CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209501Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 107333

MEETING MINUTES

Pfizer, Inc.
445 Eastern Point Road
Groton, CT 06340

Attention: Lu Zhang, PhD
Director, Worldwide Safety and Regulatory

Dear Dr. Zhang:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pregabalin Controlled-Release (CR) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 19, 2016. The purpose of the meeting was to discuss your proposed NDA submission.

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) 796-4029.

Sincerely,

{See appended electronic signature page}

Diana L. Walker, PhD
Sr. 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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 19, 2016; 1:30 p.m. - 2:30 p.m. (Eastern)
Meeting Location: Teleconference

Application Number: IND 107333
Product Name: Pregabalin Controlled-Release (CR) Tablets
Indication: Postherpetic Neuralgia (PHN); Diabetic Peripheral Neuropathy (DPN); Fibromyalgia
Sponsor/Applicant Name: Pfizer Inc.

Attendees

Industry Representatives	**Title**
Lloyd Knapp, PharmD	Executive Director, Clinical Development
Dennis Morse, PhD	Research Fellow, Drug Safety Research & Development
Beverly Nickerson	Associate Research Fellow, Pharmaceutical Sciences
Bruce Parsons, MD, PhD	Senior Medical Director, Pain, Medical Affairs
Joseph Scavone, PharmD, MSc, MB	Senior Director, Clinical Development
Diane Shoda	Senior Director, Worldwide Regulatory and Safety
Ed Whalen, PhD	Senior Director, Statistics
Monique Carter	Senior Manager, Worldwide Regulatory and Safety
FDA	**Title**
Sharon Hertz, MD	Division Director, DAAAP
Ellen Fields, MD, MPH	Deputy Director, DAAAP
John Feeney, MD	Clinical Team Leader, DAAAP
Robert Levin, MD	Medical Officer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2 (DCP2)
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer, DCP2
Haritha Mandula, PhD	Biopharmaceutics Reviewer
Daniel Mellon, PhD	Pharmacology-Toxicology Supervisor
Newton Woo, PhD	Pharmacology-Toxicology Team Leader
Kevin Snyder, PhD	Pharmacology-Toxicology Reviewer
Katherine Meaker, MS	Statistics Reviewer, OB
Shelly Kapoor, PharmD	Regulatory Project Manager, DAAAP
Diana Walker, PhD	Sr. Regulatory Project Manager, DAAAP

1.0 BACKGROUND

a. The purpose of this meeting is to discuss the planned NDA and agree upon a plan for providing the quality, safety, and efficacy data for the pregabalin ER tablet formulation. The Sponsor also seeks to solicit comments from the Agency regarding the proposed product labeling.

b. Pregabalin (LYRICA®) has analgesic, anxiolytic, and anticonvulsant activities, which are thought to be mediated through selective binding to the alpha2-delta (2-) subunit of voltage-gated calcium channels in the central nervous system. Pregabalin ER tablets have been developed to support once daily administration following the evening meal.

c. Notification of the conditional acceptance of LYRICA CR as a proprietary name was sent by the FDA in November 2015.

d. The Sponsor received the Agency's preliminary responses to the meeting questions on April 14, 2016, via email, and notified the Division that they would like to change the format of the meeting to a teleconference. On April 18, the Sponsor sent the Agency a Word document containing topics for discussion during the meeting. This document is attached to these meeting minutes.

e. 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.

2.0 DISCUSSION

A. CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 1: Does the Agency agree with the sponsor's proposed dissolution method?

FDA Response to Question 1:
Yes, we agree.

Discussion
There was no further discussion of this question.

Question 2: Does the Agency agree the data presented from the in vitro evaluation of potential alcohol interaction demonstrate no dose dumping and are adequate for NDA review?

FDA Response to Question 2:
Yes, we agree.

Discussion
There was no further discussion of this question.

B. PHARMACOLOGY/TOXICOLOGY

Question 3: Does the Agency agree with the proposal for presentation of nonclinical information in the planned NDA and that the excipient, Kollidon SR, has been adequately qualified for use in pregabalin ER tablets?

