

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212295Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



IND 102486

**MEETING MINUTES**

Cosmo Technologies, Ltd.  
c/o Conventus Biomedical Solutions, Inc.  
5414 Oberlin Drive, Suite 130  
San Diego, CA 92121

Attention: Petra Pavlickova, PhD  
Associate Director Regulatory Affairs

Dear Dr. Pavlickova:

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

We also refer to the telecon between representatives of your firm and the FDA on July 12, 2018. The purpose of the meeting was to discuss the planned 505(b) NDA application.

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

If you have any questions, call me, at (240) 402-9700.

Sincerely,

*{See appended electronic signature page}*

Selma Kraft, PharmD  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** July 12, 2018  
**Meeting Location:** Teleconference

**Application Number:** IND 102486  
**Product Name:** Remimazolam  
**Indication:** Remimazolam is an (b) (4) benzodiazepine indicated for procedural sedation.  
**Sponsor/Applicant Name:** Cosmo Technologies, LTD.

**Meeting Chair:** Rigoberto Roca, MD  
**Meeting Recorder:** Selma Kraft, PharmD

**FDA ATTENDEES**

Sharon Hertz, MD	Division Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Martha Van Clief, MD	Acting Clinical Team Leader, DAAAP
Renee Petit-Scott, MD	Clinical Reviewer, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Newton Woo, PhD	Pharmacology/Toxicology Team Leader, DAAAP
Katie Sokolowski, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader
Srikanth C. Nallani, PhD	Clinical Pharmacology Reviewer
David Petullo, PhD	Mathematical Statistics Team Leader
Kate Meaker, PhD	Mathematical statistics Reviewer
Katherine Bonson, PhD	Controlled Substance Staff
Selma Kraft, PharmD	Regulatory Health Project Manager, DAAAP

**SPONSOR ATTENDEES**

Luigi Moro, PhD	Chief Scientific Officer, Cosmo
Alessandro Mazzetti	Chief Medical Officer, Cosmo
Cristina Macelloni	Pharmaceutical Development Manager, Cosmo

Roberta Bozzella	Regulatory Affairs Manager, Cosmo
Paolo Lanzarotti	Head of Development Analytical Labs, Cosmo
(b) (4)	Clinical Consultant, Cosmo
	Clinical Consultant, Cosmo
	Clinical Consultant, Cosmo
Juergen Beck, MD	Chief Development Officer, Paion
Martin Donsbach, PhD	Director, Regulatory Affairs, Paion
Thomas Stoehr, PhD	Vice President Early Development & Regulatory Affairs, Paion
Frank Schippers, MD	Vice President Global Clinical Development, Paion
Oliver Kops, PhD	Vice President CMC, Paion
Steven Krdijan, RAC	Regulatory Affairs Advisor
Petra Pavlickova, PhD, RAC	Associate Director, Regulatory Affairs
(b) (4)	Senior Clinical Development Consultant
	CMC Consultant
	Principal Biostatistician, Consultant
	Biostatistician Consultant
	Preclinical Consultant
	Clinical Consultant, Cosmo

## BACKGROUND

- a. The purpose of this meeting is to discuss the planned 505(b) NDA application for remimazolam.
- b. The product remimazolam is a short-acting benzodiazepine. The proposed dosage form is a freeze-dried solution containing 20 mg of active ingredient in a vial, which will be administered intravenously. The proposed indication for remimazolam is for procedural sedation.
- c. The purpose of this meeting is to respond to the information and questions submitted in your meeting package. The meeting package is expected to be complete and contain all relevant data to support your questions. Do not expect any new information submitted in response to these preliminary responses to be reviewed prior to the meeting.
- a. The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

## DISCUSSION

### Question 1

*Does the Agency agree that the efficacy information from the two Phase 3 pivotal clinical studies CNS7056-006, and CNS7056-008, placebo-controlled and open label arm for midazolam,*

*reaching statistical significance, and the supportive CNS7056-015 safety study for ASA III and IV patients having favorable clinical results for procedural sedation success favoring remimazolam versus placebo and open-label midazolam as well as supportive data from Phase 2 studies, is sufficient for the remimazolam NDA filing?*

### **FDA Response to Question 1**

**The efficacy data collected from your two pivotal Phase 3 studies and your additional Phase 3 study in ASA III and IV patients appears consistent with our prior discussions, however, the adequacy of the submission for NDA filing will be determined during the filing review.**

#### Discussion:

There was no further discussion on this question.

### **Question 2**

*Does the Agency agree with this proposal for the ISE?*

### **FDA Response to Question 2**

**We agree with your plan to present the individual results of the pivotal trials for procedural sedation. Also provide the individual results of the supportive trials, CNS7056-003, CNS7056-004, and CNS7056-015.**

**We do not agree with your proposed pooled subgroup analyses for efficacy. Pooled analyses have limitations when the individual studies are not similar in design. For example, the patient populations and evaluated procedures in your Phase 3 studies differed. Therefore, interpretation of the pooled results would be difficult.**

**In general, the ISE should include a comprehensive, integrated, in-depth analysis and discussion of the overall effectiveness results, with a rationale for the methods used in the analysis. It should include information from your clinical and nonclinical studies, and the published literature if appropriate. Refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at <https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf>.**

#### Discussion:

The Sponsor provided the following response:

- *The substantial evidence of efficacy for remimazolam will come from the analyses of data from the individual pivotal studies - not from the ISE.*
  - *Both individual pivotal studies CNS7056-006 and -008 have demonstrated highly clinically and statistically significant treatment effects compared with placebo, for both the primary endpoint and key secondary endpoints.*
- *In the ISE, the Sponsor intends to conduct additional integrated efficacy analyses to explore treatment effects in certain subgroups, consistent with requirements by the guidance from the Agency*

- *These ISE analysis tables will present both results from the two individual pivotal studies 006 and 008 side-by-side as well as pooled analyses.*

The Sponsor also provided a sample ISE table. Refer to Appendix A: Pre-NDA Meeting with FDA July 12, 2018, attached at the end of this document, for more information. The Division concurred with the Sponsor's proposal.

### Question 3

*Does the Agency agree that the safety database is sufficient for NDA filing for remimazolam for procedural sedation?*

### **FDA Response to Question 3**

**It appears that your safety database consists of 1767 subjects exposed to remimazolam, with 300 subject-exposures in each of your Phase 3 studies, and that you have followed our advice from the End-of-Phase 2 meeting, held on October 17, 2013. However, a large portion of the information in the safety database has come from studies conducted outside the United States (U.S.) and not under an IND. The applicability of the data provided from non-U.S. sites to support your NDA will be determined during the review of the NDA (refer to the responses for questions 5 and 6 for additional information regarding the acceptability of foreign data).**

### Discussion:

There was no further discussion on this question.

### Question 4

*Does the Agency concur that the pooling strategy for the analyses of safety data from the remimazolam clinical studies for the ISS is acceptable?*

### **FDA Response to Question 4**

**No, we do not agree with the proposed pooling strategy for the analyses of safety data. Because of the different designs of your studies (e.g., different patient populations evaluated, procedures performed, allowable concomitant medications, etc.), the interpretation of pooled results would be difficult.**

**In general, pooling of data is acceptable when the clinical studies are of similar design, including similar patient populations, similar dosing, similar randomization schemes, and similar concomitant medication administration.**

**The ISS must contain a comprehensive discussion and detailed integrated analyses of all the relevant safety data from the clinical study reports, and published literature if applicable. Refer to the guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at <https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf>. Additionally, 21 CFR 314.50(d)(vi)(a) outlines the regulatory guidelines for the ISS in NDA submissions.**

Discussion:

The Sponsor provided the following response:

- *The Sponsor's goal in the ISS was to detect rare safety signals in larger numbers of patients by dose*
- *Therefore, data in the ISS is not currently presented by individual studies.*
  - *Individual study data is presented in the individual clinical study reports.*
- *The ISS analyses currently present pooled results, with pooled data for Group A1A (placebo-controlled studies in procedural sedation) presented by dose.*

The Sponsor can perform the proposed pooling analyses and include them in the NDA submission; however, the ISS must include the required safety information for remimazolam, described in 21 CFR 314.50(d)(5)(vi)(a), and be provided by sex, age, and racial subgroups. The ISS should include the overall extent of exposure, demographics and other baseline characteristics of the study population, analysis of adverse event rates, analysis of deaths, adverse event dropouts, and other serious or severe adverse events. The ISS must be a comprehensive discussion and overall assessment of the safety of remimazolam, and should not be simply a presentation of safety data in tables. The Sponsor agreed to provide written reports and assessments for the ISS.

Question 5

*Does the Agency agree with the rationale for the applicability of foreign data in support of the safety of remimazolam?*

**FDA Response to Question 5**

**We acknowledge your rationale for the applicability of foreign data in support of the safety of remimazolam and it appears to contain the required elements described in 21 CFR 312.120, *Foreign Clinical Studies Not Conducted Under an IND*. The determination of whether the foreign data support approval of your NDA will be determined during the review of the NDA.**

Discussion:

There was no further discussion on this question.

Question 6

*Does FDA agree with this approach for these additional foreign studies?*

**FDA Response to Question 6**

(b) (4)

Discussion:

There was no further discussion on this question.

Question 7

*Sponsor proposes to include narratives and CRFs in the NDA for all subjects experiencing a treatment-emergent serious adverse event (n=41), including those leading to death, to discontinuation of dosing or discontinuation from the study, and serious adverse events of V tach, V fib, syncope and seizure.*

*Does the Agency agree with this approach?*

**FDA Response to Question 7**

**We agree with your proposal to include patient narratives and CRFs for the subjects and clinical circumstances you have described. We remind you, however, that as per 21 CFR 314.50(f)(2), the NDA must include all CRFs for patients who died or discontinued due to an adverse event, “whether believed to be drug related or not, including patients receiving reference drugs or placebo”. Additionally, patient narratives for this population would be informative.**

Discussion:

There was no further discussion on this question.

