of the approach were reviewed. However, the Division reiterated that collecting PK data in patients initiating or discontinuing 3A4 inhibitor or inducer treatment would provide the most convincing data. The Sponsor noted that it was not possible to incorporate collection of this information in their ongoing HS-549 PK study.

Question 7:

Context: Special Population: Hepatic Impairment:
Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels have been found to be higher and the T1/2 longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment after administration of a single dose of 2.0/0.5 mg Suboxone (buprenorphine/naloxone). For subjects with moderate and severe hepatic impairment, mean C_{max}, AUC0-last, and T1/2 values of buprenorphine were increased by 8%, 64% and 35% respectively for patients with moderate hepatic impairment and by 72%, 181% and 57% respectively for patients with severe hepatic impairment (Table 4; Buprenorphine HCl Sublingual tablets label). In subjects with mild hepatic impairment, the changes in mean C_{max}, AUC0-last, and T1/2 values of buprenorphine were not clinically significant. As such, no dose adjustment is needed in patients with mild hepatic impairment. Patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. For patients with severe hepatic impairment, a lower dose at initiation of treatment is recommended.

For the CAM2038 clinical development program, (b) (4) *Sponsor has evaluated single and repeat-dose pharmacokinetics of CAM2038 in a total of 176 patients and healthy volunteers in three clinical trials: Trial HS-07-307; HS-11-426 and HS-13-487. The resulting plasma concentrations of buprenorphine following CAM2038 administration were compared with the concentrations of buprenorphine obtained after administration of SL BPN at approved doses i.e., 8 mg, 16 mg, or 24 mg doses. The table below summarizes the pharmacokinetic results of the highest CAM2038 doses evaluated: 16 and 32 mg CAM2038 q1w, 128 mg and 192 mg CAM2038 q4w in comparison to 24 mg SL Buprenorphine.*

Comparison of Pharmacokinetics of CAM2038 and SL Buprenorphine

Products	*Dose (mg)*	*Buprenorphine*			*Norbuprenorphine*		
		$C_{sd,max}$ (ng/mL)	$C_{ss,max}$ (ng/mL)	$C_{ss,av}$ (ng/mL)	$C_{sd,max}$ (ng/mL)	$C_{ss,max}$ (ng/mL)	$C_{ss,av}$ (ng/mL)
CAM2038 weekly[a]	16	3.05	4.30	2.09	0.763	0.921	0.643
CAM2038 weekly[b]	32	5.27	6.9[c]	3.8[d]	0.938	ND	ND
CAM2038	128	6.59	7.0[c]	3.8[d]	1.36	ND	ND
CAM2038	192	7.54	ND	ND	1.62	ND	ND
SL Buprenorphine[a]	24	8.23	8.45	2.66	4.96	9.29	5.81

[a] Trial HS-13-487; [b] Trial HS-11-426; [c] $C_{ss,peak}$ as predicted by simulation from a nonlinear mixed effects PK model describing observed PK data; [d] Predicted and calculated from AUC_{inf} after single dosing and assuming time-independent pharmacokinetics, ND = not determined

As can be seen from the above table, the maximal concentrations of buprenorphine following administrations of CAM2038 were comparable to or lower than those obtained from 24 mg SL buprenorphine. The Sponsor believes that the relative hepatic risk posed by buprenorphine exposures following CAM2038 can be anticipated to be comparable, or low, given the lack of the first pass effect, to those of approved doses of SL buprenorphine. (b) (4)

[redacted]

Question: Does the Agency concur with the Sponsor's approach to addressing the use of CAM2038 in patients with hepatic impairment?

FDA Response:

No, we do not agree. Buprenorphine is highly metabolized and, thus, plasma levels may be higher in patients with moderate to severe hepatic impairment. In addition, because CAM2038 is a one-week or one-month depot product, its dosing regimen may not be easily adjusted between doses once administered as the transmucosal products, a point which has safety implications in patients with hepatic impairment.

The systemic exposure comparison between CAM2038 and 24 mg SL buprenorphine needs to be based on both C_{max} and AUC, not C_{max} alone. As noted from the table in Question 7, the average steady state concentrations (AUC_{tau} /dosing interval) of buprenorphine from CAM2038 are higher compared with the SL buprenorphine. We acknowledge the lack of a first pass effect of CAM2038 products, compared with the transmucosal buprenorphine products. However, since the overall exposure of buprenorphine from high doses of CAM2038 is greater than 24 mg SL buprenorphine, provide relevant relative bioavailability (as well as safety and efficacy, as appropriate) information for CAM2038 in hepatically impaired patients and propose dosing recommendations. In addition, for your overall program, provide justification that the greater exposure in high doses of CAM2038 compared to 24 mg SL buprenorphine will not be a systemic safety concern.

Meeting Discussion:

The Sponsor stated that they provided updated data on March 10, 2017, for the steady state PK parameters for CAM2038 weekly 32 mg and monthly 128 mg. They noted that PK information on monthly 160 mg will be available in 6 weeks, though they anticipate that the buprenorphine C_{max} for CAM2038 monthly 160 mg will exceed the C_{max} of 24 mg SL buprenorphine. The Division responded that a scientific bridge is needed, and additional comments may be provided when the data are submitted for review.

The Division added that there may be additional need to characterize toxicological data properly, if the C_{max} or AUC for 160 mg CAM2038 exceeds concentration with 24 mg SL BPN.

The Sponsor asked if data on hepatitis C can be used in lieu of hepatic impairment. The Division responded that it will not be helpful, as hepatitis C is not the same as hepatic impairment.

The Division also noted that the ability to rely on data from the referenced product may be limited. Because of the high first-pass effect, hepatic impairment is expected to have a more significant impact on PK for a SL product compared to CAM2038. The Sponsor must propose adequate dose recommendations for patients with hepatic impairment, especially when the patients are switched from a SL product to CAM2038, noting that hepatic impairment will have a different impact on the PK between the two products. The Division also commented that Probuphine is not recommended in patients with moderate and severe hepatic impairment. Without PK data for CAM2038 in patients with hepatic impairment, the same recommendation as for Probuphine will likely be made.

Question 8:

Context: Buprenorphine is cleared mainly through biliary excretion. Further, no differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine (Subutex PI). Therefore it is not expected that the CAM2038 buprenorphine systemic exposure and clearance would be impacted by renal function. No specific precautions or restrictions are recommended for buprenorphine in patients with renal impairment in approved buprenorphine labels including that of the Listed Drug. The Sponsor proposes that with respect to patients with renal impairment, similar precautions and restrictions pertaining to approved SL Buprenorphine would apply to CAM2038 and if additional labeling precautions are needed, a statement regarding dose reductions or lower starting doses with frequent monitoring could be sufficient, (b) (4)

Question: Does the Agency concur with labeling strategy for the use of CAM2038 in patients with renal impairment?

FDA Response:

We acknowledge you may rely on the renal impairment findings in Subutex labeling and your proposal appears reasonable. However, we do not agree with your rationale that (b) (4) **Propose adequate dosing recommendations in labeling for patient with renal impairment when submitting the NDA.**

Meeting Discussion:

No further discussion occurred at the meeting.

Question 9:

Does the Division agree to a waiver for pediatric subjects 16 years and younger?