FDA Response to Question 3:
Based on the information provided in the meeting package, we agree that Kollidon SR appears to be adequately qualified for use in pregabalin ER tablets. However, final determination of the adequacy of your drug product formulation can only be made upon review of the NDA submission.

Discussion
There was no further discussion of this question.

Question 4: Three additional excipients are at amounts per tablet higher than those in the IIG Database [accessed 28 October 2015 and 21 January 2016]. Pfizer would like confirmation from FDA that the nonclinical safety data for each excipient supports their use in pregabalin ER tablets.

a. (b) (4)

Does the FDA agree that the nonclinical data for (b) (4) *support the clinical use at 135 mg/day in pregabalin ER tablets?*

FDA Response to Question 4a:
As (b) (4) **is present in a previously-FDA-approved chronic-use drug product associated with higher daily intake levels, clinical use of** (b) (4) **in pregabalin ER tablets appears adequately qualified for safety. However, final determination of the adequacy of your drug product formulation can only be made upon review of the NDA submission.**

Discussion
There was no further discussion of this question.

b. Crospovidone

Does the FDA agree that the nonclinical data for crospovidone support the clinical use at (b) (4) *mg/day in pregabalin ER tablets?*

FDA Response to Question 4b:

As crospovidone is present in a previously FDA-approved chronic-use drug product associated with higher daily intake levels, clinical use of crospovidone in pregabalin ER tablets appears adequately qualified for safety. However, final determination of the adequacy of your drug product formulation can only be made upon review of the NDA submission.

Discussion
There was no further discussion of this question.

c. Polyethylene Oxide

Does the FDA agree that the nonclinical data for polyethylene oxide support the clinical use at [redacted] (b) (4) *per day in pregabalin ER tablets, and also the maximum use of* [redacted] (b) (4) *mg?*

FDA Response to Question 4c:
We cannot provide a definitive response until we review the available nonclinical data for polyethylene oxide and the information contained in the drug master file for this material. We note that higher levels of a lower molecular weight form of polyethylene oxide have been qualified for clinical use in a comparable FDA-approved product. Provide a letter of authorization to reference the DMF for this material so that a thorough review of this material can be performed at the time of NDA review.

Discussion
There was no further discussion of this question.

Additional Nonclinical Comments

1. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. The exposure margins in the previously approved label for the immediate- release product must be updated to reflect exposures from your extended-release drug product.**

2. **Include in your NDA submission 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 the discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**

3. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose**

of the product, how these levels compare to 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 thresholds should be adequately justified for safety from a toxicological perspective.

4. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2). In order to provide adequate qualification:**

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

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

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

    and

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

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

6. **We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety.**

Discussion

The Sponsor requested clarification of the Division's response to Additional Nonclinical Comment 4b, and stated in their response document (attached): "*One impurity,* (b) (4)

(b) (4)

The proposed acceptance criterion in the Lyrica CR drug product is (b) (4)%, which would result in a maximum daily exposure of (b) (4) mg/day at the highest pregabalin dose of 660 mg/day, or (b) (4) mg/kg/day for a 60 kg patient. (b) (4)

Regarding point 4b, in which a 90 day toxicity study is requested for any impurity that exceeds ICH thresholds to support the proposed indication, Pfizer believes (b) (4) *is sufficient to support a specification of NMT* (b) (4) *in the drug product given the large safety margin and lack of genotoxicity. Does the Division agree?"*

The Division did not agree and stated that current practice regarding qualification of an impurity that exceeds ICH thresholds is to conduct a 90-day repeat-dose toxicology study for a chronic-use drug product. The Division acknowledged (b) (4) for the impurity, (b) (4) to support a specification of (b) (4)%. However, the proposed specification in Lyrica CR is (b) (4)%) the original specification for this impurity and, therefore, a 90-day toxicology study is required for the NDA. The Division inquired whether the Sponsor can tighten the specification to an acceptable level of (b) (4) The Sponsor replied that they will discuss this internally to see whether this would be possible.

