CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209229Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 047857

MEETING MINUTES

US WorldMeds, LLC
4010 Dupont Circle, Suite L-07
Louisville, KY 40207

Attention: Polly F. Eifert
Regulatory Project Manager, Clinical Lead

Dear Ms. Eifert:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for lofexidine HCl 0.2 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 24, 2015. The purpose of the meeting was to discuss preparations for submitting a New Drug Application for your product.

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, RPh
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

MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type B, Pre-NDA
Meeting Date and Time: Thursday, September 24, 2015 at 4:00 pm
Meeting Location: White Oak Building 22, Conference Room 1315
Application Number: IND 047857
Product Name: lofexidine HCl 0.2 mg tablets
Indication: Mitigation of symptoms associated with acute withdrawal from opioids
Sponsor/Applicant Name: US WorldMeds, LLC
Meeting Chair: Celia Winchell, MD, Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Center for Drug Evaluation and Research (CDER)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAAP

US WorldMeds, LLC Representatives	**Title**
Paul Breckinridge Jones	Chief Executive Officer US WorldMeds , LLC (USWM)
Kristen Gullo	Director, Strategic & Clinical Operations, Acting Director, Regulatory Affairs, USWM
(b) (4)	Consultant, USWM
(b) (4)	Consultant, USWM
(b) (4)	Consultant, USWM
Thomas Clinch	Associate Director, Biometrics, USWM
Adam Reuther	Associate Director, Regulatory Affairs, USWM
Polly Eifert	Regulatory Project Manager, Clinical Lead, USWM
Jenny Vessels	Project Manager, USWM
(b) (4)	
Phil Skolnick, PhD, DSc (hon)	Director, DPMC Division, National Institute on Drug Abuse (NIDA)
Bob Walsh	Regulatory Director DPMC Division, NIDA
Kim New (via phone)	Director, Clinical Operations, USWM
Henry van den Berg, MD (via phone)	Vice President, Medical Affairs, USWM
FDA	**Title**
Sharon Hertz, MD	Director, DAAAP
Pamela Horn, MD	Medical Officer, DAAAP
Rigoberto Roca, MD	Deputy Director, DAAAP
Celia Winchell, MD	Clinical Team Leader, DAAAP

Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP, CDER
Newton Woo, PhD	Acting Pharmacology/Toxicology Team Leader, DAAAP, CDER
Julia Pinto, PhD	Acting Branch Chief, Branch IV, Division of New Drug Products II (DNDPII), Office of New Drug Products (ONDP), Office of Product Quality (OPQ)
Ciby Abraham, PhD	Acting Quality Assessment Lead, Branch IV, DNDPII, ONDP, OPQ
Wei Qiu, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), CDER
Yun Xu, PhD	Team Leader, OCP, CDER
David Petullo, PhD	Biostatistics Team Leader, Division of Biometrics II (DBII)
Li Feng, PhD	Biostatistics Reviewer, DBII
Kim Compton	Sr. Regulatory Project Manager, DAAAP, CDER
Alla Bazini, MD	Medical Officer, DAAAP
Emily Deng, MD	Medical Officer, DAAAP
Laura Lee Johnson, PhD	Biostatistics Reviewer, DBII

BACKGROUND

The Sponsor has stated their objective for this meeting was to a) confirm that guidance provided by the Agency during the Guidance Meetings on February 5, 2009, (Type C) and November 10, 2009, (Type A) have been addressed, and b) confirm that development activities conducted by USWM would provide sufficient CMC, nonclinical, and clinical safety and efficacy data to support a fileable NDA.

The product is a synthetic, centrally acting alpha-2A agonist for which the firm intends to seek an indication for the mitigation of symptoms associated with acute opioid withdrawal and facilitation of the completion of a 5- to 7-day abstinence treatment ("detoxification") program following abrupt discontinuation of opioids at a dosage of 0.8 mg, 4 times daily (QID) for up to 7 days (b) (4) The product has been marketed at a lower total daily dosage in the UK since 1992 as BritLofex Tablets 0.2 mg to relieve symptoms in patients undergoing opioid detoxification.

The firm plans to submit two pivotal Phase 3 clinical trials, Study USWMLX1-3002 and Study USWM-LX1-3003-1 (also referred to as Study 3002 and Study 3003-1 in this document), along with various other completed clinical safety, pharmacokinetic, and efficacy studies to support their NDA. The firm is planning to conduct an interaction study with naltrexone and pharmacokinetic studies in with their product in patients with hepatic and renal impairment.

FDA sent Preliminary Comments to USWM on September 22, 2015. These comments are shown in **bold** font below, with the Sponsor's original questions and responses provided via email on September 24, 2015, (and at the meeting in written form) in *italic* font. Discussion that took place at the meeting follows the item to which it pertains in regular font.

Attachment 1 and 2 from our September 22, 2015, Meeting Preliminary Comments letter are not reproduced here. Refer to that letter for our standard Pre-NDA guidance material.

DISCUSSION

Discussion
Chemistry, Manufacturing, and Controls Questions

Question 1
GMP Starting Materials: Does the FDA concur with USWM's proposal to designate (b) (4) *as the GMP starting materials in the manufacture of the API?*

FDA Response
The designation of (b) (4) **as starting materials appears acceptable.** (b) (4)

Discussion
There was no further discussion on this item.

Question 2
Drug Substance Stability Package: Does the Agency concur with USWM that the proposed scope of the drug substance stability package will be acceptable for the NDA filing?

FDA Response
Your proposed scope of the drug substance stability package appears acceptable for NDA filing.

Discussion
There was no further discussion on this item.

Question 3
Quality Target Product Profile (QTPP) and Control Strategy: Does the Agency concur that USWM's QTPP and control strategy are sufficient to ensure reproducible manufacturing with consistent quality of the drug product in terms of its identity, purity, potency, and stability?

FDA Response
The QTTP and control strategy approach you have outlined appears reasonable and will be evaluated during the NDA review. (b) (4) (b) (4)

Discussion
There was no further discussion on this item.

Question 4
Drug Product Stability: Does the Agency concur with USWM's proposed drug product stability package?

FDA Response
The proposed stability package appears reasonable.

Discussion
There was no further discussion on this item.

Question 5
Microbial Limits Testing: Does the Agency concur with the proposal [redacted] (b) (4)

FDA Response
The proposal [redacted] (b) (4) **will be evaluated during the NDA review when the totality of the CMC information is received.**

Discussion
There was no further discussion on this item.