FDA Response:

In the March 31, 2015, meeting minutes, you were advised to submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 meeting. We remind you again that an agreed iPSP is required prior to filing your NDA. Submit an iPSP for us to review.

Meeting Discussion:

The Sponsor agreed to submit the iPSP to the IND.

Question 10:

Does the Agency concur that a Priority Review is acceptable?

FDA Response:

A priority review status will be determined at the time of NDA filing. Submit a justification for priority review explicating how the application meets the relevant criteria.

Meeting Discussion:

No further discussion occurred at the meeting.

Question 11:

Does the Agency concur that a rolling submission of M3(CMC) and M4(Non- clinical) is acceptable?

FDA Response:

Because your program has received Fast Track designation, you are eligible for rolling review. However, note that although this means that you may submit completed sections of your NDA for review, but the regulatory time line does not begin, until you have submitted the entire application.

Meeting Discussion:

The Division reiterated that, although the Sponsor proposes to submit the nonclinical and CMC data early for their NDA application, the review clock will not start until all the required data are submitted to the application.

Question 12

Does the Agency concur that the overall plan for the structure and contents of the CAM2038 NDA to be submitted as an electronic CTD is acceptable?

FDA Response:

Yes, the overall plan appears acceptable.

Meeting Discussion:

No further discussion occurred at the meeting.

ADDITIONAL COMMENTS:

Clinical Pharmacology:

1. **We remind you of our comments regarding the manufacturing site change, which were communicated in the December 6, 2016, Type C (CMC only) meeting written comments.**
2. **Note that the final to-be-marketed formulation must be used in all clinical or clinical pharmacology studies intended to support your NDA, or you need to provide adequate bridging information or justification as to why the study results using a different formulation apply to your final to-be-marketed product.**
3. **If you plan rely on any other buprenorphine products' findings of safety or efficacy, you must establish a scientific bridge (e.g., via a comparative bioavailability study) between your product and that particular buprenorphine product in order to fulfill the 505(b) (2) regulatory requirements. In the relative bioavailability study, that particular buprenorphine product must be administered using its approved dosing regimen in the label**
4. **We note that you will obtain the injection-site effect PK data, i.e., injecting your product at multiple sites from study HS-15-549. For the effect of reinjection of CAM2038 at the same site, animal PK data may be supportive but cannot replace human PK data. Provide human PK data on the effect of reinjection of CAM2038 at the same site, or clarify how you intend to support labeling the product for chronic use.**

Meeting Discussion:
No further discussion occurred at the meeting.

Nonclinical:

5. **New excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. As noted in the guidance, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and**

diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*." (emphasis added).

6. **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*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

      And

      Guidance for industry: *Q3B(R2) Impurities in New Drug Products*, available at: 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.**

7. **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, how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

8. **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.**

9. **The NDA submission must contain adequate 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. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature, etc). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.**

   Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day depending on the duration of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day or higher in order, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **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**

The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted 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). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. 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. Include copies of all referenced studies upon which a safety assessment is based.

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**
- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study**

endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.**

10. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, safety justification for a new or novel excipient, or safety characterization of extractables and leachables.**
11. **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.**
12. **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.**
13. **Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

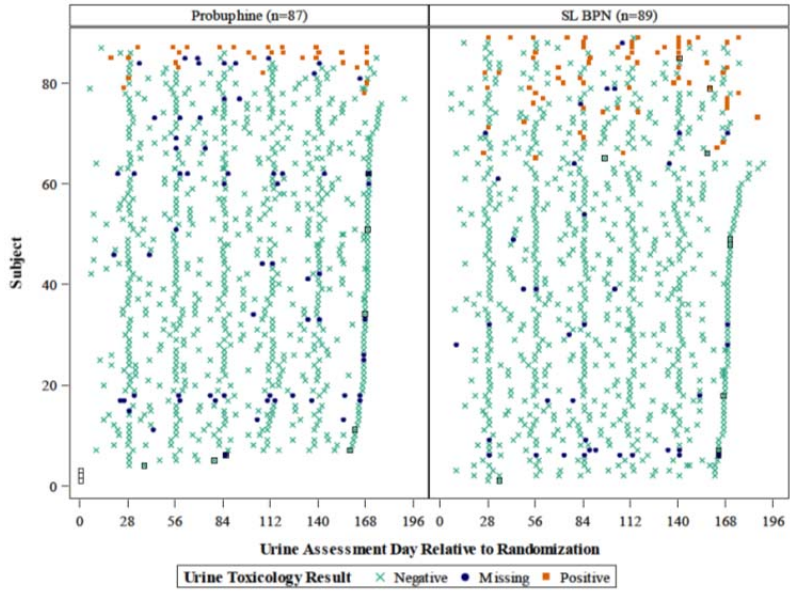
Meeting Discussion:

No further discussion occurred at the meeting.

Statistical:

14. Provide a graphical display of subject-level urine toxicology data where urine test results are considered as negative, positive or missing. An example of this type of graph was presented at the Advisory Committee Meeting held on January 12, 2016, for Probuphine.

Figure 3: Urine Toxicology Test Results



Meeting Discussion:

The Sponsor provided an example graphic display (Slide 7, attachment) for comment, offering two potential approaches. The Division concurred that a presentation that allows differentiation of the individual lines of data is preferable, but recommended that the data be sorted by time to discontinuation, rather than by patient number.

The Sponsor also noted that analyses of the mean morphine concentrations detected in urine samples were possible, and provided an illustrative example (Slide 17, attachment). The Division stated that analyses of this nature did not seem informative and would not add to the understanding of the effect of the drug.

CMC:

Please note that your proposed combination product must comply with 21 CFR Part 4 regulations which describe how manufacturers are to meet the CGMP requirements applicable based on the constituent parts of the combination product, in this case those under 21 CFR 210/211 and 21 CFR 820. A CGMP operating system based on 21 CFR 210/211 may also comply with provisions of 21 CFR 820 as specified in Part 4. Likewise, a CGMP operating system based on 21 CFR 820 may also comply with provisions of 21 CFR 210/211 as specified in Part 4.

For each facility responsible for manufacturing the finished product(s), you should identify the established operating system as described in Part 4 in the submission. If you do plan to operate under the 21 CFR 210/211 GMPs via the streamlined approach for the finished combination product, please provide the following information with your application submission to demonstrate compliance with 21 CFR Part 4:

Management Control

Specify which manufacturing firm has ultimate responsibility to ensure the combination product is manufactured in compliance with applicable 21 CFR Part 4 requirements at all levels of the organization. Also, provide a description and responsibility of each facility involved at the different levels of the organizational structure.

Design Control, General

Provide a description of your design control system, which should include requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Provide a copy or a summary of the plan used to design the combination product. Explain how you implemented the design control system to develop the combination product under review.

Purchasing Controls

Provide a summary of the procedure(s) for purchasing controls. The summary should:

• Describe your supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.
• Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
• Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you applied the purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e. supplier's agreement).

Corrective and Preventive Action

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of:
• Sources of quality data to identify existing and potential causes of nonconforming practices and products;
• Investigation of the cause of nonconformities;

• Identification of actions needed to correct and prevent recurrence of non-conformances;
• Verification or validation of the actions.

If you have any questions regarding these requests, please contact the Office of Combination Products combination@fda.gov.

Meeting Discussion:

No further discussion occurred at the meeting.