Question 8

*Data for 11 studies will be converted to SDTM formats consistent with the implementation guides (SDTM IG v3.1.3) which are valid per FDA’s Data Standards Catalog v5.0 and will be used to create the integrated SDTM database which forms the basis for both ISS and ISE data analysis and reporting. To ensure consistent medical coding within the ISS and ISE, MedDRA version 18.0 will be used for recoding or up versioning all adverse event and medical history data, and WHO DDE version 2015-03 will be employed for recoding (or up versioning) medications in the integrated database. In addition, all studies started since 2015 used these dictionary versions. The original medical coding used for the individual study CSRs will be placed in the integrated database in SUPPAE, SUPPMH, or SUPPCM for the sake of traceability.*

*Does the Agency agree with this approach?*

**FDA Response to Question 8**

**Because you plan to include the original medical coding used for individual CSRs in the integrated database in SUPPAE, SUPPMH, AND SUPPCM, we agree with your proposal for recoding or up-versioning all adverse events, medical histories, and concomitant**

**medications. In addition to the original medical coding, provide the verbatim language recorded in the individual CSRs, for the verification of proper coding.**

Discussion:

There was no further discussion on this question.

Question 9

*Does the Agency agree that the nonclinical studies including pharmacology, pharmacokinetics, and pharmacodynamic drug-drug interaction studies conducted for remimazolam are sufficient for NDA filing and no additional nonclinical studies are required?*

**FDA Response to Question 9**

**We cannot agree at this time that no additional nonclinical studies will be required. From your preNDA package, it is unclear if all male fertility and pre- and postnatal development endpoints were adequately assessed. See our response to Question 10.**

Discussion:

There was no further discussion on this question.

Question 10

*Does the Agency agree that the additional 28-day repeated dose toxicity study in minipigs and a combined segment I-III reproductive toxicity study in rabbits conducted by the Sponsor, as recommended by the FDA during the End of Phase 2 meeting is sufficient for NDA filing?*

**FDA Response to Question 10**

**At this time, we cannot agree that the species selected and the endpoints assessed in the developmental and reproductive toxicity (DART) studies are appropriately justified. In your NDA, provide justification for the species selected for the 28-day repeat dose toxicity and the DART studies and why rabbits are an appropriate species given that a paradoxical response was exhibited in these species and is not an issue when interpreting the results of the DART study.**

**Adequacy of the number of animals evaluated for fertility and assessment of postnatal development as per ICH S5A and S5B guidances will be determined during the review of the NDA. From the summaries in your pre-NDA package, it is unclear if male fertility was assessed in an appropriate species as per ICH S5B, including an evaluation of implantation sites and conceptuses. Additionally, it is unclear if your rabbit DART study adequately assessed postnatal developmental endpoints as per ICH S5A guidance, particularly learning/behavior/memory development and reproductive parameters (i.e., fertility) in the F1 kits.**

Discussion:

There was no further discussion on this question.

Question 11

*Does the Agency agree with the proposed approach regarding the scope, format, and documentation of the electronic datasets and case report tabulations for nonclinical studies to be submitted?*

**FDA Response to Question 11**

**Yes, we agree. Your proposal is acceptable and is in line with the FDA's published expectations with respect to submission of SEND data with NDAs.**

Discussion:

There was no further discussion on this question.

Question 12

*Does the Agency agree with the proposed indications and usage statement?*

**FDA Response to Question 12**

**The proposed indication and usage language must be supported by data in your NDA submission, which will be a matter for review.** (b) (4)

**\_\_\_\_\_ should not be included in the INDICATIONS AND USAGE section of the Full Prescribing Information.**

Discussion:

There was no further discussion on this question.

Question 13

*Does the Agency agree that the statement regarding \_\_\_\_\_ (b) (4) presented in the draft full prescription labeling is appropriate and sufficient?*

**FDA Response to Question 13**

\_\_\_\_\_ (b) (4)

Discussion:

There was no further discussion on this question.

Question 14

*Does the Agency agree that the draft labeling is structured appropriately and includes the required information?*

**FDA Response to Question 14**

**It appears that your draft labeling is in the appropriate PLR format and includes the required information. The final language for labeling will be determined after the review of the NDA.**

Discussion:

There was no further discussion on this question.

Question 15

*Assuming comparability of the registration and validation batches is demonstrated at least at the earliest points of the accelerated and long-term stability program conditions and an analysis of the stability data from the validation batches is comparable to that of the registration batches, does the Agency agree that the expiration period for the drug substance may be established from the registration batch data?*

**FDA Response to Question 15**

**Provided that comparability can be established between the remimazolam registration and validation batches (batch results consistent in terms of chemical/physical characteristics and impurity profiles), we agree that the expiration period for the drug substance may be established based on stability data obtained from the remimazolam registration batches.**

Discussion:

There was no further discussion on this question.

Question 16

*Assuming comparability of the registration and validation batches is demonstrated, at least at the earliest points of the accelerated and long-term stability program conditions and an analysis of the stability data from the validation batches is comparable to that of the registration batches, does the Agency agree that the shelf life for the drug product may be established from the registration batch data?*

**FDA Response to Question 16**

Yes, we agree that the data from the registration batches can support the shelf-life of the product assuming the batch scale of the registration batches represents 10% of the commercial batch size, and the other modifications to the process are as outlined in the Pre-NDA package.

Discussion:

There was no further discussion on this question.

Question 17

Does the Agency agree that the [REDACTED] (b) (4) are appropriate GMP starting materials for preparation of remimazolam besylate?

**FDA Response to Question 17**

Additional information, not provided in your Meeting Package, is needed [REDACTED] (b) (4) before a conclusion can be made regarding their potential designation as regulatory starting materials for the synthesis of remimazolam besylate drug substance. Include the following information for [REDACTED] (b) (4)

- a. Specifications
- b. Description of the route of synthesis
- c. Potential/identified impurities
- d. Origin of formation of impurities
- e. Evaluation of carryover of impurities into the drug substance to ensure that impurities in the starting material do not impact the impurity profile of the drug substance
- f. Certificates of Analysis or batch analysis data on several batches showing a history of compliance with specifications

For additional guidance, refer to ICH Q11 and the associated Q11 Questions and Answers, with particular emphasis on the Answer to Q7.

Guidance for industry: *Q11 Development and Manufacture of Drug Substances*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf>

and

Guidance for industry: *Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Questions and Answers*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM542176.pdf>

Question 18

Does the Agency agree with the validation strategy for [REDACTED] (b) (4) as the process referred to in the validation plan and report?

**FDA Response to Question 18**

**The proposed strategy seems reasonable. However final evaluation of the validation process is deferred to the review of the full validation data and report.**

Discussion:

There was no further discussion on this question.

Question 19

Does the Agency agree with the drug substance [REDACTED] (b) (4)

**FDA Response to Question 19**

Your proposed [REDACTED] (b) (4) appears reasonable, provided that [REDACTED] (b) (4) Refer to guidance for industry: *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf>.

Discussion:

There was no further discussion on this question.

Question 20

Does the Agency agree with the proposed temperature approach?

**FDA Response to Question 20**

**ICH Stability data may support the excursion statement, provided that the container used is not a permeable container.**

Discussion:

There was no further discussion on this question.

Question 21

Does the Agency agree the Agreed Pediatric Study Plan does not need to be amended, that the protocol for the proposed study will be submitted to this IND no later than 1 year after adult phase 3 studies are completed, and that the study will be initiated no later than 18 months after NDA approval?

### **FDA Response to Question 21**

**The proposed timeline for submission of the final pediatric protocol, as outlined in the Agreed PSP, is acceptable. However, in the absence of safety signals or other clinically significant findings from the adult studies, we recommend initiation of the pediatric studies sooner than 18 months after NDA approval.**

**From a nonclinical perspective, the studies and timeline proposed may require amendments as new data have emerged from published literature that raises our concern for sedative-induced developmental neurotoxicity as indicated by our Safety Labeling Change issued December 14, 2016. We strongly recommend that you discuss any juvenile animal protocol with the Division prior to initiating nonclinical juvenile animal studies.**

### **ACTION ITEMS:**

1. The Sponsor will provide the required information under 21 CFR 314.50(d)(5)(vi)(a) in their ISS.
2. The Sponsor will conduct analysis of efficacy data from the individual pivotal studies for the ISE.

### **GENERAL COMMENTS**

### **CLINICAL PHARMACOLOGY COMMENTS**

**In previous submissions, you had indicated the use of population PK/PD in support of your clinical development plan. In the NDA, submit the following datasets to support the population PK or PK/PD analysis:**

1. All datasets used for model development and validation should be submitted as a SAS transport file (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
2. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g., myfile\_ctl.txt, myfile\_out.txt).
3. A model development decision tree and/or table which gives an overview of modeling steps.

**For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and**

**units. For example, SC route clearance should be presented as CL/F (L/h) and not as THETA(1). A description of the clinical application of modeling results should be provided in the summary of the report.**

### **NONCLINICAL COMMENTS**

- 1. We note that your IND was partially a paper submission. We strongly recommend that you submit all completed studies to the EDR to facilitate documentation and review of your NDA.**
- 2. In your NDA, you must justify a reasonable maximum daily dose (MDD) of your drug product based on clinical use data. The MDD is essential for evaluating safety of your drug product including setting drug substance and drug product specifications and determination a NOAEL and exposure margins for labeling.**
- 3. Include a detailed discussion of the nonclinical information in the published literature, if any, and specifically address how the information within the published domain impacts the safety assessment of your drug product in Module 2 of the NDA submission. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.**
- 4. We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis 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> .**
- 5. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2) and ICH Q3B(R2). 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 14 days should be completed.**

Refer to

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

and

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

6. If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.
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 and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds must be adequately justified for safety from a toxicological perspective.
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.**
- 10. We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the recommended qualification thresholds, if novel excipients or metabolites are not justified for safety, or if the application lacks adequate safety justification for extractables and leachables.**

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. See discussion above for more information.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

### **CONTROLLED SUBSTANCE STAFF REQUESTS**

Provide a summary of the Abuse Potential Assessment you have conducted with remimazolam and a list of the abuse-related studies that will be submitted in the NDA.

Your abuse assessment of remimazolam should conform with all previous communication with the Controlled Substance Staff and with the 2017 guidance for industry: Assessment of Abuse Potential of Drugs, which can be assessed at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>.

The adequacy of the abuse-related studies and the resulting data is a review issue, once the NDA has been submitted.