Question 6
Comparability protocol(s) for CMC changes: Does the Agency concur with USWM that inclusion of comparability protocol(s) in the NDA submission is an appropriate mechanism for facilitating specific changes in excipient source and the introduction of additional container closure systems for lofexidine HCl 0.2 mg tablets?

FDA Response
The inclusion of the comparability protocol in the NDA submission appears acceptable. The determination of the adequacy of the comparability protocol will be determined during the NDA review.

Discussion
There was no further discussion on this item.

Question 7
Salt Naming: Does the Agency concur with USWM's labeling plan to describe lofexidine doses in terms of the salt form (in increments of 0.2 mg lofexidine HCl)?

FDA Response

No, we do not agree. According to the FDA guidance for industry, *Naming of Drug Products Containing Salt Drug Substances*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf, the name and strength of the active moiety should be used instead of the name and strength of the salt.

Sponsor Response (via email September 24, 2015)

We agree to label in terms of the active moiety and will present dosing as 0.18 mg per tablet. USWM would like to include a parenthetical reference to the equivalent dose in salt form, i.e., ("(0.2 mg)," in the label (and application) as well to enable conversion between the US label and previous publications and public information on UK Britlofex prescribing information which US prescribers may reference and which universally express lofexidine doses in terms of the salt. USWM seeks confirmation that we can continue to prepare the application, including all individual CSRs and write ups in the ISS/ISE with dosing information expressed in the salt form, with the only active moiety references being included in the draft label for review.

Discussion

The Division agreed that 0.175 mg could be rounded to 0.18 mg, and also stated that the salt was listed appropriately as well. The Division suggested that in the cover letter or at the start of the Chemistry section of the application, the firm clearly state that the base equals 0.18 mg and the salt is 0.2 mg. The firm should consider mentioning this in other sections of the application, where appropriate, as well.

Nonclinical Question

Question 1

Nonclinical Package: Does the Agency concur that the proposed nonclinical package to support the NDA fully addresses the requests made by FDA at the Type-C guidance meeting on February 5, 2009 related to nonclinical filing requirements and that no additional nonclinical studies are required for acceptance of the NDA?

FDA Response

Yes, we generally concur that the proposed nonclinical package addresses all of the nonclinical requests made at the 2009 Type C guidance meeting, including the request to repeat the Ames assay, an evaluation of whether lofexidine is a P-gp substrate, and to conduct a nonclinical and clinical comparison of the pharmacokinetic properties and metabolism of lofexidine. No additional nonclinical studies appear to be required to support filing of your proposed NDA, as the nonclinical program outlined in your meeting package, which includes the newly conducted studies and the previous studies conducted by the previous developer, appear to address all the nonclinical filing requirements. Submit all of the outlined nonclinical studies as final study reports to the

NDA, including the 3-month repeat dose toxicology dog study. We remind you that your carcinogenicity data must also be submitted in SAS transport format.

Additional nonclinical studies may be required if previously unidentified adverse toxicities are identified in the newly submitted toxicology studies and/or if impurities/degradants exceed qualification thresholds (see below). The adequacy of the studies to support approval of the NDA can only be determined upon review of the complete nonclinical package and final study reports.

Sponsor Response (via email September 24, 2015)
USWM confirms its plans to submit the lofexidine NDA as a 505(b)1 application. USWM owns all clinical and nonclinical data which it intends to rely on to establish the safety and efficacy of the drug. With regard to the historical or "legacy" nonclinical studies planned for the application, USWM has access to full study reports, most of which were generated in the 1980s and, as such, in some cases do not have full data listings. For these older studies, all information that is available will be submitted and if not available in USWM's files is unobtainable from any source at this time. Literature included in the application is supporting information only.

Specifically, USWM wishes to address the Agency's request for SAS transport format files for the two carcinogenicity studies. Full reports are planned for submission, however only summary tables are provided in those reports and no raw data listings are available to enable recreation of SAS files. These reports were discussed in earlier milestone meetings and were not identified as studies that should be bridged to current standards through a repeat study under GLP. Of note, the carcinogenicity studies which evaluated repeat dosing in rats and mice for durations of 18 months to 2 years showed no carcinogenetic effects. (b) (4) [redacted]

USWM agrees to submit the 90 day repeat dose toxicology dog study. USWM wishes to clarify that all historical/ "legacy" studies planned for inclusion in the application, including the requested 90 day dog study, are available as scanned, non-searchable PDF files and seeks the Agency's agreement that reports in this format are acceptable.

Discussion
The Division stated that the Sponsor should submit study reports and clearly specify any deviations or omissions in the submission, such as the absence of raw data, and provide justification for why they conclude that the studies are adequate to support their NDA submission. The firm should indicate which studies are GLP and which are not, noting any deviations from GLP and how such deviations affect the results or conclusion of the study. The Division requested that the firm convert all study data to electronic submission format to meet current requirements to the best of their abilities and apply optical character recognition (OCR) to all PDF study reports that will be submitted to the NDA. The Division stated that

when the firm is preparing annotated labeling, they should be very specific regarding the source of the information or data, i.e., study report, publication, etc. This will be reviewed in detail to confirm the application is a 505(b)(1) application and to ensure that proprietary data are not inadvertently referenced, which could constitute an approval deficiency.

Additional Nonclinical Comments:

1. **In your meeting package, several impurities that exceed ICH qualification thresholds are identified (b) (4) In your NDA submission, provide scientific justification (b) (4) Otherwise, nonclinical qualification studies will be required as noted below.**

2. **Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICH Q3A(R2) and ICH Q3B(R2) guidances. In order to provide adequate qualification, you must conduct:**

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

      Refer to guidance for industry, *Q3A Impurities in New Drug Substances,* available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

      and

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

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

4. **Any novel excipients in your drug product must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients,* available at, *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf* . As noted in the document cited above, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance), and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration." (emphasis added)**

5. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to ICH M7 guidance document, *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying or controlling these impurities. This guidance is available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.**

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

7. **NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical**

and nonclinical literature for your 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.

8. **Failure to submit adequate impurity qualification or new excipient safety justification for the safety of new excipient use at the time of NDA submission can result in a Refusal-to-File or other adverse action.**

9. **It is unclear from your meeting package if you intend to submit your NDA under Section 505(b)(1) or Section 505(b)(2). If literature is required to support your NDA application in any way, your NDA will be designated a 505(b)(2) application. Refer to the regulatory comments regarding 505(b)(2) applications under "Other Important Information" near the end of this document.**

Discussion
There was no further discussion on this item.