Additional Discussion:
Proposed proprietary name:

The Sponsor has proposed to use the same proprietary name for both the CAM2038 weekly and monthly products. The Division responded that the Division of Medication Error Prevention and Analysis had observed that marketing doses (b) (4) under the same proprietary name could increase risk of medication errors. The Division advised the Sponsor to consider how they would propose trade dress and labeling language to avoid confusion.

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

ACTION ITEMS:

1. The Sponsor agreed to acquire and submit the data from the NIDA-sponsored START study to support local tolerability for 32 mg buprenorphine exposure.

2. The Sponsor agreed to provide additional in vitro data on cardiac conduction effects.

3. The Sponsor will incorporate the Division's suggestions for presenting the data for discontinuations, and for the graphical display of urine toxicology test results.

4. Braeburn will consider how they would propose trade dress and labeling language to avoid confusion that could result in medication errors. In particular, it will be important to avoid confusion between the (b) (4) product dosage strengths.

5. Braeburn will provide adequate justification to support omitting a REMS for this product, and will include information on how the product will be distributed.

ADDITIONAL COMMENTS:

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

We note that all current buprenorphine-containing products are approved with a REMS to mitigate the risks of accidental overdose, abuse, and misuse. Your NDA submission must include a rationale for why a REMS is or is not necessary to ensure the benefits outweigh the risks. If a REMS is proposed, the submission must include an analysis of the identified risks, how the proposed REMS program will mitigate those risks, and a complete REMS submission (REMS Document and REMS Materials) with a REMS Supporting Document.

Meeting Discussion:
Braeburn did not provide a proposed REMS for discussion, and confirmed this is because they do not believe a REMS is required for their NDA application, as it will be administered by health care professionals. The Division advised Braeburn to include a discussion justification to support the lack of a REMS, including information about how the product is to be distributed.

PREA REQUIREMENTS

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

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

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your

selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

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

PRESCRIBING INFORMATION

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

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

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.

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.				

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.

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

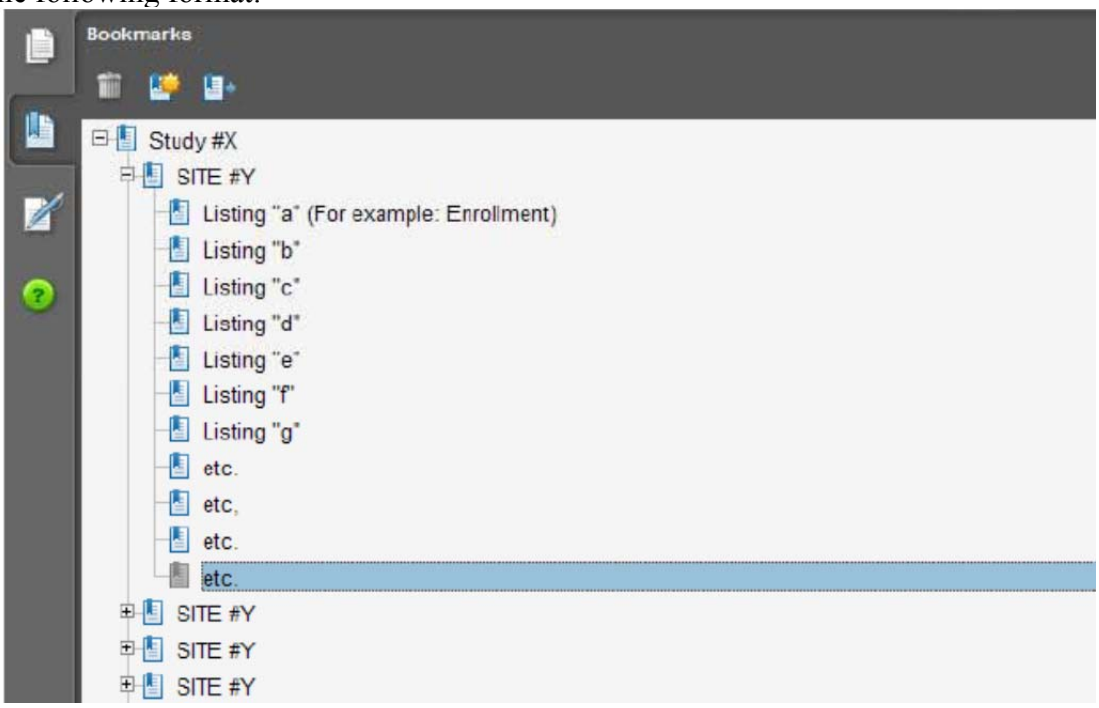
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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

The Sponsor provided handout are attached.

19 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

SWATI A PATWARDHAN
04/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 114082
PIND 124703

MEETING MINUTES

Braeburn Pharmaceuticals, Inc
47 Hulfish St., Suite 441
Princeton, NJ 08542

Attention: Frank E. Young, MD, PhD
EVP, Regulatory and Medical

Dear Dr. Young:

Please refer to your Pre-Investigational New Drug Applications (PINDs) for CAM2038 q1w and CAM2038 q4w.

We also refer to the February 24, 2015, meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss your Phase 3 development plans.

A copy of the official minutes of the meeting is attached 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:	February 24, 2015
Meeting Location:	White Oak Building 22, Room 1415
Application Number:	PIND 114082 PIND 124703
Product Name:	CAM2038 q1w CAM2038 q4w
Indication:	CAM2038 q1w: once weekly administration (b) (4) (b) (4) CAM2038 q4w: once monthly administration (b) (4) (b) (4)
Sponsor/Applicant Name:	Braeburn Pharmaceuticals Inc.
Meeting Chair:	Rigoberto Roca, MD, Deputy Division Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Minutes Recorder:	Matthew Sullivan, Supervisory Regulatory Health Project Manager, DAAAP

FDA Attendees	Title
Sharon Hertz, MD	Acting Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP
Rachel Skeete, MD, MHS	Clinical Reviewer, DAAAP
Ciby Abraham, PhD	Quality Assessment Lead, Office of New Drug Products (ONDP)
Sandra Suarez, PhD	Acting Biopharmaceutics Lead, ONDP
Gary Bond, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Jay Chang, PhD	Pharmacology/Toxicology Team Leader, DAAAP

Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, PhD	Team Leader, Office of Clinical Pharmacology (OCP)
Rachel Skeete, MD	Clinical Reviewer, DAAAP
Feng Li, PhD	Biostatistics Reviewer, Office of Biostatistics (OB)
Freda Cooner, PhD	Biostatistics Team Leader, OB
Matthew Sullivan, MS	Supervisory Regulatory Health Project Manager, DAAAP
Camurus / Braeburn Attendees	**Title**
Behshad Sheldon	President and Chief Executive Officer (CEO), Braeburn Pharmaceuticals
Fredrik Tiberg, PhD	President and CEO, Camurus
(b) (4)	Statistical and Database Consultant to Braeburn, (b) (4) (b) (4)
Markus Johnsson, PhD	Senior Director, Pharmaceutical Development, Camurus
Sheila Mathias, PhD	Senior Director, Regulatory Affairs, Braeburn Pharmaceuticals
Serena Kim, PharmD	Vice President, Clinical Development and Medical Affairs, Braeburn Pharmaceuticals
Margareta Linden, PhD	Senior Director, Project Management and Planning, Camurus
(b) (4)	Clinical Consultant to Braeburn Pharmaceuticals; (b) (4)
(b) (4)	Clinical Consultant to Braeburn Pharmaceuticals; (b) (4)
Frank E. Young, MD, PhD	Executive Vice President, Clinical and Regulatory Affairs, Braeburn Pharmaceuticals
Jonathan M. Young, JD, PhD	General Counsel and Vice President Policy/Advocacy, Braeburn Pharmaceuticals

BACKGROUND

Braeburn Pharmaceuticals, Inc., requested End-of-Phase 2 meetings to discuss their Phase 3 development plans for CAM2038 q1w and CAM2038 q4w. The Division considered the requests and elected to grant a joint meeting as the products were potentially to be labeled

together.