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions

(February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

## **PREA REQUIREMENTS**

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

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

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. For example, there has been substantial nonclinical evidence

for anesthetics/sedatives (e.g., GABA agonists) in producing neurotoxicity in very young animals during the period of rapid synaptogenesis. 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 [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **NARRATIVE SUMMARIES**

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

- Patient age and sex
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data)

- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

## **PRESCRIBING INFORMATION**

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

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

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

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

## **SUBMISSION FORMAT REQUIREMENTS**

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

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

## **MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

**ATTACHMENTS AND HANDOUTS**

**Appendix A:** Pre-NDA Meeting with FDA July 12, 2018

10 Page(s) 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. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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SELMA S KRAFT  
07/26/2018



IND 102486

**MEETING PRELIMINARY COMMENTS**

PAION UK Limited

(b) (4)

Attention:

(b) (4)

Dear Dr. (b) (4) :

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

We also refer to your correspondence, dated and received July 10, 2017, requesting a meeting to discuss the abuse liability program for remimazolam.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (240)-402-9700.

Sincerely,

*{See appended electronic signature page}*

Selma Kraft, Pharm.D  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comment



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**PRELIMINARY MEETING COMMENTS**

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Meeting Date and Time:** November 16, 2017 at 11:00 AM

**Application Number:** IND 102486  
**Product Name:** Remimazolam injection  
**Indication:** For the use as an intravenous sedative in adult patients undergoing diagnostic or therapeutic procedures.  
**Sponsor/Applicant Name:** PAION UK Limited

**FDA ATTENDEES (tentative)**

Sharon Hertz, MD	Division Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Rigoberto Roca, MD	Deputy Division Director, DAAAP
Leah Crisafi, MD	Clinical Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader
Katherine Bonson, PhD	Pharmacologist, Controlled Substance Staff (CSS)
Selma Kraft, PharmD	Regulatory Health Project Manager, DAAAP

**SPONSOR ATTENDEES**

Martin Donsbach	Director Regulatory Affairs, PAION
Frank Schippers	Vice President Global Clinical Development, PAION
Thomas Stöhr	Vice President Early Development & Regulatory Affairs, PAION
Juergen Beck	Acting Chief Development Officer, PAION
Oliver Kops	Vice President CMC, PAION
Marija Pesic	Associate Director, Early Development, PAION
Alice Burger	Associate Director, Regulatory Affairs, PAION
(b) (4)	
Cristina Macelloni	Pharmaceutical Development Manager, Cosmo Pharmaceuticals
Luigi Moro	Chief Scientific Officer, Cosmo Pharmaceuticals
(b) (4)	
	US Agent for Cosmo Pharmaceuticals
	Clinical Expert Consultant for Cosmo Pharmaceuticals
Alessandro Mazzetti	Chief Medical Officer, Cosmo Pharmaceuticals

### **Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled November 16, 2017, between PAION UK Limited and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

### **BACKGROUND**

- a. The purpose of this meeting is to discuss the abuse potential program for remimazolam to support the marketing application and scheduling of remimazolam as a controlled substance.
- b. The initial abuse potential program was discussed at the End-of-Phase 2 (EOP2) meeting held on October 17, 2013. PAION submitted an abuse potential protocol, CNS7056-014, synopsis on June 12, 2014. The Division sent a general advice letter regarding the protocol synopsis and general advice on the abuse potential program on January 26, 2015. Subsequently, additional comments and recommendations were sent regarding CNS7056-014 in two emails dated February 17, 2015, and June 11, 2015.

On July 21, 2016, PAION requested a Type C meeting to discuss the abuse potential program. The Division granted this as a written response only meeting on July 26, 2016. The Division provided final written responses on November 21, 2016, to the questions in the meeting package in support of the Type C meeting submitted on September 16, 2016.

On March 31, 2017, PAION submitted an intranasal abuse liability trial protocol, CNS7056-019. An advice letter with recommendations for the protocol was sent on June 9, 2017.

On April 26, 2017, PAION submitted an oral and oral combined with alcohol abuse liability trial, CNS7056-020. A teleconference was held between PAION and the Division on June 28, 2017, to discuss the starting dose and stopping criteria for protocol CNS 7056-020. After the teleconference, the Division notified PAION that no further

changes to protocol CNS 7056-020 were necessary at that time. An advice letter was sent on September 20, 2017, with additional recommendations for CNS 7056-020.

On July 10, 2017, PAION requested a Type C guidance meeting to discuss the abuse potential program which was granted as a teleconference on July 18, 2017.

- c. The Sponsor's original questions from the meeting package submitted October 6, 2017, are incorporated below in *italics* followed by the FDA Response in **bold** font.

## DISCUSSION

### Question 1

*Does the Agency agree that the design of PAION's* [REDACTED] (b) (4)

### FDA Response to Question 1

**On further consideration, the Controlled Substance Staff (CSS) has determined that the intravenous human abuse potential study, in conjunction with the intranasal and oral bioavailability studies in humans, are sufficient to provide necessary data regarding the abuse potential of remimazolam in humans. Thus,** [REDACTED] (b) (4)  
[REDACTED] **will not be required.**

### Question 2

*Does the Agency agree that the data from clinical abuse liability studies are adequate to support NDA filing and allow the Agency to make recommendation on the scheduling of remimazolam as a controlled substance?*

### FDA Response to Question 2

**CSS has previously provided feedback to you regarding the design of the clinical studies. We also have informed you that specific additional preclinical and clinical studies would be required and we provided feedback to you on these study designs. Further information on evaluating abuse potential can be found in the 2017 guidance for industry, *Assessment of Abuse Potential of Drugs*, available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>.**

**However, the adequacy of the studies and the resulting data with relation to a final abuse potential determination is a review issue, once the NDA has been submitted.**

## GENERAL COMMENTS

### PREA REQUIREMENTS

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

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

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

### DATA STANDARDS FOR STUDIES

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

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

Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

## **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

### **SUBMISSION FORMAT REQUIREMENTS**

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

### **SECURE EMAIL COMMUNICATIONS**

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

### **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 Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### **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).

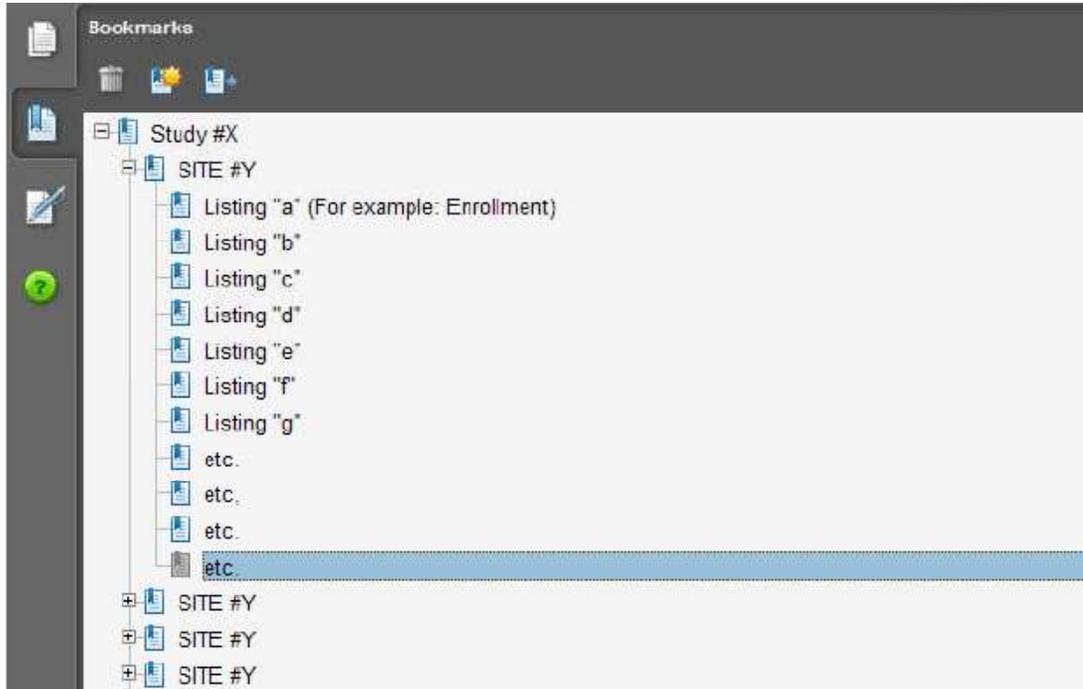
**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
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.

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<sup>1</sup> 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](mailto:ESUB@fda.hhs.gov)

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SELMA S KRAFT  
11/13/2017



IND 102486

**MEETING REQUEST-  
WRITTEN RESPONSES**

PAION UK Limited

(b) (4)

Dear Dr. (b) (4) :

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

We also refer to your submission dated July 21, 2016, containing a Type-C meeting request. The purpose of the requested meeting was to discuss the abuse potential program.

Further reference is made to our Meeting Granted letter dated July 26, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your September 16, 2016, background package.

If you have any questions, call me at (240)-402-9700.

Sincerely,

*{See appended electronic signature page}*

Selma Kraft, PharmD  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## WRITTEN RESPONSES

**Meeting Type:** Type C  
**Meeting Category:** Guidance

**Application Number:** IND 102486  
**Product Name:** Remimazolam  
**Indication:** Procedural sedation  
**Sponsor/Applicant Name:** Paion UK Limited  
**Regulatory Pathway:** 505(b)(1)

### BACKGROUND

The Sponsor would like to discuss the abuse potential program for remimazolam in support for the filing of the NDA. The Sponsor's stated objectives of this meeting include the following:

1. Gain Agency agreement on the design of nonclinical studies to assess physical dependence and route of administration, as well as the adequacy of the overall nonclinical program to evaluate abuse potential of remimazolam to support NDA filing and allow scheduling of remimazolam as a controlled substance.
2. Gain Agency agreement on the adequacy of the clinical Human Abuse Potential (HAP) study to support NDA filing and allow scheduling of remimazolam as a controlled substance.
3. Gain Agency agreement (1) that nonclinical evaluations of the potential intranasal route of administration have adequately assessed the abuse risk associated with this route of administration, and (2) that a study evaluating the intranasal route of administration in humans is not required.
4. Gain Agency agreement as to whether the chemistry, manufacturing, and controls (CMC) aspects (b) (4) in the production of remimazolam besylate are adequately addressed in context of the abuse potential of the active ingredient remimazolam.

