CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204326Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204326

COMPLETE RESPONSE

Neos Therapeutics, Inc.
Attention: Dorothy Engelking, MS, RAC
Vice President, Regulatory Affairs
2940 N. Highway 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated December 27, 2012, received December 28, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets (b) (4), (b) (4).

We acknowledge receipt of your amendments dated:

January 4, 2013	April 19, 2013	September 9, 2013
January 11, 2013	June 28, 2013	September 13, 2013
March 26, 2013	August 1, 2013	

We also refer to our Discipline Review (DR) letter dated May 29, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Product Quality

Your responses to deficiencies 4, 5b, 6a, 6b, 6c, 6l, 7, 9, 10, 13, 16, 17, 18, 19, 20, 30, 31, and 32, as outlined in our Discipline Review (DR) letter dated May 29, 2013, were adequate. The remaining deficiencies have not been adequately addressed.

We, therefore, request that you:

1. Provide full responses to the remaining deficiencies in the DR letter and provide all modified data such as drug product and drug substance specifications, stability protocols, analytical methods, etc.
2. Provide a detailed summary of changes made to each section – preferably in a tabular format.

3. We note that a [redacted] is proposed in response to deficiencies 5a, 5e and 11c. We recommend that each dosage strength be represented in the stability program at this time [redacted] in the registration lots. We expect full stability data for three lots each of at least the highest, lowest, and an intermediate strength; however, a reasonable reduction in the number of lots of each of the other intermediate strengths tested will be considered. [redacted] In accordance with the ICH Q1A(R2) guidance, it is expected that long-term testing should cover a minimum of 12 months' duration at time of submission.
4. Similarly, considering the differences in manufacturing process, controls and packaging we recommend that you manufacture and provide data for at least three lots [redacted] of each tablet strength, although reduction of the number of the intermediate strength lots manufactured will be considered.
5. Provide the original CoA for lot 1E040A in response to deficiency #6h (a recent revision was provided in the 1 AUG 2013 response). We expect that lots undergo full testing to ensure that they meet the drug product specification before their use in the clinic.
6. In response to deficiency #8 you propose [redacted] This approach is unacceptable. [redacted]
7. Regarding the response to deficiency #11c: we request that these studies be carried out on [redacted]. In addition, we request stability data for these lots as most of the issues being investigated were not detected [redacted].
8. Regarding the response to deficiency #12: in order to evaluate the particle size specification for the [redacted], the requested data from the [redacted] lots used in the drug product lots manufactured thus-far will be required. Although this is a compendial excipient, [redacted] has the potential to impact drug product quality, [redacted].
9. Regarding the response to Deficiency #24: The response discusses [redacted] The response does not address [redacted] Please address this in your response.

Facility Inspections

Field inspections of NEOS Therapeutics, Inc. and [redacted] could not be completed as these sites were not ready for inspection. NEOS was determined to be not ready due to the acknowledgments made in NEOS' [redacted] response to FDA's [redacted] Discipline Review letter. [redacted] was found not ready during the attempted pre-approval inspection by the [redacted] district office from [redacted].

All facilities listed in this application must be found in compliance with current good manufacturing practices for their listed responsibilities before this application can be approved.

Biopharmaceutics

We also have the following biopharmaceutics comments:

1. We agree with your sampling proposal included in your response of collecting the dissolution data sets on the new clinical and registration batches using the following time points; 0.25, 0.5, 0.75, 1.0, 2.0, 2.25, 2.5, 2.75, 3.0, and 4.0 hours. Note that until the dissolution method and acceptance criteria are finalized, you should collect all future dissolution data using these time points.
2. The data submitted in your response supports 75 rpm as the optimal paddle speed, (b) (4) (b) (4) If you decide to continue development of your proposed product using this dissolution method, the paddle speed should be changed to 75 rpm.
3. The experiments conducted for the selection of the apparatus and rotation speed are not adequate to evaluate the discriminating capability of the method. (b) (4) (b) (4) (b) (4) Perform discriminating experiments once the method has been optimized.
4. You did not provide the individual vessel dissolution data (b) (4) (b) (4) used for setting the proposed acceptance criteria. Provide these data.
5. We note that you plan to submit additional dissolution data on newly manufactured clinical and primary stability batch(es) at some future date. Consider the following general guidelines in setting of acceptance criteria once the dissolution method is optimized and your new clinical and stability batches have been tested:

    a. Identify the lots/batches selected for setting your proposed dissolution acceptance criteria including the lot numbers, the PK and clinical studies in which they were used, and if they were registration batches on stability. Provide tabulations of individual vessel dissolution data for all the selected batches (n = 12) for assessment of variability at the individual time points.

    b. Based on the characteristics of your formulation and the mechanism of drug release presented in your NDA, the acceptance criteria in both the Acid and Buffer stages should be set as follows:

        i. ***Acid Stage***: *The initial sampling time point for the acid stage should be selected when not less than (NLT)* (b) (4) *% dissolution is reached.*
        ii. ***End of Acid Stage***: *At the 2 hour time point, the mean dissolution should not be more than (NMT)* (b) (4) *% of label claim.*
        iii. ***Buffer Stage:*** *The sampling time point for the buffer stage should be selected when Q =* (b) (4) *% dissolution is reached.*

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

Clinical Pharmacology

If you plan to submit an NDA for the reformulated product to correct for the CMC/ manufacturing deficiencies, you should plan to conduct the following in support of the application for your resubmission:

1. A bioequivalence study using the highest strength of the reformulated product and comparing it to a reference listed drug (RLD) such as ADDERALL XR ®. There is no need to demonstrate bioequivalence between the reformulated product and the early formulation. To demonstrate bioequivalence, you should include partial AUCs (i.e., pAUC $_{0\text{-}5}$ and pAUC $_{5\text{-}t}$) as pharmacokinetic variables, in addition to AUC and C_{max}, for bioequivalence assessment, if ADDERALL XR ® will be used as the RLD.
2. A food effect study using the highest strength of the reformulated product. To assess food effect, pAUC $_{0\text{-}5}$ and pAUC $_{5\text{-}t}$ should be used as additional pharmacokinetic variables.
3. An *In vitro* alcohol dose dumping study to assess potential alcohol effect on drug release from the reformulated product.

You should also provide justifications for biowaiver of lower strengths of the reformulated product if no additional bioequivalence study is planned.

Labeling

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Safety Update

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Other

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

MITCHELL V Mathis
09/24/2013