The Sponsor states that CAM2038 q1w and CAM2038 q4w have been developed as therapeutic alternatives for treatment of Opioid Use Disorder, providing long-acting weekly and monthly formulations, respectively, in multiple dose strengths that cover the spectrum of available sublingual buprenorphine/naloxone doses approved for maintenance treatment.

The Division's responses to the questions from the January 12, 2015, meeting package were sent to the Sponsor on February 23, 2015. The Sponsor provided brief written responses on February 24, 2015.

Presented below are the Division's comments and responses to questions in the background meeting package. The sponsor's questions are listed in italics, with Agency responses and comments in bold. The Sponsor's brief written responses follow the response to which they pertain are in bold, italic text, and discussion that took place at the meeting is captured in normal text.

GENERAL COMMENTS

We agree that your proposed products have the potential to offer valuable treatment alternatives to currently-available buprenorphine products for the treatment of opioid dependence. However, we do not agree (b) (4)

(b) (4)

(b) (4)

Opioid addiction is a chronic, relapsing disorder for which pharmacologic treatment is anticipated to be prolonged and even lifelong. Trials to support opioid addiction treatments should be a minimum of six months in duration to demonstrate a change in drug-taking behavior that can be anticipated to be predictive of a lasting change in behavior. This represents a surrogate endpoint for a drug that is intended to be used chronically.

For products intended for use in opioid addiction, you will need to demonstrate the durability of effect on drug-taking behavior for the two products in trials of a minimum of six months duration.

Braeburn February 24, 2015, brief written responses:

1. New entrant to treatment patient population

- ***Q1W for 3 months, then transition to Q4W for 3 months. Total study duration = 6 months***
- ***Endpoints: proportion of negative urine tox at 3 months and at 6 months***
- ***Comparator = Active comparator of SL BPN***
- ***NI margin to be justified***

2. Stable patient population

- ***Same study design as PRO-814 (Probuphine), clinically stable patient population on treatment for 6 months and abstinent for 90 days prior to randomization***
- ***Total study duration = 4 months; Endpoint of opioid-free months***
- ***Comparator = Active comparator of SL BPN***
- ***20% NI margin (same as PRO-814 study)***

Safety Database

- ***Total of at least 500 patient exposed to CAM2038***
- ***Open-Label Extension study***
- ***Approximately 100 patients to be enrolled from the 2 above studies for an additional 6 months for total exposure of 12 months (CAM2038 Q4W)***
- ***Submission at 120 day safety update***

Discussion:
The Sponsor acknowledged that the Division views the continuum of care for opioid addiction differently than the paradigm the Sponsor envisioned (b) (4)

(b) (4)

The Sponsor noted (b) (4) The Sponsor responded that they were aware of this concern, and that they would be sure to address it.

Discussion then turned to how the two products would be used clinically, with patients transitioning from weekly depot injections to monthly (b) (4) (b) (4) However, in clinical trials, the point at which patients would switch from the once-weekly depot to the once-monthly depot would be fixed, due to logistical concerns. The Division responded that it understood the need for predictability, but that allowing study physicians to determine the appropriate time to switch patients based upon a set of protocol-specified criteria would provide helpful information for the labeling, particularly for physicians who may not treat opioid-dependent patients routinely. The Sponsor responded that statistical analyses become more challenging when the transition point is not fixed. The Division acknowledged that it may be more difficult, but it reiterated that the information gained from allowing the flexibility may be worthwhile to provide appropriate guidance about the clinical criteria that can be used for making decisions about transitioning between the formulations. The Division also stated that it may be desirable to better define the switch point in a study which precedes the pivotal trials, or to conduct one trial with a fixed switch and one trial with a dynamic switch point.

Post-Meeting Note:
A study design with a fixed timepoint for transition may prove difficult to demonstrate treatment success. For some patients, the fixed transition point may be premature, and clinicians will not have the option to transition back to more intensive treatment, when deemed clinically necessary.

The Division questioned (b) (4)

[redacted] (b) (4)

The Sponsor further explained [redacted] (b) (4)

The Division indicated that there were two principal approaches to support approval of both products: (l) a single compelling clinical safety and efficacy trial in which both products were used for patients in the active treatment arm, supported by an opioid challenge study, or (2) two separate clinical trials, each including the weekly and monthly formulations. The Division recommended a single trial and an opioid challenge study as the more expedient approach. The Sponsor explained that it had not proposed a blockade study because blockade is not generally measured clinically. However, the Division views the demonstration of blockade as a supportive approach to establishing that the correct dose is being delivered. The Sponsor asked for detailed guidance from the Division about how to conduct an opioid challenge study, including the doses of the challenge product. The Division indicated that the capability for opioid blockade should be evaluated for the target starting dose of the proposed drug product, and that higher doses could be inferred to be effective in achieving blockade based on results from lower doses. The Division stated that it would provide a post-meeting note regarding considerations for an effective blockade study.

> **Post-Meeting Note:**
> The opioid challenge study should be designed to demonstrate blockade, not only attenuation, of the subjective effects of exogenously-administered opioids at doses that are capable of producing relevant effects in the target population. A challenge dose of at least 18 mg of hydromorphone or equivalent should be assessed in the opioid blockade study. We refer you to the Guidance for Industry: *Assessment of Abuse Potential of Drugs*, available at http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM198650.pdf for study design considerations in designing an opioid challenge study. You may submit a proposed protocol to the IND for the depot products for review

The Sponsor noted a preference for conducting two safety and efficacy trials, rather than the single safety and efficacy trial and opioid challenge study, and for conducting the two trials concurrently. The Division recommended that the Sponsor conduct one study at a time. Successful trials are not guaranteed, and conducting the trials sequentially allows for evaluation of the findings from the first, identification of potential study design issues, and an opportunity to address them before proceeding with a second clinical trial. The Division further reminded

the Sponsor that, in addition to demonstrating statistically significant effects, the trial would also need to be compelling from the standpoint of anticipated clinical benefit.

The Division noted the Fast Track designation may be appropriate for this product, and encouraged the Sponsor to consider submitting a request for designation.

The Sponsor inquired about the possibility of submitting longer-term safety data as part of the 120-Day Safety Update, the Division noted that an NDA must be complete at the time of submission, and that a refuse-to-file determination may be made if required data, to specifically include the full safety database, are not available. The Sponsor acknowledged this requirement, and stated that they would provide a complete NDA.

The Sponsor aims to submit protocol(s) to the IND(s) and sought clarification as to whether they should submit one or two INDs for their products. The Division stated that a post-meeting note would be included addressing the question.

> **Post-Meeting Note:**
> As the products are to be studied together, a single IND is preferable. This would not preclude separate NDAs in the future if the Sponsor wished to submit them.