Clinical Questions

Question 1
Adequate and Well Controlled Studies: Does the Agency concur that studies USWMLX1-3002 and USWM-LX1-3003-1 constitute two adequate and well controlled registration trials in support of an NDA for lofexidine treatment for the proposed indications:

a. *Mitigation of symptoms associated with acute withdrawal from opioids?*

b. *Facilitation of the completion of a 5- to 7-day abstinence treatment ("detoxification") program following abrupt discontinuation of opioids?*

FDA Response
Yes, on face it appears that Study 3002 and Study 3003-1 may support filing of an NDA application. The wording of the indication(s) and assessment of the adequacy of the trials will be determined upon review of the submission. We note that on p. 90 of the meeting package, you describe a primary efficacy analysis of the "Evaluable" population for Study 3002, which is defined as all subjects in the ITT population who received at least 1 dose of study medication and completed the postdose SOWS-Gossop on Day 1 or any subsequent study day. This is not an acceptable population for the primary efficacy analysis. The primary efficacy analysis must be done on an intent-to-treat population that received at least one dose of study medication.

Sponsor Response (via email September 24, 2015)
In 3002, the primary analysis specified by the SAP used the Evaluable population, however all of the key analyses were also performed on the ITT population and these results are included in the 3002 CSR. In addition to the predefined endpoints for study 3002, USWM also intends to submit analyses following the primary endpoint approach as agreed with the Division for study 3003-1.

Discussion
There was no further discussion on this item.

Question 2a
Does the Agency concur with USWM that safety data integrated from the proposed studies (LX1-3001, -3002, -3003-1, -3003-2, 1005-2, 1006) will meet the requirements for a fileable NDA and that no additional studies are required for acceptance of the NDA?

FDA Response
Yes, assuming that you complete Study 3003-2 as planned with exposure of at least 300 subjects for at least 7 to 10 days, it appears that you will have collected adequate safety data for the safety database from the studies in the clinical development program.

Discussion
There was no further discussion on this item.

Question 2b
Does the Agency agree with the studies selected for integration and the analyses planned in the ISS SAP?

FDA Response
Your plan for integration and analyses is generally acceptable with the following exceptions:

- **In addition to the planned tabulations in section 9.5.4 of the ISS SAP, for subjects with missing orthostatic blood pressure values, summarize and report the reasons for the missing values. If there was documentation of subjects not being able to stand up, then this information should be summarized and provided for review. Additionally, take these missing values into account in your assessment of the overall risk of hypotension and bradycardia with your product. Address how such missing values are handled in calculations and tabulations of measures of central tendency (e.g., mean blood pressure), and consider presenting calculations in which values which are missing for these reasons are imputed with, for example, the lowest recorded values.**

- **We note that in the presentation of adverse events on p.103 of your meeting package, you include statistical comparisons of adverse events between treatment groups with p-values. Such comparisons are not appropriate to report in your clinical study reports or ISS, because your studies were not designed to make statistical comparisons on safety endpoints. Accordingly, your discussion of the safety results should not be focused on whether or not the difference between treatment groups was statistically significant for a particular event.**

Sponsor Response (via email September 24, 2015)
USWM acknowledges and agrees that no statistical inference will be made on safety endpoints in the application.

Discussion
There was no further discussion on this item.

Question 3
Primary Efficacy Database/ ISE: Does the Agency agree with USWM's plans for presenting integrated efficacy in the NDA, in terms of the studies selected for integration (USWM-LX1-3002 and -3003-1) and the analyses planned in the ISE SAP?

FDA Response
Yes, your plan for presenting integrated efficacy in the NDA is generally acceptable. However, note that for the purposes of making a regulatory decision, we will consider the evidence for replication/ independent confirmation of efficacy and will thus be placing the emphasis of the efficacy review on the individual results of Study 3002 and Study 3003-1, rather than pooled efficacy data.

Discussion
There was no further discussion on this item.

Question 4

(b) (4)

(b) (4)

Discussion
There was no further discussion on this item.

Question 5
Methadone and Buprenorphine Maintained Population Data: Does the Agency concur with USWM that the data regarding concomitant use of lofexidine and methadone and lofexidine and buprenorphine will be acceptable to support an NDA for lofexidine for its proposed indications?

FDA Response
Yes, we agree that you have collected data that will aid in the safety evaluation of co-administration of lofexidine and buprenorphine or methadone. Ultimately, whether the risk/benefit balance supports use of the product in the context of agonist or partial agonist taper will be determined upon review of the data, as it does not appear that the application will include data supporting the *efficacy* of lofexidine in that context (i.e., that it offers symptomatic benefit).

Discussion
There was no further discussion on this item.

Question 6
Clinical Data Standardization:. Does the Agency concur with USWM's data standardization plan for the clinical program?

FDA Response
Yes, the data standardization plan appears generally acceptable. However, submit the datasets and the define.pdf file on which your Clinical Study Report (CSR) is based for each study. For example, if the CSRs for Study USWM-LX1-3002 and Study USWM-LX1-3003-1 are based on Legacy SAS datasets, submit the Legacy Tabulation and Analysis datasets, the corresponding define.pdf file, and the SAS codes for creating these datasets, as well as the efficacy tables and figures in the clinical study report for review.

Discussion
There was no further discussion on this item.

Question 7
Legacy/Investigator-Initiated Studies: Does the Agency concur with USWM's plans for the study reports and protocols to be included as PDFs in Module 5 in the NDA for "legacy"/investigator-initiated clinical studies?

FDA Response
Yes, it is acceptable to submit Studies 1001, 2001, 2002, 2003, and 2004 as described. The PDF format should permit the reviewer the capability to electronic search the document.

Sponsor Response (via email September 24, 2015)
USWM would like to clarify that for studies 2002 and 2003, the report type planned for submission is a publication. USWM intends to submit searchable PDFs when available from the publisher. Some older manuscripts are not searchable PDFs. USWM seeks agreement that these publications can be submitted as standard scanned PDF.

Discussion
The Sponsor should include the best version of the report that they can obtain. The Sponsor stated that the studies were conducted under IND, but prior to USWM ownership. They further stated that that they have the reports and own the data.

Pharmacokinetic Questions

Question 1
PK Program: Does the Agency concur that the planned clinical pharmacology package is sufficient to support the planned NDA submission?