Remimazolam is a novel benzodiazepine for which the Sponsor is pursuing a procedural sedation indication. The Sponsor states that it is designed to be rapidly metabolized in the body to an inactive metabolite, shortening the duration of action as compared to currently marketed sedative agents. It is presented as a sterile, preservative-free, white to off-white lyophilized powder for reconstitution. The Sponsor intends to follow the 505(b)(1) regulatory pathway.

The Sponsor met with the Division on October 17, 2013, for an End-of-Phase 2 (EOP2) meeting. An advice letter relating to the EOP2 meeting was sent January 12, 2014. Advice letters regarding remimazolam's abuse potential program and human abuse potential study were sent on January 26, 2015 and February 16, 2016. Comments pertaining to the HAP study CNS7056-014 was also sent in an e-mail dated, June 11, 2015.

## **QUESTIONS AND RESPONSES**

*Question 1: Does the Agency agree with the proposed design of the rat study and that conducting physical dependence/tolerance in groups of male and female rats using the clinical (intravenous) route of administration for remimazolam will address its potential to induce physical dependence and withdrawal in comparison to other benzodiazepines and opiates?*

### **FDA Response to Question 1:**

**The rat physical dependence study is generally well-designed. However, we have the following comments:**

**Typically, the route of administration of all drugs in a physical dependence study is the same, so that pharmacokinetics (PK) are similar between treatments. However, rats in this study will receive a single intravenous dose of remimazolam per day while the positive control drugs (morphine and diazepam) will be dosed orally twice a day. Differences in PK may produce differences in the ability of a drug to produce physical dependence.**

**The drug discontinuation period should last for at least two weeks. During this time, animals should be monitored every day for the first week and every other day for the second week. The behavioral observations should last for 10 minutes during each monitoring period.**

*Question 2: Does the Agency agree that the design of the completed drug discrimination study and the self-administration study are appropriate to allow for assessment of relative abuse liability?*

### **FDA Response to Question 2:**

**The Controlled Substance Staff (CSS) previously provided feedback to you on the design of these studies in the advice letter dated January 26, 2015. A drug discrimination study should be conducted with doses that produce plasma levels of the drug that are similar to those produced by the therapeutic dose, as well as 2 to 3 times greater (if this can be done safely), in order for the study results can be meaningful. The timing of the behavioral testing should occur at  $T_{max}$ . For the self-administration study, the dose should be high enough so that a drug with rewarding properties would require only a few bar presses to produce a cumulative dose that has a rewarding response.**

**Your drug discrimination study showed full generalization between remimazolam and midazolam in rats. However, you did not respond to a previous CSS request that you provide an explanation for these findings, given that the pharmacokinetics from a 4-week intravenous toxicity study in rats showed that exposure to remimazolam was negligible.**

*Question 3: Does the Agency agree that the nonclinical program for assessment of abuse potential of remimazolam, as supported by relevant CMC and clinical data, is complete to support NDA filing for remimazolam and allow scheduling of the drug?*

**FDA Response to Question 3:**

**A complete preclinical abuse-related assessment for an NDA submission includes chemistry, receptor binding for all major CNS-active sites, general behavioral studies conducted during toxicology testing, specific abuse-related behavioral studies (drug discrimination and self-administration) and a physical dependence evaluation. The clinical assessment of abuse includes an evaluation of abuse-related adverse events and a human abuse potential study.**

**Currently, your evaluation of whether oral and intranasal administration of remimazolam have abuse potential is not complete (see responses to Questions 5 and 6).**

**Further, the solubility study seems to demonstrate that remimazolam is soluble in 10% ethanol and moderately soluble in 40% ethanol. Provide data for the solubility in 20%-25% ethanol and with increased volume.**

*Question 4: Does the Agency agree that:*

- a) *The design and execution of HAP study CNS7056-014 is acceptable for assessing abuse potential by the intravenous route of administration in humans?*

**FDA Response to Question 4a:**

**When the full detailed final study report is submitted in the NDA and reviewed, we will be able to state whether its design and execution are appropriate. However, CSS previously provided feedback to you with recommendations regarding study design, including suggestions on the addition of VAS measure Take Drug Again. As long as the protocol used for the study conforms to our previous recommendations, the study should be adequate.**

**Notably, we cautioned you that subjects in the intravenous HAP study needed to have appropriate experience with benzodiazepines, not just depressants such as opioids, in order to qualify for participation in the study. The protocol summary submitted in the meeting package stated that individuals needed to have only a single lifetime experience with benzodiazepines, but may have had more, in order to**

qualify as a subject. Typically, subjects in a HAP study have at least 10 lifetime experiences with the drug class that is similar to the test drug, at least 3 experiences with the drug in the past year and at least 1 experience with the drug in the last month. Whether the subjects have additional experience with opioids is not the issue because many drug abusers have extensive history with other classes of abusable drugs. However, in the HAP study, subjects were able to differentiate the effects of the positive control from placebo on the VAS for Drug Liking in both the Qualification Phase and the Treatment Phase. These data are sufficient to show that subjects were qualified to participate.

Additionally, we previously informed you that you should include an assessment of memory/amnesia effects from remimazolam. Based on the summary of the HAP study provided, it appears the study evaluates memory/amnesia as adverse events, rather than using a validated behavioral measure that tests memory.

- b) *Upon review, will the results from this study be acceptable for FDA to make a determination regarding the relative abuse potential of remimazolam compared to that of midazolam and allow scheduling of the drug?*

**FDA Response to Question 4b:**

**When the NDA is submitted, the final study report for the HAP study will be one part of the abuse potential assessment for remimazolam.**

*Question 5: Does the Agency agree, upon review, that:*

- a) *The oral route of administration, as a potential route of abuse, has been adequately and satisfactorily characterized, and no further investigations are needed in support of the NDA?*
- b) *The data from these investigations will allow for the evaluation of the oral route as compared to the intravenous route for potential abuse?*

**FDA Response to Question 5a and 5b:**

**No, we do not agree that investigations into the oral route of administration for abuse purposes have been adequate.**

***Insufficient Oral Dosing***

**The final study report for the human pharmacokinetic (PK) study comparing oral versus intravenous administration of remimazolam has not yet been submitted, so we cannot state whether its design and execution are appropriate. However, the summary of the study does not provide justification for the oral dose used. The reason that oral (and intranasal) administration is an abuse-related safety concern is because a single vial of your drug product contains (b) (4) mg of remimazolam as sulfate salt (20. (b) (4) mg as base) as a powder**

for reconstitution prior to intravenous administration. Thus, the oral dose used in human studies should represent utilization of the full (b) (4) mg of remimazolam sulfate per subject, unless there are safety reasons that preclude use of this dose. Based on a 70 kg person, the oral dose of 0.14 mg/kg that was used in the PK study equates to only 9.8 mg of remimazolam sulfate, which is (b) (4)% of the available (b) (4) mg in a drug vial. This dose is insufficient to evaluate the abuse potential of an oral dose of remimazolam compared to an intravenous dose.

Additionally, the doses of remimazolam used for oral and intravenous administration to assess abuse potential should produce plasma levels that are as similar as possible. This would necessitate knowing the plasma levels produced by an oral dose of (b) (4) mg of the sulfate salt and then identifying an intravenous dose that produces similar plasma levels.

#### *Method of Reconstitution*

You do not detail the method of reconstitution of the drug powder in the study summary. The instructions for reconstituting remimazolam for intravenous injection involve the addition of 8.2 mL 0.9% saline solution for a final drug concentration of 2.5 mg/mL. If a different method was used, it should be described and justified.

#### *Lack of Pharmacodynamic Evaluations*

We previously informed you that your study should include a pharmacodynamic (PD) evaluation (which would include abuse-related subjective measures such as a visual analog scale (VAS) for Drug Liking). However, the PK study does not include any PD measures. Thus, there are no means through which to evaluate whether oral administration produces different abuse-related responses than intravenous administration of remimazolam.

- c) *The necessary assessments have been made to evaluate the potential to incapacitate a victim with a combination of remimazolam and alcohol?*

#### **FDA Response to Question 5c**

##### *Potentiation of Remimazolam by Ethanol*

The rabbit behavioral study conducted with remimazolam, ethanol and the combination of the two drugs showed that ethanol can potentiate the sedative effects of remimazolam. These data strongly suggest that remimazolam can be used to incapacitate a human for victimization purposes.

In the advice letter dated January 26, 2015, we informed you that it was necessary to identify the oral doses of remimazolam in alcoholic beverages that produce impairment in humans. The evaluation of this question would involve testing a variety of alcoholic beverages that have different relative concentrations of ethanol and water-based solutions, since higher concentrations of ethanol appear to reduce remimazolam solubility. CSS can review a protocol for such a study.

*Question 6: Does the Agency agree that the intranasal route of administration, as a potential alternative route of abuse, has been adequately and satisfactorily addressed and that no further investigations, including an intranasal HAP study, are required to support the NDA and for scheduling of remimazolam?*

**FDA Response to Question 6:**

The final study reports have not been submitted for the intranasal feasibility studies, so we cannot state whether their design and execution are appropriate. However, the intranasal studies in mice and rats appear to administer remimazolam as intranasal sprays, rather than as powder forced into the nostrils of the animals. Given the tiny intra-nostril space of rodents, it is not surprising that little drug was apparently absorbed in some animals. However, despite these administration limitations, some animals experienced sedation and analgesic responses, suggesting that remimazolam can produce psychoactive effects through intranasal administration. These responses were similar to the ones produced when remimazolam powder was directly applied to the nostrils of minipigs.

These data support the conclusion that remimazolam powder may be snorted by humans for abuse purposes. In the advice letter dated January 26, 2015, we informed you that the intranasal doses of remimazolam powder required to produce a psychoactive effect are unknown and must be evaluated and submitted as part of the NDA. CSS is available to review a protocol for such an intranasal study in humans, which should include both PK and PD evaluations.

As previously communicated, you must provide adequate nonclinical support of safety for the clinical administration of the product. This nonclinical data must be submitted prior to clinical dosing.