The Sponsor aims to submit protocol(s) to one or both of the CAM2038 INDs. The Division noted that if a Phase 3 protocol is submitted as the IND-opening protocol, a safety decision will be made by Day 30, but that comments regarding study design and statistical analysis will be provided at a subsequent time via correspondence.

Question 1: Does FDA agree that possible future excipient manufacturer changes can be performed based on the approach proposed by the Sponsor?

Division Response:

In addition to the studies proposed, submit multipoint dissolution profile comparisons in three different media for the drug product, as manufactured using the current vs. new manufacturer of the excipients. It is noted that you plan on introducing a new manufacturing site (new manufacturer) for supply of the commercial product after Phase 3 development. We remind you that changes in drug product manufacturing site for modified release drug products are considered major changes requiring in vivo bioequivalence (BE) studies.

The proposed data to support the change in excipient manufacturer are not sufficient. Additional data must include: full characterization of the excipient, including release specifications; certificate of analysis for the excipient; comparative batch analysis data of the drug product manufactured with the excipient from both manufacturers; and stability data at long-term and accelerated conditions. Further, the specifications for the new manufacturer's excipient must be comparable with those currently used to release the excipient batches that are used to prepare the clinical drug product batches. Similarly, to

support a second drug product manufacturing facility, assuming comparable process and equipment will be used, comparative batch analysis data as well as stability data for the drug product made at both sites will need to be provided in order to qualify the second facility.

Your proposal to conduct a rat PK single-dose study to support a change in excipient and drug product manufacturer may be adequate if all of the CMC requirements noted above are met and equivalent PK profiles are demonstrated between the changed and unchanged excipient and drug products. If any of these criteria are not met, a bridging toxicity study in an appropriate species may be required.

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

Question 2: Does FDA agree to the proposed drug product specifications for CAM2038 q1w and CAM2038 q4w products, i.e., the relevant release and stability tests are included and that the acceptance criteria are reasonable?

Division Response:
The in vitro release drug product acceptance criteria will be determined during the NDA stage based on batches tested in pivotal clinical trials (refer to additional biopharmaceutics comments).

From the CMC perspective, the drug product specifications should include an impurity profile that includes process impurities and degradants for buprenorphine. The specifications for the impurities arising from the drug substance should be monitored according to ICH Q3A(R2), and those impurities that arise from the drug product manufacturing process should be monitored according to ICH Q3B(R2). Residual solvents should also be evaluated and specifications set according to USP <467> and ICH Q3C.

Further, the specifications must also include the following:

- **Optical purity of buprenorphine**
- **Two identification methods for buprenorphine**
- **pH and volume delivered**

Sterility, particulate matter, and endotoxin testing should be carried out per USP methods. All specifications should be established at the time of NDA submission. The acceptance criteria will be evaluated at the time of submission, when the totality of data can be reviewed.

We advise taking a conservative approach by considering the maximum daily dose of buprenorphine to be injected at one time. Therefore, based on a maximum daily dose of 32 mg for the CAM2038 q1w drug product and (b) (4) for the CAM2038 q4w drug product,

the specification limits for unspecified degradation products for both products must not exceed 0.2% or 2 mg, whichever is lower.

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

Question 3: Does FDA agree to the use of accelerated multipoint QC in vitro dissolution methods based on USP1 for finished product?

Division Response:

There are insufficient data in the meeting package to reach a conclusion on the adequacy of your proposed dissolution method as a QC method for your proposed product. Submit the following data/information to your IND for our review:

A dissolution method report supporting the selection of the proposed test. The report must include the following information:

1. **The pH solubility profile.**
2. **A detailed description of the in dissolution method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least six samples per testing variable.**
3. **The complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the amount of drug release with time.**
4. **Data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., aberrant formulations and manufacturing conditions) for the relevant manufacturing variables and material attributes. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.**

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

Question 4: *Does FDA agree that the scope of the CMC studies presented in this briefing package are adequate to support the initiation of Phase 3 studies and eventual NDA filing for the proposed drug products, including the container closure system?*

Division Response:
The proposed CMC studies seem reasonable. However, upon review of the data, further studies may be needed. Refer to the Human Factors additional comments below regarding your planned submission of a human factors protocol.

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

Question 5: *Does FDA agree that, in addition to the Sponsor's short-term safety studies, reliance on published literature data to address the reproductive toxicity and carcinogenic potential of glycerol dioleate (GDO) is acceptable to support the Phase 3 clinical trials and registration of CAM2038 q1w and CAM2038 q4w, and that no further reproductive toxicity or carcinogenicity studies are needed for GDO?*

Division Response:
We cannot concur at this time that reproductive toxicology and carcinogenicity studies will not be required for glycerol dioleate (GDO). While your plan to rely on published literature may be acceptable, we note that this strategy may be risky as these articles typically do not include any underlying data and the designs of the studies may not have been conducted in the spirit of Good Laboratory Practices. We also note that if no specific information can be found for GDO, toxicity information for a "related" compound such as diacylglycerol (DAG), which contains GDO, may be supportive only if the levels of GDO tested in those studies can be clearly discerned and adequate levels of GDO were generated under the conditions tested, or if a persuasive argument can be made to support that the "related" compound would be predicted to have a similar or greater toxicity profile than GDO. We remind you that your safety risk assessment for GDO must address all of the standard toxicological endpoints per the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. This includes evaluations for reproductive toxicology that include assessing: (1) the potential to affect fertility or early embryonic development to implantation; (2) teratology in both a rodent species and a mammalian nonrodent species; and (3) effects on prenatal and postnatal development, including maternal function. We highly recommend that you provide your detailed literature-based toxicological assessment to justify a waiver for reproductive toxicity and carcinogenicity studies as early as possible

to avoid delays in your development program. Include copies of all cited references. The final adequacy of the study designs and the data can only be determined upon a review of the information submitted.

Braeburn February 24, 2015, brief written responses:
Sponsor will provide the documentation and literature review requested by the Agency

Discussion:
The Sponsor stated that it would provide the requested information, which it felt would support the safety of the GDO excipient.

Question 6: Does FDA agree that the proposed TK bridging studies are sufficient to support reliance on the Subutex level regarding Section 8.1 (Pregnancy) and Section 13.1 (Carcinogenicity, Mutagenicity, and Impairment of Fertility) of the Subutex label?

Division Response:
The proposed toxicokinetic bridging studies with the CAM0238 drug products appear appropriate to bridge to the Agency's findings for Subutex as described in the product label as the proposed dosing intends to use doses equivalent to the amount of buprenorphine administered in Subutex.

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

Question 7: Does FDA agree that the nonclinical program and data presented are sufficient to support initiation of Phase 3 clinical trials of the CAM2038 q1w and CAM2038 q4w drug products?