FDA Response
No, we do not agree, for the following reasons:

1. **In your renal impairment study, LX1-1008, a substantial effect (71% increase in AUC_{inf}) was found in the End Stage Requiring Dialysis (ESRD) patients in comparison to subjects with normal renal function. In addition, your data suggest that dialysis will help drug elimination. Thus, the results of your "reduced design" study indicated that a "full" renal impairment study in patients with all intermediate levels of renal functional impairment ("full study design") must be conducted (see 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).**

2. **In your proposed draft labeling, you stated that** (b) (4) [redacted]

(b) (4)
[redacted]

3. **You stated that in the mass balance study LX1-1003, parent lofexidine and three metabolites contained 10% or more of the circulating radioactivity. The three metabolites are LADP (N-(2-aminoethyl-2-(2,6-dichlorophenoxy) propanamide), LDPA (2-(2,6-dichlorophenoxy) propionic acid), and DCP (2,6 dichlorophenol). Because unchanged lofexidine accounted for approximately 15% to 20% of the circulating plasma radioactivity, the metabolites represent more than 50% of the parent drug exposure. Therefore, provide human PK data on these metabolites. The potential for drug interactions with these metabolites must also be considered. (See guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations,* available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf).**

In addition, confirm that the to-be-marketed product was studied in all the PK and clinical studies.

In your NDA submission, submit all datasets from the PK studies in SAS transport file format with a define.pdf file explaining the dataset variables and overall format of the dataset. Provide analytical method validation reports as well as bioanalytical report for each study.

Sponsor Response (via email September 24, 2015)
Comment 1:
We agree with the Agency's request to conduct a full renal impairment study. USWM study in End-Stage-Renal Disease subjects showed that the decrease in clearance associated with this extreme state of renal impairment resulted in a less than 2x change in clearance. The result will allow us to propose dosage adjustment recommendations for the intermediate stages of renal impairment as well as in the ESRD case. However, USWM recognizes that the intermediate stages of renal impairment would depend on assumptions regarding the gradation in clearance with decreasing renal function.

(b) (4)
[redacted] *ESRD is not expected to be a common comorbidity in the opioid dependent population; less severe degrees of renal impairment may be more common in the target patient population. USWM may be able to locate information regarding the prevalence of renal impairment in the target population and identify the population potentially not able to take advantage of lofexidine aided detoxification until the more extensive results are available. USWM wishes to discuss this proposal with the Agency.*

Comment 2:
USWM has reviewed the preliminary data from its CYP substrate study. Specifically, the study has confirmed that CYP3A4 is not involved in lofexidine metabolism. The results indicate that CYP2D6 is the predominant CYP enzyme involved, and that one primary metabolite (LADP) is the product of CYP2D6 activity. The other 2 principal metabolites (LDPA and DCP) appear to probably be secondary/tertiary metabolites of LADP. The metabolism information is still being assessed by USWM consultants.

USWM understands that a DDI studies involving a known strong CYP2DY6 inhibitor (such as paroxetine) may be of interest; however USWM-LX1-1005-2 provides insight regarding the likely outcome of such a study having evaluated the interaction of lofexidine and methadone, a known weak CYP2D6 inhibitor. In this study, lofexidine concentrations were approximately 50% higher during concomitant methadone use than at steady state when lofexidine was administered in a nearly identical population in a very similar protocol (concomitant administration with buprenorphine). The 1005-2 study was intentionally designed as a worst case scenario in which methadone doses were continued at the full maintenance dose while lofexidine was titrated to 3.2 mg (maximum recommended labeled dose). This magnitude of effect is not expected in actual clinical use scenarios during which methadone would be either significantly reduced in dose or discontinued before a withdrawal syndrome would emerge which could be treated with lofexidine. While the results support the safe use of concomitant lofexidine and methadone, particularly in a likely treatment scenario in which methadone concentrations are decreasing before lofexidine is introduced, the study still provides sufficient evidence of the likely interaction with stronger CYP2D6 inhibitors. USWM proposes that the studies conducted to date are sufficient to inform the lofexidine product label and plans to include labeling to properly inform physicians of this potential interaction.

Given lofexidine is indicated for acute use, temporary discontinuation (e.g. for no more than 14 days) of such medications is unlikely to have a significant impact on the patients long-term treatment for comorbidities requiring known CYP2D6 inhibitor therapy while addressing their acute detoxification and/or withdrawal management goal with lofexidine. USWM wishes to discuss this proposal with the Agency.

Comment 3:
USWM agrees with the Agency's request. PK information on major metabolites will be provided at the time of submission. USWM believes that this information can be obtained from existing plasma sample retains from previously conducted Phase 1 and/or 3 studies; and accordingly does not plan to conduct a new study to fulfill this request.

Discussion
The Sponsor stated that they conducted a reduced renal impairment study, noting that (b) (4)

(b) (4) The Division noted that changes were observed in the severe renal impairment population, and that the firm does not have data for mild to moderate renal impairment. The rationale for conducting a reduced renal impairment study is that if no effect is observed, then further evaluation in less severe impairment is not needed, but if an effect is observed, then a full study is required. (b) (4) If the Sponsor chooses to submit their NDA without fulfilling this requirement, they should submit an argument for why it would be acceptable not to fulfill this regulatory requirement prior to marketing approval and the Division will examine it in the context of our review. The Sponsor should include this in the Clinical Pharmacology section under Module 2.

Regarding drug-drug interaction studies with metabolic inhibitors, the Sponsor acknowledged that DDI studies have not been performed with strong CYP2D6 inhibitors. The Sponsor stated that there is no metabolism by CYP3A4, noting that CYP2D6 appears to be the (b) (4) enzyme in the metabolic pathway. About 30% of the drug is removed via first pass, leaving 70% of the product bioavailable. In cross-study comparisons between lofexidine dosed alone and dosed with methadone, an increase in exposure to lofexidine was noted, but the Sponsor did not believe it affected safety. However, the Sponsor acknowledged that methadone is a weak CYP2D6 inhibitor and that lofexidine would likely be affected by strong CYP2D6 inhibitors. The Division stated that this presents a large safety problem, since the Agency cannot specify how the product would be dosed without the information on drug interaction with CYP2D6 inhibitors. The Division noted that a significant number of CYP2D6 inhibitory products are used in the detoxing population (e.g., antidepressants) and allowing the product on the market without adequate information for prescribers is an enormous safety concern, since CYP2D6 is the primary enzyme for the metabolism of the proposed product. Simply making assumptions about the effect and recommending dose reduction is not an option, because this could result in using an inefficacious dose. Additionally, if the product is contraindicated in certain populations at the product's first release, it will be necessary to re-educate and change prescriber behavior after the interaction is evaluated.

The Division also noted that CYP2D6 has a lot of polymorphism and, while the Sponsor may not need to study all variants, they would need to propose in their NDA how the issue of polymorphism would be addressed in the label.