*Question 7: Does the Agency agree that the studies proposed, along with the data that will be generated, are adequate and sufficient to allow the Agency to make a determination regarding abuse potential, and ultimately, the scheduling of (b) (4) and (b) (4)*

**FDA Response to Question 7:**

(b) (4) are not evaluated for abuse potential and thus will not be considered for scheduling under the Controlled Substances Act.

**ADDITIONAL COMMENTS:**

**CMC**

- 1. It appears that the API is a pure S isomer. Therefore, optical rotation should be controlled at release and on stability.**
- 2. Provide the structure and identification of the two degradants:** (b) (4)  
[REDACTED]
- 3. The Vial Content measured at release should be expressed as the quantity of besylate salt in the vial.**
- 4.** [REDACTED] (b) (4)
- 5. Provide data to demonstrate the maximum amount of the** (b) (4)  
**that can be present in remimazolam.**

**CONTROLLED SUBSTANCE STAFF**

- 1. It is unclear from the study summaries that you have submitted whether the abuse-related studies conducted with remimazolam calculated the doses based on the weight of the drug as the sulfate salt or as the base.**
- 2. When you submit the NDA, you should standardize and report drug doses as either sulfate salt or base in preclinical and clinical studies, so that comparisons between the studies are possible.**

**PREA REQUIREMENTS**

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant

endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **SECURE EMAIL COMMUNICATIONS**

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

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SELMA S KRAFT  
11/21/2016



IND 102486

**MEETING MINUTES**

PAION UK Limited

(b) (4)

Attention:

(b) (4)

US Agent

Dear Dr. Putnam:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Remimazolam (CNS 7056).

We also refer to the meeting between representatives of your firm and the FDA on October 17, 2013. The purpose of the meeting was to discuss the Sponsor's plans for Phase 3 of their development program.

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 301-796-1191.

Sincerely,

*{See appended electronic signature page}*

Kimberly Compton, R.Ph.  
Senior Regulatory 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**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type/Category:** Type B (EOP2)

**Meeting Date and Time:** October 17, 2013, 1:13 PM

**Meeting Location:** White Oak, Bldg 22, Rm 1313

**Application Number:** IND 102486

**Product Name:** Remimazolam (CNS 7056).

**Indication:** Intravenous (IV) sedative in adult patients undergoing diagnostic or therapeutic procedures

**Sponsor Name:** PAION UK Limited

**Meeting Chair:** Christopher Breder, M.D., Ph.D., Clinical Team Leader,  
Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

**Meeting Recorder:** Kim Compton, Sr. Regulatory Project Manager, DAAAP

<b>PAION UK Limited Representatives</b>	<b>Title</b>
Mariola Soehngen, M.D.	Chief Medical Officer
Karin Wilhelm-Ogunbiyi, M.D.	Vice President/Medical Director
Keith Borkett	Director of Clinical Operations
(b) (4)	Clinical/Regulatory Consultant
	Gastroenterology Consultant
	Senior Statistical Consultant
	Regulatory Consultant
	CMC Consultant
<b>FDA Representatives</b>	<b>Title</b>
Bob Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Rigoberto Roca, M.D.	Deputy Director, DAAAP
Leah Crisafi, M.D.	Medical Officer, DAAAP
Christopher Breder, M.D., Ph.D.	Clinical Team Leader, Anesthesia Drug Products, DAAAP
Kate Meaker, Ph.D.	Biostatistics Reviewer, Division of Biometrics II (DBII)
Janice Derr, Ph.D.	Biostatistics Team Leader, DBII
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Yun Xu, Ph.D.	Clinical Pharmacology Team Leader
Newton Woo, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Adam Wasserman, Ph.D.	Supervisory Pharmacologist, DAAAP
Julia Pinto, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Silvia Calderon, Ph.D.	Team Lead, Controlled Substances Staff (CSS)
Chad Reissig, Ph.D.	Pharmacologist, CSS
Somya Dunn, M.D.	Risk Management Analyst, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)
Morgan Walker, Pharm.D., MBA	Acting Team Leader, Division of Medication Error and Prevention (DMEPA), OSE
Rachna Kapoor, Pharm.D.	Safety Evaluator, DMPEA, OSE
Lisa Skarupa, R.N., M.S.N.	Sr. Regulatory Project Manager, OSE
Kim Compton	Sr. Regulatory Project Manager, DAAAP

## BACKGROUND

The Sponsor stated that the purpose for this meeting is to obtain FDA feedback on all aspects of the Phase 3 development plan for their product.

Specifically, the firm stated they have the following objectives for the meeting:

1. To obtain Food and Drug Administration (FDA) feedback on the acceptability of adding dextran 40 as an excipient to remimazolam in the CMC process before initiating the Phase 3 study with remimazolam and filing of an NDA.
2. To obtain FDA feedback on the acceptability of the nonclinical toxicology and clinical pharmacology program to support the conduct of the pivotal Phase 3 clinical study and filing of an NDA.
3. To obtain FDA guidance on the remimazolam clinical development plan and the pivotal Phase 3 clinical study design to replicate the prior pivotal efficacy study and to support the proposed indication as an intravenous (IV) sedative in adult patients undergoing diagnostic or therapeutic procedures and filing of an NDA.
4. To obtain FDA guidance on the abuse liability expectations for remimazolam for filing of an NDA.
5. To obtain agreement on the proposed labeling and labeling claim for remimazolam based on the proposed clinical development plan and Phase 3 study design to support filing of an NDA.

The product is remimazolam, a novel, short-acting benzodiazepine. The Sponsor proposed a clinical program for the indication of Procedural Sedation consisting of trials of sedation for colonoscopy. The IND was opened in May of 2008 with a first-in-human Phase 1 study to determine the safety, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy adults.

The questions from the Sponsor's September 5, 2013, meeting package are included below in *italic* font with the Agency responses and comments following in **bold**. The Sponsor provided responses to the Agency's Preliminary Comments via email on Wednesday, October 16, 2013. They are included after the question to which they pertain in *italic* font. Discussion that took place at the meeting follows the question to which it pertains in normal font.

After receiving and reviewing the Agency's Preliminary Responses on Wednesday, October 16, 2013, the Sponsor indicated that they would like to discuss the following questions at the meeting in this order: Questions 16, 4-5, 6, 3, 14, 11, 2, and 8. Allotted time expired before questions 11, 2 and 8 could be discussed. It was agreed that Agency feedback on the Sponsor's offered response would be included in the Meeting Minutes.

## DISCUSSION

### Introductory Comment

For an indication of sedation in patients undergoing diagnostic or therapeutic procedures, the data from your clinical development program should be generalizable to the full clinical context of procedural sedation and not be limited to that from trials of sedation for colonoscopy. You need to identify a representative set of procedures, such that the data can be generalized to the broad indication of procedural sedation in terms of attributes, such as:

- Depth of Sedation
- Dose range employed
- Duration required
- Need for amnesia
- Expected patient tolerability for the procedure
- Population demographics (age, gender, and possibly race if relevant)

As part of your clinical development program, you should conduct a trial of sedation for a clinical procedure that is likely to require minimal rescue medications or concomitant analgesics to provide a clearer interpretation of your drug's effect. We can discuss other design features you may consider to achieve this goal. We appreciate that you have included midazolam as an active control in your proposed Phase 3 trial. You should also include clinical trial(s) with other comparators that are commonly used for procedural sedation to more fully inform the product labeling.

We appreciate that many aspects of your proposal are similar to what is described in the (b) (4). However, our understanding of the challenges associated with sedation clinical trial design and interpretation has improved significantly in the 10 years since the (b) (4) trials were designed and conducted. We participated in a scientific workshop on the design of trials for the study of sedation that raised many of the issues that need to be addressed (<http://www.fda.gov/Drugs/NewsEvents/ucm301022.htm>). Consider the discussion from the workshop as you reconsider your proposal.

### Chemistry Manufacturing and Controls (CMC)

#### *Question 1*

*Based on the history and use of dextran 40 in FDA-approved IV products, PAION does not believe that the addition of dextran 40 into the formulation would impact the safety or efficacy requirements of the phase 3 study and that the use of the formulation in the phase 3 study would adequately justify its use in the proposed commercial product. Does the Agency agree?*

#### FDA Response

**It is acceptable to switch to the dextran formulation for the Phase 3 trials from CMC perspective. Provide both long-term and accelerated stability data for the clinical trial batch(es) with your IND submission.**

Sponsor Response

*Thank you for the response.*

Discussion

There was no further discussion on this point.

**Nonclinical**

*Question 2*

*Does the Agency agree that no additional nonclinical studies would need to be conducted to support the addition of dextran 40 as a new excipient in the remimazolam drug product?*

**FDA Response**

**At this time, we cannot agree that no additional nonclinical studies will be required to support the addition of dextran 40 as a new excipient in the remimazolam drug product. Although it is recognized that dextran 40 is an excipient in a marketed product at a higher dose, its inclusion does not provide support due to its use in a markedly different patient population.**

**Therefore, in your NDA submission, provide either adequate scientific justification, or data from the conduct of nonclinical studies, to support the safety of dextran 40 at a level associated with maximal use of remimazolam.**

**If you plan to rely on the Agency's previous finding of safety for dextran 40 you will need to submit your NDA through the 505(b)(2) pathway. Note that a 505(b)(2) application may not rely on any specific data for the referenced drug (e.g., such as that included in a summary basis of approval). Additionally, the referenced drug relied upon for approval must have been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (i.e., NDAs); applications approved under section 505(j) (i.e., ANDAs, also known as generics) may not be relied upon. Furthermore, carefully review the additional 505(b)(2) comments at the end of this document.**

**You may still submit as a 505(b)(1) application if you rely on "general knowledge" to address NDA requirements. However, you must clearly delineate why the referenced information is general knowledge. Reliance on information in textbooks does not always equate to general knowledge, as textbooks have been known to cite specific drug product labeling.**

**After your clinical batch for Phase 3 is characterized, amend the IND to include adequate safety information for any impurity or degradant that has not been previously identified prior to initiating Phase 3 clinical protocols.**

Sponsor Response

*Based on FDA approved nature of dextran 40 as an excipient and active ingredient, its GRAS status, its use in the Ono clinical studies in anesthesia (with a much higher dose and for longer exposure, see Table 38, page 141 of the meeting information package), as well as its use in the proposed Phase 3 studies, we believe there is adequate scientific justification to support the safety of dextran 40 for the proposed indication. We will provide additional supportive data in the IND for FDA review.*

Discussion

There was no further discussion on this point due to time constraints, but the Sponsor had previously indicated they wished to receive feedback on their emailed response. The Division agreed to review the Sponsor's response and provide any follow-up feedback in the meeting minutes.