Division Response:
As noted in our General Comment above, clinical studies of at least six months duration are required to support opioid addiction treatment indications for the CAM2038 q1w and q4w drug products. Therefore, the following nonclinical studies are necessary to support initiation of these long-term clinical studies:

- **A chronic repeat-dose subcutaneous toxicity study in a single appropriate species of adequate duration (e.g., 6-months in a rodent or 9-months in a nonrodent) to evaluate the local safety of buprenorphine. Note that buprenorphine is not approved for this route of administration.**

- **Information to support the safety of FluidCrystal or the individual excipients of your two formulations for chronic use as indicated in the original PreIND meeting minutes for CAM2038 (dated 4/12/12). This includes local toxicity studies with chronic dosing in both a rodent and nonrodent species for GDO. As you have**

already conducted a 6-month rodent subcutaneous toxicity study with GDO, a 9-month repeat-dose subcutaneous toxicity study in an appropriate nonrodent species is needed to support your Phase 3 clinical trials. We note that you have provided a justification in your meeting package for a single species safety evaluation for the excipient GDO based on the rat being the most sensitive species, no notable systemic effects in rat with high doses for up to 26 weeks, and similar local toxicity profiles observed in rat, dog, and minipig in shorter term studies. This is a reasonable proposal, but the final determination on the acceptability of this approach is a review issue.

We also note that reliance upon the Agency's previous finding of safety for the Eligard drug product alone will not be adequate to support the safety of N-methyl-2-pyrrolidone (NMP) as this drug product was approved for advanced prostate cancer and the development programs for such indications are generally limited and may not be sufficient for the currently proposed indication. As such, all of the standard toxicological endpoints outlined in the FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf, will be required for NMP unless otherwise justified.

- **We also remind you that the fate, disposition, and lifespan of the FluidCrystal depot and/or its components must be characterized and its status (i.e., integrity) described for any necropsies and histology evaluations.**

- **Additionally, you must characterize the toxicity associated with inadvertent intramuscular injection of the drug product.**

Braeburn February 24, 2015, brief written responses:

Chronic repeat dose study of SC buprenorphine

- ***As suggested in PIND 124,703, an 18 Week Subcutaneous Administration Repeat Toxicity Study including Toxicokinetics and Local Tolerance of CAM2038 q1w and q4w was performed (TO-13-489)***
- ***Dose and time dependent resolution of CAM2038 q1w and q4w was established over 4 months with partial to complete resolution in multiple studies (including study TO-13-489 and an 8 week dog study, TK-12-448)***
- ***During injections at the same injection site (eg TO-13-489) there were no indications that the two ongoing inflammatory processes were influencing each other***
- ***Furthermore, relating to SC buprenorphine, sponsor can ask for right of reference to 52 weeks toxicity study of subcutaneous buprenorphine (Probuphine® implants) in dogs***

Safety of GDO/FluidCrystal

- ***26 weeks toxicity and local tolerance study in rats of daily SC injections of GDO and weekly SC injections of FluidCrystal vehicle was performed as advised in preIND 114082 (dated 4/12/12)***

- ***Final report to be submitted to FDA***

- ***Further safety data will be provided in the form of a literature review for GDO NMP***
- ***NMP exposure at maximum clinical*** (b) (4) ***mg dose of CAM2038 q4w is*** (b) (4) ***mg, corresponding to 90 μg/kg/day for 60 kg body weight***
  - ***Exposure below PDE ICH-Q3C***
  - ***Carcinogenicity studies of NMP were conducted in rats (24 months) and mice (18 months) (ref. Eligard NDA 21-343) with over 1000-fold safety margin for carcinogenicity***

"Fate, disposition, and lifespan of the FluidCrystal depot"

- ***Reports and data are available and will be provided***

Intra-muscular injections

- ***PK studies have been performed with CAM2038 q1w and q4w***
- ***Additional toxicity study relating to inadvertent IM injections of CAM2038 may be performed during Phase 3***

Discussion:
Discussion centered on the availability of non-clinical data to address local safety. The Sponsor has completed a 4-month subcutaneous dog toxicity study, but not the 9-month study that the Division had requested. The Sponsor asked whether data (b) (4) could address the need for a chronic evaluation of the local safety of buprenorphine, as this could be incorporated if the Sponsor obtained a right of reference. The Division noted that the (b) (4) data would only be supportive if the Sponsor could demonstrate that higher buprenorphine concentrations were tested and adequate local buprenorphine exposures were achieved to support the safety of the CAM2038 products for chronic use at the doses and concentrations proposed. The Sponsor noted that, in the 4-month dog study where injections were rotated around several sites to mimic the clinical dosing regimen, some of the animals had exhibited full recovery of local inflammatory effects at a particular injection site by the time the same site was to receive another injection. The Sponsor inquired if, based on this information and with a right of reference to the (b) (4) evaluation could be submitted after initiation of the Phase 3 development program. The Division reminded the Sponsor that the purpose of the chronic evaluation is to characterize the long-term toxicological potential of their product, but stated that a post-meeting note to address the Sponsor's proposal would be included in the meeting minutes.

The Sponsor inquired if they should analyze tissue capsules to assess the fate of their products. The Division responded that this information could be helpful.

The Division further reminded the Sponsor that their plan to reference Eligard to support the safety of NMP is problematic, because there is no carcinogenicity information for NMP in the current Eligard label, and the Sponsor cannot reference material that is contained only in the Summary Basis of Approval, and not in the label. Only acquiring a right of reference to the underlying data in the NDA would allow the Sponsor to rely on such carcinogenicity information.

Post-Meeting Note:
Based upon further internal discussion, chronic subcutaneous toxicity studies in a nonrodent model are necessary prior to initiating Phase 3 clinical studies with a duration of 6 months or longer with the CAM2038 products to fully characterize the potential local toxic effects of buprenorphine with the FluidCrystal vehicle after 9 months exposure and the reversibility of such findings if necessary. These studies can also address the systemic safety of novel excipients in the CAM2038 formulations in a nonrodent species if sufficiently high doses are tested to provide adequate coverage for the intended clinical use. Note that your rationale for basing the safety of N-methyl-2-pyrrolidone (NMP) on the permissible daily exposure level of 5.3 mg per day indicated in the guidance for industry document ICH Q3C for this class 2 solvent is not acceptable because the daily exposure to this excipient is not likely to be the total amount evenly distributed across the 28-day dosing interval. Without data to show what the daily exposures to NMP are, we advise taking a conservative approach by considering the maximum daily exposure to NMP to be the amount injected at one time or provide an adequate justification otherwise. The design of the chronic toxicity studies should reproduce as closely as possible the intended clinical dosing regimen, taking into consideration the drug concentration, the volume to be administered, and the frequency of administration. Ideally these study designs will include groups that meet and exceed the dose and concentration levels intended for human study in order to establish potential margins for safety. A chronic toxicity study with one CAM2038 formulation may be acceptable to address the safety of the other formulation if adequate bridging data are provided to demonstrate the two have a similar toxicological and toxicokinetic profile. However, note that the adequacy of such data to support the NDA will be a review issue.

Question 8: *Does FDA agree that the proposed safety database along with other safety data is sufficient to support registration of CAM2038 q1w* (b) (4) (b) (4)

Division Response:
The proposed safety databases for CAM2038 q1w and CAM2038 q4w are not sufficient to support registration of the two products (b) (4) **We remind you that the safety of repeated injections into the same site should be established (buttock, arm, and abdomen injection sites), if supported by an appropriate pharmacokinetic evaluation.**

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

Question 9: *Does FDA agree that the proposed safety database along with other safety data are sufficient to support registration for CAM2038 q4w* (b) (4) (b) (4)

Division Response:
See the response to Question 8.

