CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209844Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125184

**MEETING REQUEST-
WRITTEN RESPONSES**

Chartwell Pharmaceuticals, LLC
c/o Hyman, Phelps & McNamara, P.C.
Attention: Kurt R. Karst
Director
700 13th Street, N.W., Suite 1200
Washington, DC 20005

Dear Mr. Karst:

Please refer to your Pre-Investigational New Drug Application (PIND) file for doxycycline hyclate, USP.

We also refer to your submission dated May 6, 2016, containing a pre-NDA meeting request. The purpose of the requested meeting was to discuss the submission of two 505(b)(2) new drug applications [tablet (b) (4) (b) (4) for the treatment of early Lyme (b) (4) (erythema migrans).

Further reference is made to our Meeting Granted letter dated May 23, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 29, 2016, background package.

If you have any questions, call Kristine Park, Ph.D., Regulatory Health Project Manager, at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: PIND 125184
Product Name: Doxycycline hyclate, USP
Indication: Treatment of early Lyme (b) (4) (erythema migrans)
Sponsor/Applicant Name: Chartwell Pharmaceuticals, LLC
Regulatory Pathway: 505(b)(2)

1. BACKGROUND

The purpose of the requested meeting was to discuss the submission of two 505(b)(2) new drug applications [tablet (b) (4) for the treatment of early Lyme (b) (4) (erythema migrans).

2. QUESTIONS AND RESPONSES

Regulatory/Medical

Q1A. Based on the available information, does the Agency agree that the 505(b)(2) regulatory pathway still remains appropriate for the submission of the LYMEPAK NDA?

FDA Response: *Yes, the 505(b)(2) pathway is an appropriate mechanism for your literature-based NDA.*

Q1B. Does the Agency agree that the proposed strategy to justify reliance upon the proposed LDs, VibraTabs and Vibramycin, is sufficient to support approval of LYMEPAK tablets (b) (4)

FDA Response: *The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on VibraTabs and Vibramycin appears acceptable. FDA's findings of safety for Vibramycin and VibraTabs could be used to support the safety of Lymepak if the proposed dosage and duration of treatment falls within that described in the current labeling. Since the proposed 100 mg by mouth two times per day for (b) (4) days (b) (4) labelled dosing regimen for late latent syphilis, and is less than that labeled for the treatment of anthrax, reliance on the FDA's findings of safety for those products appears appropriate.*

Q2. Does the Agency agree with Chartwell's proposal to incorporate the ISE and ISS in the Module 2 Clinical Summary Sections (Sections 2.7.3 and 2.7.4, respectively)?

FDA Response: *Your proposal is acceptable.*

Q3. Does the Agency agree that this approach to providing post-marketing safety database information is adequate?

FDA Response: *Every attempt should be made to find safety data for patients with early Lyme disease who were treated with doxycycline. It is unlikely that the proposed strategy to find safety data (a FAERS query of the past 2 years) would identify any specific information for the proposed indication.*

Clinical Pharmacology

Q4. Will the Agency accept these studies in the format available for review?

FDA Response: *Your proposal is acceptable.*

Biopharmaceutics

Q5. Does the Agency agree that information supporting the BCS Class (b) (4) status of doxycycline hyclate should be included in the initial NDA submission?

FDA Response: *You may request an official BCS Class (b) (4) designation for your proposed doxycycline hyclate drug products (tablets (b) (4)) to the PIND. Submit all the supporting information such as solubility, permeability, gastric stability and dissolution using the attached BCS template to the PIND. Once your request is received, the FDA BCS Committee will assess your BCS Class (b) (4) designation request and communicate the final decision to you before or after the NDA is filed. Refer to the Guidance for Industry: Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based On Biopharmaceutics Classification System.*

Unless doxycycline is designated a BCS Class (b) (4) rug, BE trials will be needed to support the NDA.

Q6A. Does the Agency agree that a biowaiver can be granted for LYMEPAK tablets (b) (4) based on the proposed supportive information to be provided?

FDA Response: *No, we don't agree. The review of the biowaiver request will be made during the NDA review and will depend on the assessment of the BCS Class (b) (4) designation by the FDA BCS Committee.*

Q6B. Does the Agency agree that no additional data or submissions are required prior to NDA submission to support the proposed biowaiver strategy?

FDA Response: *See response to question 6A.*

Clinical

Q7. Does the Agency agree that the approved labeling for LYMEPAK can list (b) (4)

FDA Response: (b) (4) (b) (4)

Q8A. Does the Agency agree with Chartwell's proposed plan to collect additional information from published clinical studies?

FDA Response: *The adequacy of the study data will be an NDA review issue. Subject-level data would allow for an independent analysis and would present a more compelling scientific argument for granting the indication. Additionally, provide a clear description of how the scientific literature was searched and the studies were selected. Employing standard principles (pre-specified protocol, comparable definitions of key outcomes, quality control of data, and inclusion of all information available) will lead to more reliable evidence on the efficacy and safety of doxycycline for early Lyme disease.*[1]

Q8B. Does the Agency agree that Chartwell can rely upon published literature in which doxycycline salt form is not specified based on the available information supporting the similarity of doxycycline salt forms?