**\*\*\*Post-Meeting Note:**

We acknowledge dextran-40 is used in a marketed product at a higher level than in your product. However, it is contained in a drug product indicated for a markedly different patient population, oncology patients. Marketing approval for this oncology drug utilizes a significantly different risk-benefit assessment and therefore does not provide adequate support for dextran-40 as an excipient in a drug product indicated for procedural sedation. We understand that dextran-40 is designated as GRAS, but this designation does not provide support because your product is not for oral use but rather for parenteral use, which again utilizes a different risk-benefit assessment. We also acknowledge the accumulating human experience with dextran-40 from use as an excipient in previous clinical studies conducted by Ono and future use in planned Phase 3 studies. However, these clinical studies, while providing limited support, do not provide a histopathological assessment of various tissues that are exposed to dextran-40.

As mentioned in our prior responses, you may qualify the safety of dextran-40 by citing reliance on the Agency's previous determination of safety and efficacy of dextran-40 as an active ingredient. To do this, you must submit your NDA through the 505(b)(2) pathway. Alternatively, you may qualify the safety of this excipient through the conduct of additional nonclinical studies. We refer you to the following guidance for additional information: guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf>

*Question 3*

*Does the Agency agree that the nonclinical package is sufficient for the conduct of the phase 3 study and in support of filing an NDA for the indication of IV sedative in adult patients undergoing diagnostic or therapeutic procedures, and that no additional nonclinical studies are necessary with remimazolam?*

### **FDA Response**

**Yes, we agree that the nonclinical package appears sufficient for the conduct of a Phase 3 study, provided women of child bearing potential are either excluded or are required to use two forms of contraception, and the informed consent states there is limited reproductive and developmental nonclinical data with remimazolam to date.**

**However, we do not agree that the nonclinical package is sufficient for the filing of an NDA. For an NME, we require supportive nonclinical studies from two species. Due to the lack of systemic exposure to the parent (CNS-7056), the rat does not appear to be a relevant toxicological species. Therefore, unless scientifically justified, the 4-week repeat-dose toxicology study as well as the reproductive and developmental studies that were conducted in rats must be repeated in an appropriate and relevant species prior to the submission of the NDA. In addition, your NDA submission must also contain data that adequately qualify any impurity or degradant that exceeds ICH Q3A or ICH Q3B thresholds.**

### **Sponsor Response**

*We would like clarification on the perceived inadequacy of the rat model. We note that in our 28-day repeat dose rat study that there was relevant systemic exposure as evidenced by relevant  $C_{max}$  and AUC exposure and the observed sedative effects including death. NOASEL was 20 mg/kg/day, with  $C_{max}$  and AUC (m/f) of 19.1/16.9 ng/mL and "not determined"/24.5 ng\*h/mL, respectively (please see Table 10, page 56, and study RMN1018: Four week intravenous (bolus) repeat dose toxicity study in the rat with a two week recovery period, page 444; week 4). At 30 mg/kg (the highest dose studied),  $C_{max}$  and AUC (m/f) were 15.0/4.19 ng/mL and 4.13/3.65 ng\*h/mL, respectively (same study). It is difficult to obtain standard PK parameters in the rodent species due to the rapid metabolism of remimazolam.*

### **Discussion**

The Division agreed that the rat has been an acceptable model to characterize the pharmacodynamic effects of remimazolam, but stated that bolus administration in rats is not an appropriate model to assess toxicology because the resulting parent exposure levels in rats were only a fraction of human exposure levels. Noting the difficulties in characterizing the toxicokinetic properties due to the rapid conversion of the parent to the metabolite, the Sponsor asked the Division to suggest a nonclinical species for their repeat-dose toxicity study. The Division responded that there are several species that may be explored, which include, but are not limited to, the mini-pig, mouse, or dog, and that it is ultimately the Sponsor's responsibility to investigate and determine what species is the most appropriate. The Sponsor stated that they cannot utilize the dog because of the paradoxical effect of benzodiazepines in the canine model.

The Division stated that if the Sponsor explores all options and is unable to identify an adequate second species, they will need to submit a scientific justification which the Division will consider when evaluating the package. This justification may be submitted to the IND for review and evaluation before the NDA is submitted. The more difficult question, however, may be how to address reproductive toxicology, since these studies are usually conducted in rodents. Similar to the case of the repeat-dose study, the Division stated that the Sponsor will be required to search and evaluate an appropriate

species for the various reproductive toxicology studies. The Division clarified that, if a repeat-dose toxicology study is to be repeated, a 28-day study would suffice for the NDA.

The Sponsor stated that they may have continuous IV exposure data in rats, which evaluates the same drug product as part of their partner's development program for other indications. The Division stated that, if a continuous infusion in the rat is viable and can yield higher systemic exposures of the parent than in humans, then this model may be used to address general and reproductive toxicology study requirements.

### **Additional Nonclinical Comments**

**For your NDA submission:**

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

- *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*
- *a repeat-dose toxicology study of appropriate duration to support the proposed indication*

**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.**

#### **Discussion**

There was no further discussion on this point.

### **Clinical**

#### *Question 4*

*The results from study CNS7056-004, a phase 2b randomized, multiple dose, double-blind, parallel-group, active comparator efficacy and safety study with remimazolam and midazolam was conducted in patients undergoing colonoscopy. The study results showed not only efficacy for remimazolam,*

(b) (4)

*Does the Agency agree?*

**FDA Response**

**No, we do not agree. We acknowledge** [REDACTED] (b) (4)

[REDACTED] **and our understanding of the science underlying the design of clinical trials for the indication of sedation has evolved in the interim.**

**In light of these advances, your Phase 2b study** [REDACTED] (b) (4)

[REDACTED] **While the information on the design, conduct, and data from this trial has not been submitted for us to fully review, our preliminary concerns** [REDACTED] (b) (4)

**Regarding the components of your composite endpoint of procedure success, we have the following concerns:**

- 1. The first component of the composite endpoint is a MOAA/S score on 3 consecutive measurements, each 1 minute apart, which could be accomplished with only 2 minutes of adequate sedation. After consideration of the issues raised in the Public Workshop on the design of sedation trials noted above, we are concerned that this may not be an adequate period of assessment for determining sedation success. Rather, your primary endpoint should capture whether or not depth of sedation was adequate for the duration of the procedure.**
- 2. The fourth component of your composite endpoint is “No manual or mechanical ventilation.” While we agree that ventilatory depression is an important consideration, we have questions about this component and would like to discuss it further with you.**

**We are concerned that without standardized criteria for fentanyl administration in the study protocol, any clinical differences between your drug and the comparator would be masked by fentanyl’s sedating properties, as fentanyl can very effectively rescue otherwise inadequate sedation. The results of your study may not be interpretable depending on the amount, the relative use between treatment arms, and the symptoms prompting the use of fentanyl. Your clinical development program should address this concern in each of the trials you propose.**

**As mentioned in our introductory comments, consider the discussion from our scientific workshop on the design of trials for the study of sedation as you reevaluate your proposal.**

**Sponsor Response**

*We agree to conduct two Phase 3 pivotal trials, one in colonoscopy patients and one in upper GI endoscopy patients,* [REDACTED] (b) (4).

[REDACTED] *In clinical practice as evidenced by the literature, the standard of care for moderate sedation in such procedures is a narcotic plus a*

*benzodiazepine (Cohen 2006 and Aisenberg 2006, see attachments for literature references). Therefore, for our pivotal trials, the control arm will receive fentanyl plus midazolam; standard of care for moderate sedation. We believe that a placebo controlled trial would be unethical.*

*To fulfill FDA's desire for uniformity in narcotic dosing all patients could receive a maximum dose of 125 µg (ie, 50-100 µg initial dose plus up to 25 µg top-off dose). Although this is consistent with current labeling, this is not consistent with current standard of care.*

*The primary efficacy endpoint, as per your request, will be success rate in completing colonoscopy and upper GI endoscopy, without additional narcotics or other medications, beyond specified in the protocol.*

[REDACTED] (b) (4)

*We propose the interim analysis to confirm the sample size calculations.*

[REDACTED] (b) (4)

Discussion

The Sponsor stated that they plan to seek an indication of sedation [REDACTED] (b) (4). The Division stated that the proposed indication does not reflect the expected use, and that unless the Sponsor can demonstrate a safety reason that the product [REDACTED] (b) (4), the Sponsor should complete studies that represent the expected use of the product. The Division indicated that the Sponsor does not need to [REDACTED] (b) (4).

[REDACTED]

The Division suggested that the Sponsor consult with experts in other fields that may utilize the product for procedural sedation (e.g., emergency, pulmonary, anesthesia, and pediatric physicians).

The Sponsor asked if it would be acceptable to seek approval for [REDACTED] (b) (4).

[REDACTED]

The Division is concerned [REDACTED] (b) (4).

[REDACTED] The Division stated that we will consider the

Sponsor's proposal [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**\*\*\*Post-Meeting Note**

We acknowledged that there are studies in progress in other indications that will evaluate the use of remimazolam in a wider spectrum of patients. However, as far as the indication of procedural sedation is concerned, since there is the possibility that remimazolam may be used off-label for other procedures, it would be important to have clinical data on procedures that have more intense levels and longer periods of stimulation. A clinical trial in patients undergoing a bronchoscopy would complement the clinical trials in the GI procedures, and the three trials could potentially provide sufficient data to make a better assessment of the risks and benefits of remimazolam when used for procedural sedation.

The Division stated that the Sponsor may need to reconsider their study design, because the fentanyl regimen in the proposed study confounds the evaluation of the treatment effect of the remimazolam. Furthermore, a placebo-controlled trial could be ethical and acceptable, with appropriate monitoring and use of rescue medication. The Division would entertain the option of a dose-controlled study design.

[REDACTED] (b) (4)

The Division acknowledged the challenge of interpreting clinical trial data when patients in the comparator arm will receive another similar agent, but also emphasized the need for standardization in the design of such trials. The Division noted that similar challenges exist in the design of chronic pain trials. In those trials, rescue doses are defined, careful records are kept of timing and dosing when rescue is administered, and efficacy is assessed just before the rescue is given, so that the analgesia conferred by the rescue medication doesn't confound interpretation of the primary endpoint data.