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

Question 10: *The Sponsor proposes two Phase 3 trials in a total of 440 subjects to support the proposed CAM2038 q1w indication* (b) (4) (b) (4) *(HS-11-421* (b) (4) *) and a single Phase 3 trial in 240 subjects to support an indication for CAM2038 q4w* (b) (4) *(HS-14-499). Does FDA agree:*

a. That Studies HS-11-421 and (b) (4) *could support the following indication statement?*

(b) (4)

b. That Study HS-14-499 could support the following indication statement?

(b) (4)

Division Response:
See our General Comments, above. We do not agree (b) (4) (b) (4)

(b) (4)

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

Question 11: Does FDA agree [redacted]

Division Response:
We do not agree with the proposal [redacted] **See our General Comments, above.**

[redacted]

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

Question 12: Does FDA agree [redacted]

Division Response:
See our response to Question 18.

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

Question 13: Does FDA agree that the proposed [redacted] *are appropriate for:*

[redacted]

Division Response:
Refer to the General Comments and our response to Question 10. We do not believe (b) (4) (b) (4)

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

Question 14: Does FDA agree that the proposed study duration is appropriate for: (b) (4)

Division Response:
Refer to the General Comments and our response to Question 10.

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

Question 15: Does FDA agree that the proposed blinding strategy [for CAM2038 q1w] *is appropriate?*

Division Response:
The blinding strategy appears reasonable. It is unclear why a different brand of sublingual buprenorphine will be utilized for any potential supplemental needs, when it appears that patients will get active or placebo sublingual tablets according to their assignment, and no additional buprenorphine beyond sublingual tablets may be administered in this context.

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

Question 16: Does FDA agree that the proposed non-inferiority margin is appropriate for: (b) (4)

Division Response:
You have not provided adequate justifications for the proposed non-inferiority (NI) margin. The following considerations should be made when choosing an appropriate NI margin.

The margin in general for a non-inferiority (NI) study should be no larger than the presumed treatment effect of the active control in the NI study, which is usually referred to as M1, and the largest clinically acceptable difference (degree of inferiority) of the test drug

compared to the active control, which is usually referred as M2. M1 is estimated from appropriate historical studies of the active control, which is usually based on a 95% confidence interval of the treatment effect. Historical studies can be used to estimate the effect of the active control only when it is appropriate to conclude that they are sufficiently similar to the current NI study with respect to all important study design and conduct features that might influence the active control effect. The design features of interest include but are not limited to the characteristics of the patient population, important concomitant treatments, definitions and ascertainment of study endpoints, dose of active control, entry criteria, and analytic approaches.

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

Question 17: Does FDA agree that the proposed primary endpoint is appropriate to support registration [for CAM2038 q4w]*?*

Division Response:
Your proposed primary endpoint is (b) (4) **We disagree with this definition of a responder, although, we agree in general with the use of a responder definition for the primary endpoint. We also agree with the use of negative urine toxicology results along with self-report in determining a clinically meaningful reduction in opioid use or abstinence from opioid use. Additionally, the trial(s) must be at least six months in duration, during which a "grace period" is permitted. You may also consider an analysis that includes a response profile that evaluates the percentages of opioid-negative urines submitted and that graphs patients by grouping them into categories based on the various percentages of opioid-negative urines submitted. In such an analysis, we would expect that the separation of curves to be 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), in order to consider it to be a clinically-meaningful difference.**

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

Question 18: Does FDA agree that the proposed secondary endpoints are appropriate and no additional end points are warranted [for CAM2038 q4w]*?*

Division Response:
Your proposal to evaluate assessments of withdrawal symptoms, reduction in opioid cravings, and percentage of retention in treatment appears appropriate. We note that the typical benefits accrued with retention in treatment for methadone programs, which require frequent attendance and contact with treatment staff, may not be entirely the same for a depot product. It would be helpful to include measures of how the patient feels or

functions to document that retention in treatment translates to clinical benefit. An assessment of increasing sublingual buprenorphine and depot requirements should be made during the clinical trial. We note that the term "craving" is not a well-defined concept and that many instruments actually inquire about "desire" or "urge" to use the drug of choice. It will be important to ensure that the instruments you choose are appropriate to measure the concepts of interest.

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

Question 19: *Does FDA agree that the patient population has been appropriately selected* [for CAM2038 q4w]*?*

Division Response:
You propose to enroll patients with moderate to severe opioid use disorder (b) (4) **We cannot agree at this time that the proposed population is appropriate. It is unclear whether you intend for the drug products to be used in patients who are "stable" only, or for new entrants to treatment, or both. If you intend for the product(s) to be used only in "stable" patients, you will need to provide a definition that clearly identifies patients who are stable in treatment, rather than merely on a stable dose of buprenorphine. Clinicians are not likely to consider a patient stable until well into opioid addiction treatment, e.g., after 6 or more months of treatment. If you intend for the products to also be used in new entrants to treatment, the currently proposed entry criteria exclude new entrants to treatment and are not appropriate.**

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

Question 20: *Does FDA agree that the duration of the study is appropriate to establish efficacy* [for CAM2038 q4w]*?*

Division Response:
See above. Trials must be a minimum of 6 months in duration.

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

Question 21: Does FDA agree that the proposed non-inferiority margin is appropriate?

Division Response:
We are unable to determine whether the proposed non-inferiority margin is appropriate at this time. Refer to the response to Question 16 for general considerations that are to be made in choosing an appropriate NI margin.

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

Question 22: Does FDA agree that the selected doses and dosing regimen are appropriate for maintenance treatment?

Division Response:
We recommend that you conduct an opioid challenge study to ensure that you have established a blocking dose of your product. Opioid blockade is particularly important early in treatment of opioid addiction. We also note that the maximum daily dose for sublingual buprenorphine is 24 mg per day, and not 32 mg per day.

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

Question 23: Does FDA agree that:

a. Additional clinical studies, including drug interaction studies, special population studies, and additional PK studies, are not warranted to support registration of each of the proposed products?

b. An opioid challenge study is not required to support registration of each of the proposed products?

Division Response:
As indicated in our PIND meeting, in your NDA submission, you must address the dosing of your product in special populations, such as those with hepatic and renal impairment, elderly and obese populations, as well as your determination of whether there are any gender differences associated with your product.

Your product is proposed for use over time and with repeated dosing. In your completed studies, CAM2038q1w was dosed for 4 consecutive weeks, but PK was collected after 4 weeks only for the 16-mg dose. For CAM2038 q4w, PK data are available only after single doses. However, your prediction in Table 10 indicated that 32 mg CAM2038 q1w, and 128 mg and 160 mg CAM2038 q4w will have higher steady-state exposure compared to 24 mg of Subutex. For a 505(b) (2) application, if you plan to rely on Agency's finding of safety, you must demonstrate that the systemic exposure of your product at steady-state is comparable to, or lower than, that of the listed drug(s) or provide additional safety

information to support the safety of the proposed dosing. As such, steady-state pharmacokinetic data for CAM2038 q1w and CAM2038 q4w are required. In addition, steady-state exposure data will provide important information on dose selection in the Phase 3 study. Therefore, we strongly recommend that you characterize the steady-state PK of CAM2038 q1w and CAM2038 q4w before initiating Phase 3 trial(s), so observed PK data can be used to support dose selection in the Phase 3 study. Alternatively, you may collect the PK data in the planned Phase 3 trials. You can collect PK data in a subset of the patients, or use a population PK approach. The population-PK sampling can also be used for addressing the above-mentioned dosing recommendations for your product in special populations.