C. CLINICAL PHARMACOLOGY

Question 5: The planned review of clinical pharmacology and biopharmaceutics data in the NDA will address relevant review questions for an ER drug product with an approved IR formulation. Table 17 summarizes the studies and analyses to support the clinical pharmacology program that will be included in the planned NDA for pregabalin ER.

Table 1. Clinical Pharmacology and Biopharmaceutics Studies and Reports

Category	To be submitted as part of the pregabalin extended release formulation NDA
General Clinical Pharmacology	1. CSRs from single and multiple dose PK studies in healthy volunteers evaluating planned to-be-marketed pregabalin[a] ER to support characterization of PK and evaluation of inter- and intra-subject variability. Raw concentration-time and PK parameter datasets will be submitted as SAS transport files (*.xpt) [1225, 1188, 1198, 1215, 1216, 1226, 1227, 1228, 1238, 1239]. 2. PMARs of population PK analyses of pregabalin ER. Model codes and input datasets will be provided as ASCII text files with *.txt extension. 3. PMAR of exposure response analysis of adjunctive pregabalin ER treatment of partial seizures. Model codes and input datasets will not be provided as a partial seizure indication is not being pursued.
Intrinsic Factors	1. PMARs of population PK analyses (also noted under General Clinical Pharmacology).
Extrinsic Factors	1. CSR evaluating the effect of concurrent administration of multiple doses of the prokinetic medication erythromycin on the PK of single dose planned to-be-marketed[a] pregabalin ER. Raw concentration-time and PK parameter datasets will be submitted as SAS transport files (*.xpt). [1197]
General Biopharmaceutics	1. CSR of single dose study evaluating the PK and relative bioavailability of a colonic dose of pregabalin IR solution relative to an oral dose of IR solution in healthy adult volunteers [1008-004] 2. CSRs of single dose studies evaluating pilot pregabalin ER formulations in healthy adult volunteers [1091, 1116, 1117, 1174, 1206]. 3. CSRs of single and multiple dose studies in healthy adult volunteers evaluating planned to-be-marketed[a] pregabalin ER [1225, 1188, 1198, 1215, 1216, 1226, 1227, 1228, 1238, 1239 also noted under General Pharmacology]. 4. In vitro study report to support lack of dose dumping with alcohol. 5. The proposed commercial dissolution method, supporting method report, and acceptance criteria. In vitro dissolution data for all lots of pregabalin ER used in clinical pharmacology studies. 6. Composition of the planned to-be-marketed formulation for each of the 3 pregabalin ER tablet strengths (82.5 mg, 165 mg, and 330 mg). 7. Summary of the data supporting ER designation for pregabalin ER.
Analytical	1. Bioanalytical reports from studies evaluating planned to-be-marketed[a] pregabalin ER. Supporting validation report.

Abbreviations: ASCII = American Standard Code for Information Interchange; CSR = clinical study report; ER = extended release; IR = immediate release; NDA = New Drug Application; PK = pharmacokinetics; PMAR = population modeling analysis report; SAS = Statistical Analysis System.
[a] With possible exception of film coat color and/or no debossing.

Does the Agency agree with the proposed summary of data to support the clinical pharmacology and biopharmaceutics review?

FDA Response to Question 5:

The proposed plan appears acceptable. Confirm that the to-be-marketed formulation was used in all the supporting clinical pharmacology and biopharmaceutics studies.

Submit the following datasets to support the population PK or PMAR 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, in addition to the standard model diagnostic plots, submit 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.

Discussion
The Sponsor confirmed that the to-be-marketed formulation was used in the clinical pharmacology and biopharmaceutics studies supporting the proposed labeling. There was no further discussion of this question.

D. CLINICAL

Question 6: Does the Agency agree that the proposed efficacy data summaries as detailed in the table of contents and proposed tables (indicated by titles) for the ISE (see Appendix 2) are appropriate to support the review of the NDA?

FDA Response to Question 6:
In addition to the planned comparisons of results by age, sex, and race, provide a comparison of efficacy results by dose.