*Question 5*

*Does the Agency agree with the study design for the planned adequate and well-controlled, replication, pivotal US phase 3 trial (study CNS7056-006), utilizing the justification for claimed dosing regimen of remimazolam, based on clinical data and PK/PD modeling to support the efficacy and safety of remimazolam for NDA approval for the indication of IV sedative in adult patients undergoing diagnostic or therapeutic procedures?*

**FDA Response**

**We are concerned with several elements of your proposed study design. Our concerns with your primary endpoint and manner of fentanyl use of fentanyl were discussed in our response to Question 4.**

**In addition, you have stated that your comparator is midazolam because it is the gold standard drug used in this indication; you will need to support your rationale that midazolam is the gold standard for procedural sedation and, specifically, for sedation during colonoscopy. We suggest that other comparators be considered. As noted in the guidance for industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf>, alteration of design features between your studies (e.g., choice of comparator) may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.**

**Additional Statistical Comments**

(b) (4)

**Sponsor Response**

***Please see PAION's response above under Question 4 which addresses FDA's response for Question 5.***

Discussion

See discussion and Post-Meeting Note under question 4 above.

*Question 6*

*Remimazolam belongs to a well-known substance class, the benzodiazepines. To date, 834 healthy volunteers and patients have been exposed to remimazolam in completed studies via the route of IV administration, using varying dosing regimens with patients receiving total doses of remimazolam ranging from 0.662 to 33.12 mg. The highest single dose of remimazolam administered was 20.24 mg. With the completion of the planned pivotal phase 3 study, as well as with studies for other indications (ie, induction and maintenance of general anesthesia and ICU sedation) conducted by Ono where higher doses of remimazolam are administered by IV for longer periods of time, there will be a safety database of more than 1700 patients directly administered remimazolam. Does the Agency agree that the safety database for remimazolam would be sufficient for NDA approval for the indication of IV sedative in adult patients undergoing diagnostic or therapeutic procedures? Does the Agency agree that the foreign clinical study reports can be submitted in the NDA for the clinical studies not conducted under IND 102486 by PAION and Ono for other indications to support the overall safety database for remimazolam?*

**FDA Response**

**Your proposed safety database will not be sufficient for NDA approval. The ICH E1A guideline notes that the total number treated with the investigational drug, including short-term exposure, should be 1500 individuals. We appreciate that your drug would be for acute use in an indication of procedural sedation, but while there is not a specific guidance for the size of the database needed for drugs for acute use, we have used the 1500 subject requirement as a baseline for an adequate safety database for a drug that is a New Molecular Entity. It must also include a sufficient numbers of subjects to characterize the adverse event profile of the drug, in the intended indication as you propose to label it.** (b) (4)

**The majority of these subjects should be exposed to the highest dose and longest duration for each sedation trial type. However, should safety concerns arise during clinical trials, expansion of the safety database may be necessary.**

**You have proposed to submit foreign clinical study reports in the NDA for studies not conducted under IND 102486. We agree that you should submit such foreign clinical study reports, along with the protocols and original data. You should provide a rationale as to why these data are relevant and of such quality that they should be considered despite the studies not being conducted under IND.**

**Sponsor Response**

**Based on FDA's recommendations, we are now proposing two Phase 3 studies, one in colonoscopy and one in upper GI endoscopy** (b) (4)

**With regard to exposure and duration, the patients will be titrated to effect for procedural sedation.**

*The total safety database generated under the IND will be at least 700 patients exposed to remimazolam. The total safety database for remimazolam exposure including the foreign data (with much higher exposure to the drug and for longer duration) will be over 1500 patients.*

*Does the FDA agree that this is a sufficient safety database for NDA filing?*

**Discussion**

The Division stated that the acceptability of data from foreign studies to support the required number of exposed patients will depend on the quality of data and the conduct of the studies. The Division stated that we could review the protocols for the studies of ICU sedation and anesthesia induction conducted outside the United States to get a general sense of the quality of the data and conduct of those studies. (b) (4)

**Question 7**

*Based on the inclusion criteria and study design planned for study CNS7056-006 (see [Table 35](#)) and the data collected in elderly patients in the completed clinical trials, as well as those currently ongoing or planned with remimazolam, does the Agency agree that the available clinical data would allow adequate dosage adjustment assessment in elderly patients for the product labeling included in the NDA filing?*

**FDA Response**

**The Agency agrees that the clinical data obtained in Study CNS7056-006 may be sufficient to characterize dosing for elderly patients for the product labeling. However, in determining the adequacy of the data, we will consider the numbers, ages, and plasma exposures of subjects, as well as the resulting safety profile.**

**Sponsor Response**

*Thank you for the response.*

**Discussion**

There was no further discussion on this point.

**Question 8**

*Does the Agency agree that a separate clinical study does not need to be conducted for NDA filing to address clinical pharmacology dosage adjustments in renal-impaired patients based on the nonclinical data collected for the (renally excreted and pharmacologically inert) principal metabolite, CNS 7054?*

### **FDA Response**

**Even when the renal route is not the primary route of elimination of a drug, renal impairment can adversely affect some pathways of hepatic/gut drug metabolism and has also been associated with changes in absorption, plasma protein binding, transport, and tissue distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed. Thus, for most drugs that are likely to be administered to patients with renal impairment, including drugs that are not primarily excreted by the kidney, PK should be assessed in patients with renal impairment to provide appropriate dosing recommendations. Therefore, in addition to the rationale you provided, you will need to provide justification, such as literature or in-house data on the impact of renal impairment on esterase activity, as well as the aspects mentioned above. Refer to the guidance for industry: *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*, available at**

**<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> for details.**

**We note that you evaluated impact of mild renal impairment on the PK of remimazolam. We also note that you have PK sampling proposed in your Phase 3 study. Consider expanding the population PK approach to understanding impact of moderate to severe renal impairment in Phase 3 studies.**

### **Sponsor Response**

*Based on FDA's advice, we will conduct a small PK/PD study in renal dialysis patients.*

### **Discussion**

There was no further discussion on this point due to time constraints, but the Sponsor had previously indicated they wished to receive feedback on their emailed response. The Division agreed to review the Sponsor's response and provide any follow-up feedback in the meeting minutes.

### **\*\*\*Post-Meeting Note**

Your plan to conduct a separate PK/PD study in patients requiring renal dialysis in place of a population PK approach is acceptable. It appears that you are taking a "reduced PK study" design, as specified in the renal impairment guidance [guidance for industry: *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>.] If in fact that is your approach, ensure that you follow the design features described for "reduced PK study" in the guidance. Ensure that patients will not undergo dialysis right after dosing with the drug since dialysis may help remove the drug from body.

*Question 9*

*Does the Agency agree that no additional clinical study need to be conducted for NDA filing to address clinical pharmacology dosage adjustments in hepatic-impaired patients based on the nonclinical data and the clinical data to be generated in the ongoing study ONO-2745IVU007 in hepatic-impaired patients being conducted with remimazolam under (b) (4)?*

**FDA Response**

**Your proposed plan to address dose adjustment in hepatic-impaired patients based on the nonclinical (metabolism) studies and the ongoing clinical pharmacology study appears reasonable.**

**Sponsor Response**

*Thank you for the response.*

**Discussion**

There was no further discussion on this point.

*Question 10*

*PAION plans to request a pediatric assessment deferral in patients (b) (4) years of age until after NDA approval as a phase 4 commitment. PAION plans (b) (4) (b) (4) Does the Agency agree with this proposal for a deferral (b) (4) in the proposed age groups? Does the Agency agree with the study design for the planned phase 4 study in pediatric patients (b) (4) years of age in Table 36 for the procedural sedation indication?*

**FDA Response**

**You have proposed to defer pediatric assessment in patients (b) (4) through 16 years of age (b) (4). Your proposal to defer pediatric studies is acceptable. (b) (4)**

**Your justification for deferral (b) (4) must be presented as outlined in the guidance for industry: *How to comply with the Pediatric Research Equity Act*, available at**

**<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>.**

**We will review your pediatric study proposal when you submit your pediatric study plan (PSP). However, we have a few suggestions at this time:**

- The study should mirror the desired adult indication and, therefore, capture the entire clinical context of diagnostic and procedural sedation, whereas you**

have proposed to study only subjects undergoing diagnostic and therapeutic imaging procedures.

- You have proposed [REDACTED] (b) (4) which is not acceptable. Your study should have an efficacy-based primary endpoint. See Additional Clinical Pharmacology Comments below.
- You should incorporate age-appropriate sedation assessment scales into your protocol.
- Subjects should be evenly distribution between genders and approximately equally distributed across the age groups and within the age groups.
- You should study a sufficient number of subjects to adequately characterize common adverse events with the study drug at clinically relevant doses.

Finally, we note that you are required to submit a PSP within 60 days of this EOP2 meeting. That PSP must include any deferral or waiver requests. Further information about the content and format of PSPs is provided in the draft guidance for industry: *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plan*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

#### Additional Clinical Pharmacology Comments

We note that the population PK analysis does not support [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)  
[REDACTED] (b) (4)  
, this approach will not be acceptable.

[REDACTED] (b) (4)  
For more information on this topic, you may refer to this article: Wang, Y., Jadhav, P.R., Lala, M., Gobburu, J.V. (2012). Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. *J Clin Pharmacol.* Oct;52(10):1601-6.

#### Sponsor Response

*Thank you for the response. We will submit a PSP in 60 days as requested for Agency review.*

#### Discussion

There was no further discussion on this point.