You indicated that there will be different injection sites for your products in the Phase 3 studies. Provide data to demonstrate that the PK profile of your product will not be different due to the location of the injection. If the same injection site will be used multiple times, you must evaluate how it will affect the PK profile.

The final to-be-marketed formulation must be used in the PK studies and clinical efficacy studies. Otherwise, you will need to provide adequate bridging information or justification why the study results can apply to your final to-be-marketed product.

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

Question 24: *Does FDA agree that two Phase 3 trials* (b) (4) *are sufficient to support registration, respectively, of:*

a. CAM2038 q1w?

b. CAM2038 q4w?

Division Response:
Two adequate and well-controlled, six-month trials incorporating both the CAM2038 q1w in the earlier period of treatment and CAM2038 q4w in the later periods, transitioning patients as they are ready for less frequent health care provider contact, could provide support for a regimen involving both products. A successful clinical trial supported by demonstration that both products produce complete blockade (not simply attenuation) of exogenous opioid effects might also be sufficient.

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

Question 25: Does Agency have comments or guidance on the suitability of fast track designation for each of:

(b) (4)

Division Response:
While we do not agree with the concept (b) (4) (b) (4) **may be suitable for a fast track designation because as they may offer advantages with respect to abuse and misuse compared with the transmucosal buprenorphine-containing products that would apply across the entire continuum of care for opioid dependence treatment. Moreover, ensured compliance has the potential to translate to superior efficacy. Suitably-designed studies demonstrating superiority to transmucosal buprenorphine would be helpful in establishing the advantages and is the only way to support a superiority claim. Acceptability for fast track designation is ultimately a review issue.**

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

ADDITIONAL COMMENTS

Biopharmaceutics

1. **Dissolution acceptance criteria: For the selection of the dissolution acceptance criteria of your product, the following points should be considered:**
    - **The in vitro dissolution profiles should encompass the timeframe over which at least 80% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.**
    - **The dissolution profile data from the bio-batches (clinical & PK) and registration stability batches should be used for the setting of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values).**
    - **The establishment of at least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set. The specification ranges should be based on the overall dissolution data generated at these times and should be based on average in vitro release data for each lot under study, equivalent to USP Stage 2 testing (n=12).**
    - **In general, the selection of the dissolution specification ranges is based on mean target value ±10% and NLT 80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.**

- **The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA stage. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

2. **Extended Release Designation Claim: The following information must be submitted to support the extended release designation claim (refer also to CFR 320.25f):**
   a. **The BA profile established for the drug product rules out the occurrence of any dose dumping;**
   b. **The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.**
   c. **The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;**
   d. **The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.**

Human Factors

You state in your submission that a human factors study protocol will be submitted to the IND and that the human factors study is intended to be performed in parallel with the Phase 3 clinical study. If you have not done so already, perform a comprehensive use-related risk analysis to identify the use-related risks associated with your proposed product. Your comprehensive risk analysis must include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis or known problems), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any use errors or task failures, and the method of validating your risk mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and that the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product). Based on this comprehensive use-related risk analysis, you will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide you in the design of a human factors validation study protocol for your product. To ensure your approach and methodology are acceptable, please submit your use-related risk analysis and validation study protocol for review prior to study implementation for Agency review and comment. Note that we will need 90 days to review and provide comments under the IND.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online

at:
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm

Note that we have also published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design.

- **Applying Human Factors and Usability Engineering to Optimize Medical Device Design (Draft), available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf**

- **Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf**

- **Safety Considerations for Product Design to Minimize Medication Errors (Draft), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf**

Nonclinical

1. **For your 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.**

    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.

2. **We note that all impurities listed in your drug product contain structural alert for genotoxicity. 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 ICH M7 guidance document titled: *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.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.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.**

3. **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, how these levels compare to ICHQ3A(R2) and Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

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

5. **The NDA submission must contain information on potential leachables and extractables from the drug container closure system, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system 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 the 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. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety. From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.

ACTION ITEMS

1. The Division will provide post-meeting notes for the following items:
   - Guidance on submitting a single or two separate INDs/NDAs.
   - Guidance on an appropriate challenge dose to be utilized in the blockade study.
   - Guidance on sufficiency of the Sponsor's nonclinical program for the start of the Phase 3 program.
2. The Sponsor will endeavor to acquire a letter of authorization to the Probuphine IND.
3. At the time of NDA submission, the Sponsor will provide a safety database of at least 500 patients, with at least 100 with one year or more of exposure.

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.

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

In addition, your PSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: Nonclinical Safety Evaluation of Pediatric Drug Products, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

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

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

DATA STANDARDS FOR STUDIES

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.

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.

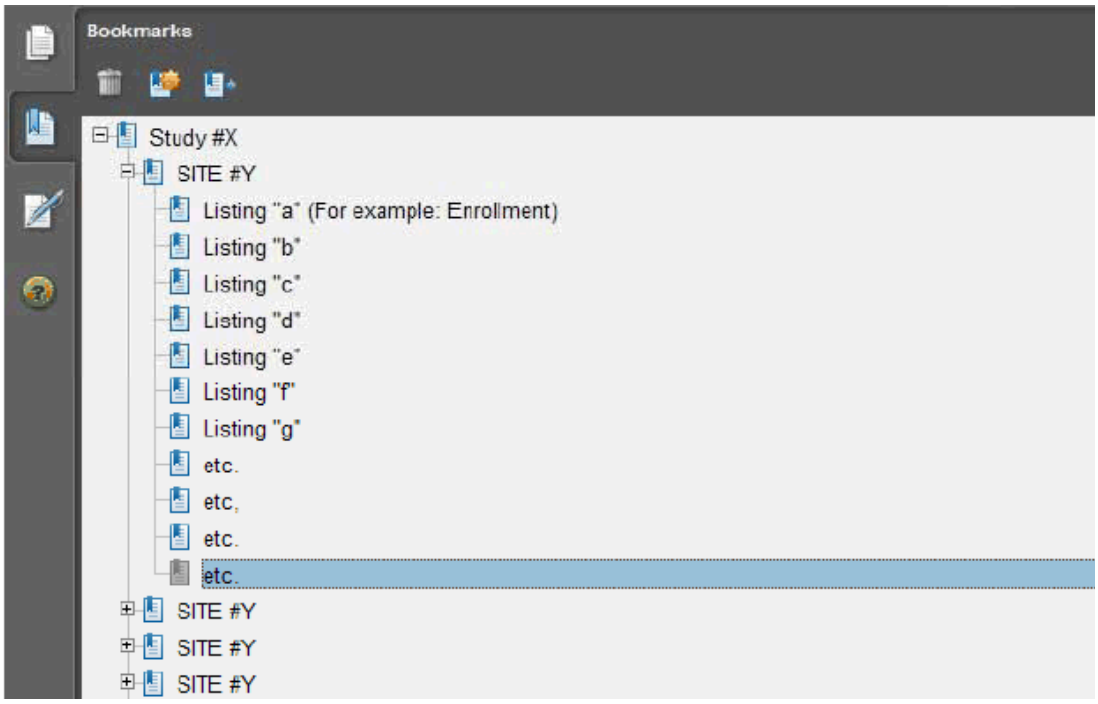
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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

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

/s/

MATTHEW W SULLIVAN
03/31/2015