Discussion
The Sponsor acknowledged the Division's request for specific analyses and will include the requested analyses by dose in the submission. The Sponsor stated in their response document (attached) that, "due to the flexible dose nature of the randomized-withdrawal design studies, interpretation of the results (efficacy and safety) may be confounded since patients are not randomized to dose." There was no further discussion of this question.

Question 7: Does the Agency agree that the proposed safety data summaries as detailed in the table of contents and proposed tables (indicated by titles) for the ISS (see Appendix 2) are appropriate to support the review of the NDA?

FDA Response to Question 7:
Include in the Summary of Treatment Exposure the duration of exposure for each dose by indication, and for the combined indications of PHN and FM. In the analyses of adverse events and discontinuations-due-to-adverse-events, compare incidence by indication and dose. Also, CNS adverse events of special interest should be a particular focus of these analyses.

Discussion
There was no further discussion of this question.

Question 8: *Pfizer proposes to include* (b) (4) *subject narratives for deaths and nonfatal SAEs, and for pregabalin-treated subjects who were discontinued due to 1 or more AEs, regardless of the relatedness assessment by the investigator or sponsor for all clinical studies included in the submission.* (b) (4) *Does the Agency agree with the proposed narrative plan?*

FDA Response to Question 8:
We agree with including subject narratives for deaths, nonfatal SAEs, and subjects who were discontinued due to AEs, regardless of the relatedness assessment. (b) (4) **Narrative summaries must provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries that merely provide the data that are already presented in the case report tabulation are of no value. A valuable narrative summary provides a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. A useful narrative summary includes 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, discussion of the diagnosis as supported by available clinical data, a list of the differential diagnoses for events without a definitive diagnosis, any treatment provided, outcome and follow-up information.**

Failure to provide adequate narratives may result in refusal to file.

Discussion
The Sponsor agreed to submit patient narratives as outlined. There was no further discussion of this question.

Question 9: *Pfizer proposes to include Case Report Forms (CRFs) for deaths and nonfatal SAEs, and for pregabalin-treated subjects who were discontinued due to 1 or more AEs, regardless of the relatedness assessment by the investigator or sponsor for all clinical studies included in the submission. Does the Agency agree with the proposed CRF plan?*

FDA Response to Question 9:
Yes. We agree with your plan to include CRFs for all deaths, nonfatal SAEs and for patients who discontinued treatment due to an adverse event for all clinical studies included in the submission.

Discussion
There was no further discussion of this question.

Question 10: Does the Agency agree with the proposal for the submission of datasets?

FDA Response to Question 10:
The NDA must include sufficient documentation to link the datasets to all results presented in the CSRs, ISS, and ISE.

Discussion
There was no further discussion of this question.

Additional Clinical Comments

The proposed development plan you have provided in the meeting packet is not sufficient to support an (b) (4) **Therefore, results from a peripheral neuropathic pain population, such as patients with PHN,** (b) (4) **.**

(b) (4)

Discussion
In the response document (see attachment), the Sponsor acknowledged the Division's position on the (b) (4) In

the response document, the Sponsor acknowledged the Division's comments regarding FM and agreed to address this in the submission. There was no further discussion of these comments.

E. REGULATORY

Question 11: Pfizer is planning to prepare a separate USPI for pregabalin ER tablets in keeping with precedents set for other prescription pain products that have IR and ER product presentations. In addition to management of FM, Pfizer proposes to list the following pain indications in the proposed USPI:

NeP associated with DPN
PHN
(b) (4)
FM

The TPP shown in Appendix 1 outlines the approach to be taken for the draft USPI. Does the Agency have any comments on the planned approach to the USPI?

FDA Response to Question 11:

(b) (4)

Also, the evidence you have presented for Lyrica CR does not appear adequate to support an indication for fibromyalgia (see Additional Clinical Comments above).

In Section 6 of the draft USPI, adverse reactions are described for PHN and FM but not for DPN. Although DPN was not studied with Lyrica CR, relevant safety information for DPN patients based on Lyrica IR studies should be included. The label should describe the dose-dependent increase in adverse reactions observed with the 600 mg dose of Lyrica in patients with painful diabetic peripheral neuropathy.