*Question 11*

*PAION has conducted a number of nonclinical drug-drug interaction studies. Due to the PK profile of remimazolam (a  $t_{1/2}$  of less than 5 minutes precludes adequate time to create a drug-drug metabolic interaction) and its metabolism via tissue esterases, remimazolam has a low liability for PK drug-drug interactions. Taking into account in vitro studies planned to investigate possible interactions with drug transporters and provided the outcome is negative, does the Agency concur that no further nonclinical or clinical drug-drug interaction studies are required for NDA filing?*

**FDA Response**

**The nonclinical (metabolism and transporter studies) plan to address pharmacokinetic drug interactions appears reasonable. However, your clinical plan to assess pharmacodynamic interactions with perioperative medications and safety of their concomitant administration is not clear. Provide information to address the potential interactions with possible concomitant medications.**

**Sponsor Response**

*The most important interaction that we anticipate clinically is the known PD drug interaction with opioids as highlighted in the TPP in Sections 5.2 (Use with Other CNS Depressants) and 7 (Drug Interactions) as well as in the approved midazolam labeling. The proposed Phase 3 studies will include administration of fentanyl and all concomitant medications will be recorded. Sub-group analysis will be performed as appropriate for concomitant medications.*

*Please advise if this is not acceptable.*

**Discussion**

There was no further discussion on this point due to time constraints, but the Sponsor had previously indicated they wished to receive feedback on their emailed response. The Division agreed to review the Sponsor's response and provide any follow-up feedback in the meeting minutes.

**\*\*\*Post-Meeting Note**

You should study the dose effect of remimazolam on ventilatory drive in the setting of concomitant opioid use.

*Question 12*

*PAION does not intend to conduct a thorough QT/QTc study due to the known pharmacology of benzodiazepines, the fact that clinical data to date have documented less of a QT effect with remimazolam than resulting from midazolam administration, the lack of relevant ECG changes associated with this pharmacological class, and the nonclinical and clinical data generated thus far on remimazolam showing no relevant ECG changes. Performing a thorough QT/QTc study may also not be considered ethical or appropriate due to the high dose needed in this kind of study to evaluate effects at high plasma concentrations, which might not be possible with a sedative/anesthetic. Does the Agency concur that PAION has already obtained sufficient QTc data to document the drug's cardiac safety for NDA filing?*

**FDA Response**

**No, we do not concur. Data obtained thus far are not sufficient to rule out small changes in QTc due to remimazolam. It may be possible to perform a thorough QT study in healthy volunteers receiving a dosing regimen of remimazolam that achieves therapeutic exposures. The design of such a study should take into account the expected increase in heart rate that has been observed with remimazolam administration. You should submit a study protocol for QT-IRT review.**

**Sponsor Response**

*We agree to conduct a QT study at the therapeutic dose and will submit a study protocol for review by the QT-IRT.*

**Discussion**

There was no further discussion on this point.

***Question 13***

***Based on the proposed overall US clinical development plan for remimazolam, does the Agency agree*** (b) (4)

[Redacted]

**FDA Response**

**No, we do not agree. Refer to the introductory comments for additional discussion.**

**Sponsor Response**

*Thank you for the response.*

**Discussion**

There was no further discussion on this point.

**Abuse Liability**

***Question 14***

***Does the Agency agree*** (b) (4)

[Redacted] are

***acceptable to address any abuse liability questions for NDA filing?***

**FDA Response**

**No, we do not agree.**

[Redacted] (b) (4)

**However, your proposal is not sufficient to address all aspects of the abuse potential characterization of remimazolam.**

**A human abuse potential study to characterize the subjective effects of remimazolam in subjects with histories of sedative abuse must be performed to fully characterize the subjective effects produced by intravenous remimazolam, including its effects on mood, psychomotor performance, and memory. For the clinical abuse potential study, midazolam injectable could be used as a positive control to support the FDA/HHS and DEA scheduling recommendation.**

**In addition, you should address the likelihood of abuse of the remimazolam through the oral and intranasal routes of administration. Unlike midazolam and other drugs indicated for sedation, remimazolam will be available as a powder for reconstitution. The powdered form of remimazolam increases the likelihood that the drug could be abused by the oral or intranasal route. Although it appears that that the oral bioavailability of remimazolam is low (lower than 10% across various animal species), you should explore if there is pharmacodynamic evidence of a drug effect at various doses when taken orally or intranasally.**

**You have assessed physical dependence in monkeys. Based on the summary provided, one of the six monkeys presented severe signs of withdrawal upon discontinuation of the drug. These withdrawal signs included systemic convulsions; please include a full assessment for this monkey in the final study report. In addition, provide data to assess the withdrawal signs of remimazolam relative to a scheduled and appropriate benzodiazepine.**

**Provide an explanation for the drug discrimination findings given the observed pharmacokinetic profile of remimazolam in rats. Based on the results of Study RMN1018, titled *Four Week Intravenous (Bolus) Repeat Dose Toxicity Study in the Rat with a 2 Week Recovery Period*, exposure to remimazolam is negligible.**

**The Controlled Substance Staff (CSS) cannot comment on the scheduling of remimazolam until all data related to the abuse potential of the drug are complete and available for review.**

**Sponsor Response**

*We agree to conduct the human abuse potential intravenous remimazolam study in subjects with history of sedative abuse and this data can be used to support scheduling the drug.*

*The current formulation is locally irritating as demonstrated in nonclinical studies (studies listed in Table 9 with specific details on page 205-207 of the meeting information package). Therefore, we do not regard it ethical to conduct the oral and nasal administration study in human volunteers in light of its local toxicity. In light of this toxicity and its extremely short half-life, we believe the formulation has minimal abuse potential.*

**Discussion**

The Agency stated that the Sponsor should submit any information about the abuse potential of the product that is relevant to its evaluation. Local irritation is related to intravenous injection, but the Agency is concerned about the use/abuse of the product by other than the injected route, so we would require more information on administration via other routes (oral, nasal, etc.), especially if the dose is greatly increased. Most abusers

will tolerate some irritation to get high. Animal data is acceptable if it can be related to humans. The Agency noted that a list of adverse events that the Sponsor will be documenting would be helpful.

### **Labeling and Target Product Profile**

#### *Question 15*

*Does the Agency agree with the proposed labeling for remimazolam presented in the TPP for the indication of IV sedative in adult patients undergoing diagnostic or therapeutic procedures?*

#### **FDA Response**

No, we do not agree. The draft labeling presented in the Target Product Profile will be reviewed after you submit the data in your NDA. However, in preparing your labeling, the following sources will be helpful:

- **Guidance for industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>**
- **Guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>**
- **Guidance for industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>**
- **21 CFR 201.57--*The Code of Federal Regulations section that describes specific requirements on content and format of labeling for human prescription drugs***

#### **Sponsor Response**

*Thank you for the response.*

#### **Discussion**

There was no further discussion on this point.

*Question 16*

*Does the Agency agree that if the safety profile for remimazolam is demonstrated to be similar to midazolam in clinical studies, that the inclusion of a statement in the labeling* (b) (4)

[Redacted]

**FDA Response**

**No, we do not agree. Your proposal to include a statement in the labeling, that**

[Redacted] (b) (4)

**is not acceptable. Our recommended language in this regard will be determined at the time of the NDA review. You should note that recent labels of drugs approved for sedation have included language about needing to be administered by a clinician trained in airway management and in a facility adequate to deal with potential airway and hemodynamic issues associated with this class of therapeutics.**

**Sponsor Response**

*In light of your advice, we propose the following text in Section 5 Warnings and Precautions of the labeling (see TTP in Appendix 3 of the meeting information package);* (b) (4)

[Redacted]

(b) (4) *Does the FDA agree that this is acceptable unless clinical data indicates otherwise?*

**Discussion**

The Division stated that the Sponsor's proposal appeared to be a reasonable framework; however, we will need to review the application before making final comments.

They inquired about the possibility of including language in labeling for the product that

[Redacted] (b) (4)

(b) (4)

Division will consider the Sponsor's concerns, and following additional internal discussion, will provide our position in a Post-Meeting Note (see below). The Sponsor stated that they would value any input on this topic as soon as possible so it could inform the design of their Phase 3 trials.

**\*\*\*Post-Meeting Note**

It is very unlikely that language will be included in the label

(b) (4)

(b) (4)

**Regulatory**

*Question 17*

*Does the Agency have any other issues it wants to call to the sponsor's attention at this time or that it believes may be relevant to obtaining eventual approval of remimazolam under a 505(b)(1) NDA as an NCE for the indication of IV sedative in adult patients undergoing diagnostic or therapeutic procedures?*

**FDA Response**

**At this time, we have no further issues. However, as you restructure your development program and revise your Phase 3 protocol(s), we may have further questions or comments as you submit them to your IND.**

**Sponsor Response**

*Thank you for the response.*

**Discussion**

There was no further discussion on this point.

The Sponsor summarized their understanding of the meeting as follows:

- The Sponsor requested feedback from the Division on the Questions they indicated they would like to discuss at the meeting but that there was not time to discuss. The Division agreed to provide any additional feedback to on these questions in the meeting minutes (see feedback following Questions 2, 8, and 11).
- The Sponsor will examine the literature and what has been done, and take the Division's statistical comments into consideration. The Sponsor will take the advice in the Post-Meeting note on trial design and analysis into consideration as well and submit an amended protocol. (b) (4)  
[REDACTED]
- Regarding Question 3, the Sponsor understands that they need to establish a second animal model in which exposure levels of the parent will be higher than human exposure levels and characterize the systemic as well as reproductive and developmental toxicity profile of remimazolam in this nonclinical model. The Sponsor will explore if a model utilizing continuous IV infusion in the rodent will be helpful in this regard.
- Regarding Question 6, the Sponsor understands that the foreign data from their development partners may be acceptable to support the safety database and exposure if they are clinically relevant and of good quality. The Division reminded the Sponsor to include information on why these data would be useful and relevant to inform on the exposure of the product.
- Regarding Question 14, the Sponsor understands that they can submit their abuse liability protocols for determination of whether animal protocols will be acceptable to support this requirement. The Sponsor also plans to outline the adverse events that they are watching for in the studies as well.
- Regarding Question 16, the Sponsor understands that the Division will need to take the indication into consideration before we can determine any specific labeling, including the (b) (4) The Division will provide a Post-Meeting note on this issue after further internal discussion.

## **OTHER IMPORTANT INFORMATION**

### **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 held on or after November 6, 2012. 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.

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*, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto: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>

## **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 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., 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 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.

<b>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</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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.

#### **ISSUES REQUIRING FURTHER DISCUSSION (Includes Action Items)**

Post-Meeting notes have been provided for the items on which the firm requested additional feedback.

#### **ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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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.**

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KIMBERLY A COMPTON  
11/14/2013