The possibility of performing some analyses using retained samples was discussed. If the Sponsor wants to analyze past plasma samples to characterize the PK of the metabolites, they will need to ensure they have data to demonstrate that the metabolites in the sample are stable.

The Division stated that CYP inhibition and induction potential of the product and metabolites must be characterized. The Sponsor will need to do an in vitro analysis to assess the inhibitory and induction capabilities of the metabolites. If the product or metabolites

show inhibition or induction potential, additional drug-drug interaction studies may be needed.

The Division emphasized that the lack of DDI information could be a filing issue, and could also make the application non-approvable. The NDA must be complete at the time of submission.

***<u>**Post Meeting Note**</u>

With regard to the discussion about the requirement for completion of the assessment of renal impairment, after further consideration, (b) (4) The available data from the completed reduced renal impairment study indicate that renal impairment does alter exposure in the setting of end-stage renal disease. Therefore, in the absence of a complete evaluation, there is a risk of dosing lofexidine incorrectly in patients with renal impairment resulting in higher exposure levels than intended. This places patients at risk for dose-related toxicity, and of particular concern is the risk of hypotension and bradycardia. The need for a renal impairment study had been identified early enough in development that there is no reason why it should not be completed as part of the initial new drug application. Refer to the minutes from the Type C meeting with FDA on February 5, 2009, (minutes issued on March 6, 2009). Furthermore, as noted in the previously cited guidance for industry, "If a reduced PK study shows a substantial effect (e.g., at least a 50-100% increase in AUC, or a lesser effect if the drug has a narrow therapeutic range) in the renal impairment patients, a "full" renal impairment study in patients with all intermediate levels of renal functional impairment ("full study design," see IV.B below) should be conducted." Therefore, you must have data from an adequately designed study or studies to determine when an adjustment in dose is necessary for the different levels of renal impairment in order to create a complete product label with instructions for prescribers. Similarly, a lack of adequate evaluation of DDI will potentially place subjects at similar risk. An application that lacks sufficient data to support approval at the time of submission will not be filed.

Question 2
BCS Classification: Does the Agency concur that lofexidine meets BCS Class I status and that it is acceptable to submit the full justification for a biowaiver with the new drug application?

<u>**FDA Response**</u>
We cannot concur with your request to grant your drug substance/product as BCS Class 1 at this stage. You will need to provide documentation in support of your request as per the Agency's guidance for industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System,* available at,

http://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf. Your submission will be reviewed by the CDER BCS committee and a final decision will be provided.

Discussion
There was no further discussion on this item.

QT Question

Question 1
ECG Analyses and Warehousing Plan: Does the Agency concur with USWM that the ECG data to be submitted will be acceptable for filing the NDA?

FDA Response
Yes, we agree that your plan for submitting ECG data appears to be acceptable for filing of your NDA application.

Discussion
There was no further discussion on this item.

Regulatory Questions

Question 1
Draft Label: Does the Agency agree that the draft labeling content is complete and includes appropriate references to the data/studies which USWM plans to rely upon for its claims?

FDA Response
On face, the draft labeling content appears adequate to allow for review during the NDA review cycle.

Discussion
There was no further discussion on this item.

Question 2
Case Report Form Exceptions: Does the Agency concur with USWM's plans for including CRFs for all subjects experiencing SAEs, and all subjects withdrawing prematurely due to an adverse event or other reason which could be attributed to an AE from any study planned for inclusion in the ISS/ISE, but excluding those CRFs for subjects withdrawing for "lack of efficacy" or for administrative reasons?

FDA Response
Yes, submit CRFs for all deaths, SAEs, and discontinuations due to adverse events. Additionally, submit CRFs for patients who had dose reductions or dose holds. Be

prepared to provide additional CRFs, such as CRFs for subjects who discontinued due to lack of efficacy, upon request.

Discussion
There was no further discussion on this item.

Question 3
Financial Disclosure: Does the Agency concur with USWM's plan to include financial disclosure and/or certification only for studies USWM-LX1-3002 and USWM-LX1-3003-1?

FDA Response
No, we do not concur. According to 21 CFR 54.2(e) and 54.3, financial disclosure is required for the clinical investigators of those studies relied upon to provide support for the effectiveness of a product or in which a single investigator makes a significant contribution to the demonstration of safety. In addition to Studies 3002 and 3003-1, provide financial disclosure information for Studies 1005-2 and 1006, because of their contribution to the safety evaluation of your product.

Sponsor Response (via email September 24, 2015)
USWM agrees to provide financial disclosure information for studies 3002, 3003-1, 3003-2, 1005-2 and 1006 as the studies which provide considerable support for safety and effectiveness of lofexidine.

Discussion
There was no further discussion on this item.

Question 4
Initial Pediatric Study Plan (iPSP) Review: Does the Agency agree that the plan for submission of nonclinical and clinical study data after NDA filing/approval as detailed in USWM's iPSP is acceptable?

FDA Response
The estimated timeline proposed in your iPSP for the planned nonclinical and clinical studies to satisfy the PREA requirements is currently under review by the Division in consultation with the Pediatric Review Committee (PeRC). You will receive a separate communication regarding your iPSP submission when this initial review and consultation is complete. Additional information regarding the requirements of the Pediatric Research Equity Act is provided below in the PREA REQUIREMENTS section.

Sponsor Response (via email September 24, 2015)
USWM has reviewed comments from PeRC, and will address the issues identified directly with the review group. USWM wishes to clarify if the Division is amenable to accepting

a request for deferral for all pediatric nonclinical and clinical work (currently planned and to be planned per ongoing discussions/agreement with PeRC). Specifically, USWM plans to initiate the nonclinical work described in the iPSP with updates to address PeRC's comments; however with the current filing timeline, this study is not planned for inclusion in the application and USWM would like the Division's agreement that this is acceptable

Discussion
The Division stated that an agreed iPSP is required at NDA submission. No pediatric data would be required for NDA review if there were no pediatric indication for the product in the initial NDA.

Question 5
Submission without REMS: Does the Agency concur that USWM's proposal to submit the NDA without a REMS program is acceptable?

FDA Response
If you do not believe that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, then you may submit your NDA without a REMS. At this time, we have not concluded that a REMS is necessary for your product. However, we may determine that a REMS is necessary for your product during review of the NDA application. If we do determine that a REMS is necessary, we will notify you as early in the NDA review cycle as is possible, and the goal date for notification is not later than 6 weeks prior to the PDUFA goal date.

Discussion
There was no further discussion on this item.

Question 6
Priority Review: Does the Agency concur with USWM that a priority review request may be considered at the time of NDA submission based on the Division's prior guidance regarding criteria for establishing lofexidine as a treatment for a serious or life threatening condition?