Discussion
The Sponsor agreed to include relevant DPN safety data from the IR studies. There was no further discussion of this question.

Question 12: At the time of the review and approval of LYRICA® Capsules, the Agency opened administrative NDAs to administer the separate indications. Does the Agency foresee doing this for pregabalin ER tablets and if so, is there any advice for Pfizer regarding the administrative NDAs?

FDA Response to Question 12:
No, additional administrative NDAs will not be required.

Discussion
There was no further discussion of this question.

Question 13: It is likely that there will be no additional completed or ongoing studies, nor any postmarketing data for pregabalin ER tablets between the time of the finalization of the NDA safety database and the end of the NDA review period.

Would the Agency consider granting a waiver for the 120-day safety update should there be no changes to this highly likely or anticipated situation?

FDA Response to Question 13:
No. We would not grant a waiver for the 120-day safety update. However, if no new information is available, the update can simply report that.

Discussion
The Sponsor agreed to submit a 120 day safety update. There was no further discussion of this question.

Question 14: Pfizer considers Studies 1224 (PHN) and 1245 (FM) to be the only covered studies per 21CFR50.2(e) in the planned submission. Therefore, financial disclosure certification is proposed only for these 2 studies. Does the Agency agree with Pfizer's proposal regarding financial disclosure?

FDA Response to Question 14:
Yes, we agree. You only need to submit financial disclosure certification for the two new efficacy studies.

Discussion
There was no further discussion of this question.

Question 15: Pfizer considers Studies 1224 and 1245 to be the only studies supporting safety and effectiveness in the planned submission of the proposed indications and therefore the only studies that would be subject to clinical site inspection. Does the Agency concur with this proposal?

FDA Response to Question 15:
In general we agree, but the final decision regarding inspections will be made during the NDA review.

Discussion
There was no further discussion of this question.

Additional Discussion
The Division stated that the Controlled Substances Staff (CSS) has been consulted about this application, as Lyrica is a controlled Schedule V product, and that any comments from CSS will be relayed to the Sponsor via a post-meeting note.

Post meeting note: There are no further comments from the Controlled Substances Staff.

3.0 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 (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/U

CM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** 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.

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

a. Number of subjects screened at each site
b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

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

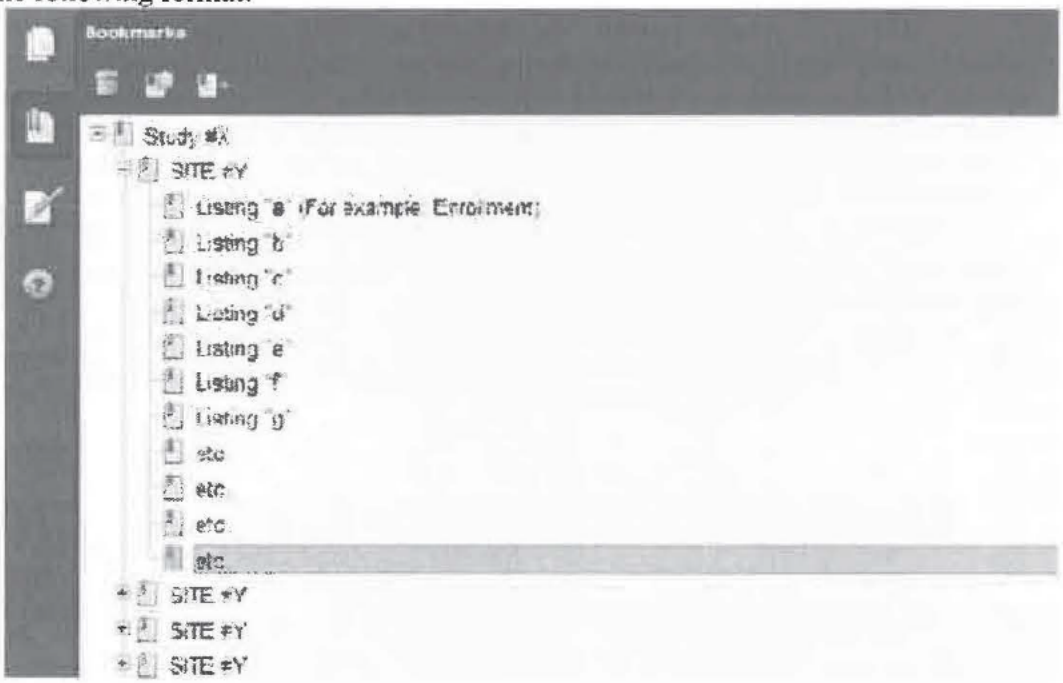
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