FDA Response: *The identity of the salt should be available for each publication on which you rely. In addition if you need to rely on publications using doxycycline monohydrate, you either need to provide comparative PK data between doxycycline hyclate and doxycycline monohydrate salts or request a designation for doxycycline monohydrate as BCS Class* (b) (4)

[1] One such example, "Efficacy and safety of pharmacological agents in the treatment of erythema migrans in early Lyme borreliosis: a systematic review", can be found here: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037932

Q8C. Does the Agency agree that if additional information is not available from published clinical literature, then Chartwell can still rely upon those published studies to support the safety and efficacy of its LYMEPAK (b) (4) tablets for the treatment of Lyme borreliosis (erythema migrans)?

FDA Response: *The adequacy of the submitted data can only be determined once we review the information. In general, scientific data from the published literature should be collected and analyzed in a systematic, non-selective manner with methods that are clearly described. Differences in measures, outcomes and analysis among the studies should be discussed.*

Q9. Does the Agency agree that the above summarized clinical information sufficiently supports the efficacy and safety of the proposed dosing regimen?

FDA Response: *Please see the responses to Question 8. We note that the referenced paper by Wormser and colleagues did not show a significant difference in outcome between 10 and 20 days of doxycycline treatment; and the study Massarotti also involved a 10 day treatment. Clinical data to justify the proposed (b) (4) day treatment course for erythema migrans should be provided with your submission.*

Q10A. Does the Agency agree with the proposed approach to evaluate the efficacy of doxycycline hyclate from published non-inferiority trials in support of its NDA approval for LYMEPAK tablets (b) (4)

FDA Response: *We agree with the proposed approach.*

Q10B. Based on the information identified in the published literature, will the Agency be able to provide a recommendation for M1 and M2 values to evaluate the efficacy of doxycycline hyclate for the treatment of early Lyme disease?

FDA Response: *We recommend you select a primary endpoint first, and then use your proposed method to derive a noninferiority margin. M1 should be defined based on the treatment effect seen with antibacterial treatment and M2 should be based on clinical judgment.*

We recommend that you conduct the above outlined analyses and propose an estimate of M1 and a justification for M2. It will be important that you clearly describe your literature search, the definitions of the endpoints considered and how they relate to the trials that you will be using to assess the efficacy of doxycycline. If you will consider multiple endpoints, you will need to determine margins for the different endpoints separately.

Nonclinical

Q11. Does the Agency agree that no additional nonclinical studies are required to support approval of LYMEPAK (b) (4) tablets?

FDA Response: *We agree,* [redacted]

Chemistry, Manufacturing and Controls

Q12. Does the Agency agree that no additional studies of product stability or packaging are required to support approval of LYMEPAK [redacted] tablets?

FDA Response: *We understand that the intended blister pack would use primary packaging materials identical to the existing marketed blister pack and would differ only in the proposed configuration of the tablets. We note that no mention is made of the packaging to be used for the* [redacted] *To address your question we would need more details concerning the existing and proposed packages. This would include materials, configurations, sealing processes, and data from USP <671> moisture vapor permeation testing. Also, we would need to see the quality of the stability data from the existing product that you propose to use to support the stability of the proposed product. This would include both the tests that are used at each time point and the adequacy of the results that are generated.*

Q13. Are the drug product release specifications as stated acceptable for the release for commercial doxycycline tablets ([redacted])?

FDA Response: *The adequacy of the drug product release specifications will be made upon review of the NDA. However, your proposals seem generally appropriate. Please indicate if these specifications will also apply to stability. You should include two identity tests. Describe which related substances are controlled as impurities in the drug substance and which are controlled as degradants in the drug product. Information in your NDA submission should clarify whether the limit for "Total impurities/degradation products" in the drug product apply to the sum of process impurities and degradants.*

The [redacted] *content limits for the tablets* [redacted], *which seem* [redacted] *at NMT* [redacted]*%, are much higher than the USP recommendations of NMT* [redacted]*% and NMT* [redacted]*%, respectively, and, therefore, not acceptable.*

You have not identified the proposed dissolution method in this meeting package. The acceptability of the dissolution method and the acceptance criterion will be made during the NDA review.

Q14. Does the Agency concur that the comparative dissolution data between the ANDA Immediate Release product and the proposed Immediate-Release NDA product (b) (4) tablet-to-tablet) measured by the ANDA product release dissolution method will be sufficient to support a biowaiver request based on the BCS (b) (4) classification?

FDA Response: *The difference between the proposed drug products and the ANDA Immediate Release products (* (b) (4) *tablet-to-tablet) appears to only entail a* (b) (4) *Therefore, comparative dissolution data between the proposed drug products and the ANDA Immediate Release products can support the* (b) (4) *does not require BE studies; therefore, a biowaiver request is not needed to support this change.*

Q15A. Would the Agency be willing to accept for review an NDA in which all applicable eCTD Module 3 sections are included, but which contain cross-referenced to the corresponding ANDA sections as appropriate to provide applicable information?

FDA Response: *No. Information submitted to FDA was paper-based from 1984 to 2006 and thereafter was submitted electronically, but in non-eCTD format. This makes it almost impossible for FDA to determine which sections are current.*

Q15B. If the response to Q16A is no, would the Agency be willing to accept for review an NDA in which all appropriate sections of the corresponding ANDA are included as PDF documents, with cross-links from the eCTD Module 3 sections to the appropriate ANDA data sections?

FDA Response: *No. You should submit complete current CMC information for each NDA. We strongly recommend, but do not require, that this be in the eCTD format.*

3. General Application Information

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 *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.

SECURE EMAIL COMMUNICATIONS

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

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.

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

/s/

SUMATHI NAMBIAR
07/05/2016