FDA Response
As outlined in the May 2014 guidance for industry, E*xpedited Programs for Serious Conditions- Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf, you may submit a request for priority review at the time of NDA submission and you will be notified about whether the request has been granted in the filing letter. There are available therapies for treating withdrawal from opioids and facilitation of detoxification completion and you must provide evidence of a significant improvement in safety or effectiveness over available therapies to support your request. If your rationale is that your product has an efficacy advantage over available

therapies, then you must also provide evidence that it has comparable safety. If you your rationale is that your product has a safety advantage over available therapies, then you must also provide evidence that it has comparable efficacy. For the purposes of your product, buprenorphine, methadone, and clonidine are considered available therapies. If you believe that your product meets the criteria for priority review as outlined in the Guidance, then submit the rationale and supporting evidence with your NDA submission.

Discussion
There was no further discussion on this item.

The Sponsor inquired if there were any other Agency advice or comments to be shared.

Discussion
The Division stated that the Sponsor should also analyze the renal impairment study by removing the data points after dialysis, since dialysis can help remove the drug from the body. The Sponsor commented that based on their analysis, dialysis plays a minor role in this drug's elimination and its effect on the renal impairment study result is small. The Division acknowledged the Sponsor's comment and asked them to include their analysis result in the NDA submission.

The Division stated that there is no replicated evidence for the lower dose. The Agency will need to review the risk/benefit of the proposed doses, so the Sponsor should clearly state the rationale for their proposed doses since dose-dependent safety issues (such as cardiovascular issues) will be examined carefully in the application review. The Division discouraged the Sponsor from making claims of benefits over clonidine if they are not going to propose to label the product for the dosages that were used in the studies that compared lofexidine to clonidine.

OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 29, 2015, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

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

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

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

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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

ABUSE POTENTIAL ASSESSMENT

As we shared with you in our February 2009 meeting, we remind you that, 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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

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

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

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

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

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

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

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

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

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

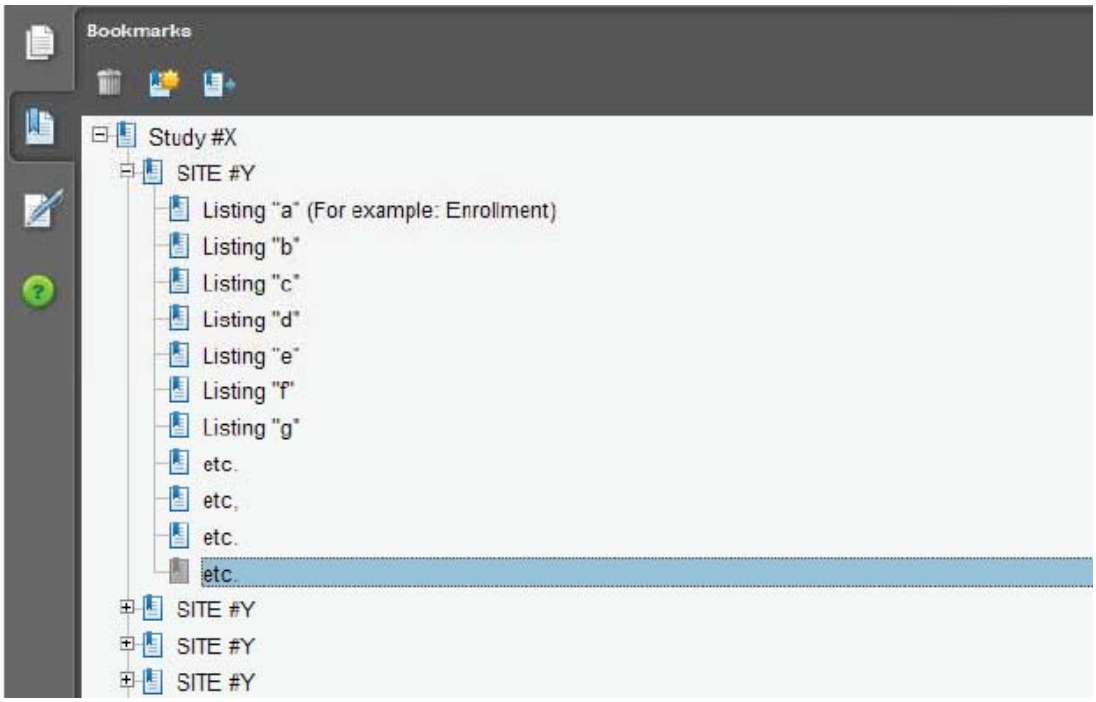
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that require additional discussion.

ACTION ITEMS (Includes Sponsor Summary of Meeting)

1. The Sponsor understands that absence of information about potential 2D6 drug-drug interaction issues may be a refuse to file issue, or make the product difficult to approve, so these need to be addressed.

2. The Sponsor understands that metabolite stability studies are needed for retained samples.

3. The Sponsor understands that they need to complete a binding screen and a 2D6 induction and inhibition study.

4. The Sponsor understands that completed studies with full data are a requirement from the Office of New Drugs for applications to be filed.

5. The Sponsor will clarify in their application that they are not relying on any published literature.

6. The Sponsor understands that the Agency agrees that, since electronic data are not available, the carcinogenicity study data do not have to be submitted in SAS format. Regarding PDF file formatting, the Sponsor understands they are to do the best they can to provide bookmarks and OCR throughout as much of the submitted final study reports as possible.

7. The Sponsor understands that they can include salt conversions in the label and may submit the application with clinical studies reported as salts, not that they need to highlight this very clearly throughout the application.

8. The Sponsor understands that no nonclinical pediatric studies are needed at the time of NDA submission; however, the studies will be required to support pediatric clinical trials as per the comments provided in the iPSP discussions to date.

9. The Sponsor understands that while Studies 2002 and 2003 are USWM studies, they will be submitted as publications and with the best versions possible as searchable PDFs, etc.

ATTACHMENTS AND HANDOUTS
There were no handouts or attachments for this meeting.