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

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

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

References:

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

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

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

Discussion
There was no further discussion of these General comments.

4.0 ACTION ITEMS

a) The Agency agreed to provide comments from the Controlled Substances Staff, if any, in a post-meeting note or as soon as possible. A post-meeting note is included in these minutes.

5.0 ATTACHMENTS

Document entitled: "April 19 FDA meeting response 18Apr2016".

April 19 FDA meeting response 18Apr2016

Pfizer thanks the Division for their preliminary comments for our preNDA meeting for pregabalin extended release tablets (IND 107333). We would like to reduce the agenda and change the format to a teleconference. Dial in details for the proposed teleconference are provided at the end of this message.

For the teleconference, Pfizer would like to further discuss additional PharmTox comment, 4b, regarding impurities.

One impurity, [redacted] was negative in both genotoxicity assays.

The proposed acceptance criterion in the Lyrica CR drug product is [redacted]%, which would result in a maximum daily exposure of [redacted] mg/day at the highest pregabalin dose of 660 mg/day, or [redacted] mg/kg/day for a 60 kg patient. [redacted]

Regarding point 4b, in which a 90 day toxicity study is requested for any impurity that exceeds ICH thresholds to support the proposed indication, Pfizer believes [redacted] is sufficient to support a specification of NMT [redacted] in the drug product given the large safety margin and lack of genotoxicity. Does the Division agree?

Please find below acknowledgement of the Division's comments with no further discussion required and Pfizer's go forward thinking, if applicable.

CMC
Q1 & 2: No further discussion needed.

Pharm Tox
Q3, 4a, 4b, 4c: Additional nonclinical comments (1-3, 5 & 6) – No further discussion required.

Clin Pharm
Q5: Pfizer confirms that the to-be-marketed formulation was used in the clinical pharmacology and biopharmaceutics studies supporting the proposed labeling. No further discussion needed.

Clinical
Q6 & 7: Pfizer acknowledges the Division's request for specific analyses and will include the requested analyses by dose in the submission. Pfizer wants to emphasize that due to the flexible dose nature of the randomized-withdrawal design studies, interpretation of the results (efficacy

and safety) may be confounded since patients are not randomized to dose. No further discussion needed.

Q8: Pfizer agrees to submit patient narratives as outlined. No further discussion needed.

Q9 & 10: No further discussion needed.

Additional Clinical Comments: Pfizer acknowledges the Division's position on (b) (4). (b) (4) . No further discussion needed.

Pfizer acknowledges the Division's comments regarding FM and agrees to address this in the submission. No further discussion needed.

Regulatory

Q11: Pfizer acknowledges the Division's comments. Pfizer agrees to include relevant DPN safety data from the IR studies. No further discussion needed.

Q12: No further discussion needed.

Q13: Pfizer agrees to submit a 120 day safety update. No further discussion needed.

Q14 & 15: No further discussion needed.

General Comments:

Pediatric Study Plan (PSP): Pfizer submitted the initial PSP for pregabalin extended release tablets to IND 107333 on 08Apr2016.

Dial in details are as follows:

+1-855-797-9481 Call-in toll-free number (US/Canada)

+1-415-527-5004 Call-in toll number (US/Canada)

Access code: 645 582 576

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

/s/

DIANA L WALKER
05/20/2016