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

/s/

KIMBERLY A COMPTON
11/16/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 47,857

(b) (4)

Attention: (b) (4)
General Manager

Dear (b) (4)

Please refer to the meeting between representatives of your firm and FDA on November 10, 2003. The purpose of the End of Phase 2 meeting was to discuss the development plans for lofexidine hydrochloride.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Date/Time: November 10, 2003 / 3:30 pm

Location: Parklawn, Conference Room C

Application: IND 47,857

Sponsor: (b) (4)

Drug: lofexidine hydrochloride

Indication: to relieve symptoms in patients undergoing opiate detoxification

Type of Meeting: End-of-Phase 2 (type B)

Meeting Chair: Celia Winchell, M.D., Team Leader, Drug Abuse Products

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

(b) (4)	Title
Maxwell E. P. Noble	Managing Director, Britannia
Alex Duckworth	Director, Britannia
Keith Davies	Technical Director, Britannia
(b) (4)	
P. Breckinridge Jones	CEO, US WorldMeds
Jeffrey A. Staffa, PhD	Regulatory Affairs, US WorldMeds
Karl V. Gallegos, MD	Clinical Head, US WorldMeds
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Meeting Objective(s): The purpose of the End of Phase 2 meeting was to discuss the development plans for lofexidine hydrochloride.

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the October 3, 2003, meeting package. The Sponsor's questions are presented below in italicized text. Agency responses, prepared prior to the meeting and presented on slides, are in italics. Discussion is presented in normal text.

CHEMISTRY

Question 1A: Does the Agency agree that the proposed stability data are sufficient for filing the NDA?

FDA RESPONSE

Based on ICH recommendations, a minimum of 12 months of room temperature stability and 6 months accelerated data should be provided.

Limited stability data will not however be a filing issue.

Note that, the expiry dating will be based on the amount of stability data provided in the application.
The stability data from Europe will be considered supporting in nature.
ICH Q1AR recommended stability study conditions.
ICH-Q1F based extrapolation of the stability data beyond the real time data is a possibility.
Quality of the long-term, intermediate, and accelerated storage data
Understanding of the pathways for the degradation of the drug product.
Stress studies recommended in the ICH.

DISCUSSION
The Division stated that the stability data from Europe would only be supporting data and would not be considered primary data at this time. The Sponsor should provide data on 3 lots from the United States. The Sponsor replied that they planned to submit only 3 months of stability data at the time of filing and would provide additional data during the review cycle. The Division reminded the Sponsor that timeliness is important during the review cycle and if the data was submitted late in the review cycle, it might not get reviewed and the expiry dating would be based on the 3 month data. The Division also stated that any extrapolation of the expiration dating beyond the real time data would be evaluated according to the ICHQ1F standards.

Question 1B: Does the Agency agree that the proposed dissolution data are sufficient for filing the NDA?

FDA RESPONSE

The proposed multi-point and multi-media dissolution testing proposed appears to be satisfactory, however the adequacy of the dissolution method for regulatory purposes will be assessed during the NDA review.

The method should be shown to be discriminatory in nature.

Acceptance criteria (Q and the time point) would be based on the time-profile data submitted in the NDA.

Is IVIVC being developed for this product?

Additional Manufacturing Issues

(b) (4)

DISCUSSION

The Division stated that the complete time profiles in multi-buffer media should be submitted in the NDA and that based on the data, appropriate media and time points will be selected. Need for a two-point time specification for dissolution will be assessed based on the data.

The Sponsor stated that the dissolution profile presented in the meeting package would be used to show the similarity between the to-be-marketed and clinical formulations in the NDA. The Sponsor clarified that they intend to (b) (4) The Division stated that the adequacy of the bridging based solely on dissolution profile comparisons would be determined during the NDA review.

The Sponsor clarified that they will be performing (b) (4). The Division requested that the Sponsor provide adequate description of the manufacturing process including process controls and in-process specifications. The Division reiterated that this is very important for this drug product, because it is a very potent drug and is being formulated at a very low dose.

(b) (4)

(b) (4)

PRECLINICAL PHARMACOLOGY/TOXICOLOGY

Question 2: Does the Agency agree with the proposed approach which is planned to complete the information to be submitted in an NDA filing for the proposed indication?

FDA RESPONSE

Comparison of the non-clinical ADME data with the clinical ADME data should be completed early in the development process to accurately evaluate safety margins for proposed studies. Any human specific metabolites may be required to be adequately qualified for the NDA.

- *Bio-bridging exposure data with existing carcinogenicity and teratogenicity studies appears reasonable.*
- *Carcinogenicity studies are not generally required for indications of less then 3-6 months duration. Available information should be included in the labeling.*
- *Segment III reproductive toxicology studies will be required for the NDA.*
- *The sponsor should conduct a thorough/enhanced non-clinical evaluation of the potential for lofexidine to alter the QT interval.*
  - *Refer to the published draft ICH guideline S7B "Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" for guidance on nonclinical testing strategies and methods.*
  - *In particular, useful tests could include:*
    - *Ionic current assay (i.e., hERG channel assay)*
    - *Repolarization Assay (e.g., Purkinje fiber assay)*
    - *In vivo assessment*
- *A standard genetic toxicology battery (ICH S2B) should normally be completed prior to phase 2 studies. The sponsor should submit data from an in vitro cytogenetic study and the proposed in vivo mouse micronucleus assay prior to further clinical studies.*
- *The sponsor is encouraged to submit the Ames Assay contained in NDA* (b) (4) *to the IND for evaluation in light of current standards.*
- *Novel excipients should be adequately qualified.*
- *Any impurities or degradation products in the drug substance or product that exceed ICH guidelines should be adequately qualified.*
  - *in vitro mutagenicity study*

– *in vitro chromosome aberrations assay*

Repeat-dose toxicology study in one species of adequate duration to cover the indicated clinical use

DISCUSSION
The Division stated that the Sponsor should submit the Ames Assay data from NDA (b) (4) to the IND for evaluation based on current standards. The Sponsor agreed.

The Division also requested that full study reports, not just summaries, should be submitted to the IND. Any information from the literature would be helpful as well.

CLINICAL PHARMACOLOGY

Question 3: Does the Agency agree that these proposed single-dose and multiple-dose pharmacokinetic studies, added to the currently existing information on the pharmacokinetics, are sufficient to support an NDA filing for the proposed indication?

FDA RESPONSE
No. The following additional information should be provided in the NDA:
– *Food effect;*
– *Metabolism*
  - *Metabolic pathways*
  - *Activity of metabolite(s);*
  - *In vitro metabolism (whether lofexidine in an inducer/inhibitor of CYP450 enzymes)*
– *Special population*
  - *Hepatic impairment*
  - *Renal impairment*
– *Drug interaction*
  - *drugs most likely to be co-administered in relief of symptoms during detoxification*
  - *Naltrexone*
  - *Buprenorphine*
  - *Methadone*
  - *Based on the in vitro metabolism information, any other drugs which will potentially interact with lofexidine*

– *Please provide the PK study protocol for review comments*

– *Please confirm that to-be-marketed formulation will be used in pivotal clinical trials; please note that a bridging PK study may be needed if clinical and to-be-marketed formulations are different.*

DISCUSSION
The Division stated that food effect information should be provided at the time of the NDA filing, to assess for possible dose dumping phenomenon.

The Division stated that there was not much information on the metabolism. The Sponsor stated that it is difficult to perform PK studies in the addict population. The Sponsor suggested performing some of the work in a normal population and including a sparse

sampling in the addict population. The Division stated that drug interactions, examining common drugs used by the addict population, should be examined. However, where feasible, these studies can be done in normal volunteers. The Division suggested that the Sponsor send in their PK package, including population PK proposals, for comment. The Sponsor agreed.

The Division also requested dissolution profile for the clinical and to-be-marketed tablets. The Sponsor agreed.

CLINICAL

Question 4: Does the Agency concur with the design of the proposed trial?

FDA RESPONSE:

For the proposed claim "to relieve symptoms in patients undergoing opiate detoxification" efficacy at 48 hours (of a 7-day course of treatment) would not be an adequate primary outcome measure

Proposed Phase 3 Study: Design Issues

- *For the indication as phrased, symptomatic relief should be the primary outcome measure, e.g. using Objective Opiate Withdrawal Scale (OOWS) and Short Opiate Withdrawal Scale (SOWS)*
- *Assessing difference in cumulative proportions of 7-day completers, along with characterization of symptom relief, would be a suitable outcome measure for a claim that the product facilitates completion of opiate detoxification through providing symptomatic relief of withdrawal discomfort*
- *Treating placebo drop-outs with active drug (resuming a detoxification attempt) is acceptable; however, these patients should not be included in the lofexidine group for efficacy analysis*
- *Justify exclusion of patients dependent on fentanyl, alfentanil, and sufentanil.*

DISCUSSION
Although the indication currently proposed refers only to relief of withdrawal symptoms, the Division would be enthusiastic about a study that demonstrates that lofexidine facilitates completion of detoxification. Division stated that treatment retention is an attractive endpoint. The 7-day completer definition proposed by the Sponsor would be the appropriate outcome for a study of this type.

The Division stated that the Sponsor should also characterize symptomatic relief, which is presumably the mechanism by which the drug helps people successfully complete a course of detoxification, for the purpose of description in the labeling. The Division stated that there are some real challenges in this part of the study design because of the difficulty in handling missing data and data from subjects who self-medicate during treatment. In addition, the Division stated

that the Sponsor would actually need two studies with a retention in treatment endpoint to support this claim.

The Division stated that an alternative plan would be to bring the product to market initially, with a claim that lofexidine provides symptomatic relief of discomfort associated with opiate withdrawal. The labeling would note that the product had not been shown to affect the likelihood of completing detoxification, or to have any other benefit in detoxification or addiction treatment outside of making patients more comfortable. The Sponsor could then subsequently submit an efficacy supplement to add a retention in treatment claim.

The Division reminded the Sponsor that to support the palliation-only claim two studies would be required that show symptomatic relief, and that show that symptoms are better throughout the course of treatment—in order to justify using the product for the recommended duration of treatment. The Division stated that the current proposed study doesn't have a primary endpoint of symptomatic relief over the course of treatment, and it will be challenging to obtain that information given the problems of missing data and self-medication in outpatients. (b) (4)

The Sponsor confirmed that an outpatient study with a primary endpoint of treatment retention (completion of detoxification) would be acceptable to them. The Division agreed that this would be acceptable, (b) (4)

In summary, the discussion identified that the outcome measure should match the intended labeling claim, and that two studies would be needed for a given claim, whether a claim of palliation of withdrawal discomfort or a claim of facilitation of completion of detoxification treatment.

The Division questioned the exclusion of patients dependent on fentanyl, alfentanil and sufentanil. The Sponsor stated that these drugs are difficult to measure in urine and the tests can be expensive. The Division stated this was an acceptable explanation.

Development Plan Issues

- (b) (4)
- *A definitive clinical study evaluating lofexidine effects on cardiac repolarization must be conducted*

- *The Clinical Evaluation of QT/QT_c Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (ICH Concept Paper, 01/2003)*

- *You will need to submit an adequate safety database*

  - *≈ 300 - 500 patients treated for the labeled duration. A significant portion of these patients should be representative of your target patient population*

- *The development program as envisioned offers no information regarding whether lofexidine provides any symptomatic relief during agonist-assisted detoxification (e.g. methadone or buprenorphine taper). Use in this context may be reasonably anticipated, ~~if~~ clonidine is used in this fashion.*

  - *Significant safety concerns may exist regarding the appropriateness of lofexidine use during methadone taper, depending on results of the cardiac evaluation.*

If not contraindicated based on cardiac conduction studies, efficacy evaluation in the setting of agonist-assisted withdrawal is recommended

DISCUSSION

(b) (4)

The Division stated that the Sponsor must evaluate lofexidine effects on cardiac repolarization. The Sponsor stated that the British labeling includes a warning about potential cardiac conduction effects which the Sponsor proposes to include in the application. However, rather than including a warning without further evaluation of the problem, the Division stated that further exploration of this issue is indicated. The Division stated that significant safety concerns may exist regarding the appropriateness of lofexidine use during methadone taper, depending on results of the cardiac evaluation, because methadone itself causes QT prolongation. If lofexidine is also a QT prolonger, it may be necessary to contraindicate combined use. The Sponsor acknowledged that clonidine is used during methadone taper, and agreed that use of lofexidine in this context can be reasonably anticipated.

The Sponsor asked if marketing experience would provide beneficial data for the Division to review. The Division stated that safety data collected through routine post-marketing surveillance programs offers some reassurance but is of limited utility in characterizing the safety profile for labeling. Data gathered in prospectively-designed trials with source data and case report forms available for review form the primary database for evaluation of a drug product's safety profile. The Sponsor stated that there has been a low number of adverse events over the past ten years.

The Sponsor will compile safety data from previous lofexidine development programs and provide the Division with the source data and appropriate CRFs.

OTHER QUESTIONS

Fast Track Designation (FDAMA)

- *You may request to have your application considered under "Fast Track" conditions*

- *21 USC 356, Section 506 states:*
  The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition.

DISCUSSION

The Division stated that the Sponsor can request a fast track designation. It was noted that lofexidine is not seen as a treatment of opiate addiction, per se. However, a fast track designation could be possible based on the Division's view that the discomfort associated with opiate withdrawal is "serious," akin to other pain syndromes. However the Division clarified that fast track designation does not guarantee qualification for a priority 6-month review.

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/s/

Sara Stradley

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