



BLA COMPLETE RESPONSE

Our STN: BL 125579/0

SmartPractice Denmark ApS
Attention: Kim Sullivan
3400 East McDowell Road
Phoenix, AZ 85008

Dear Ms. Sullivan:

This letter is in regard to your biologics license application (BLA) for Rubber Panel T.R.U.E. TEST manufactured at your Hillerød, Denmark location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

1. In order to perform a meaningful clinical review of your application, please organize your Biologics License Application submission, in electronic format, to include the following information regarding your pediatric study, entitled “Mekos 07 29P1/2/3 401: Clinical Evaluation of T.R.U.E. TEST® Panel 1.1, 2.1, and 3.1 in Children and Adolescents:”
 - a. Please submit a Clinical Overview. This document typically contains product development rationale, clinical pharmacology, efficacy, safety, and conclusions regarding benefit and risk of your product. Please submit a tabular listing of all clinical studies, which should include the study identifier, hyperlink to the location of study report, objectives of the study, study design and type of control, test products/dosage regimen and route of administration, number of subjects, location of the study, brief description of the study population, and study status.
 - b. For each clinical study in this supplement, please provide the following:
 - i. Clinical Study Report (Please see comment #2 for more details on the clinical study report.)
 - ii. Study protocol and protocol amendments
 - iii. List of independent ethics committees and institutional review boards
 - iv. Sample informed consent forms
 - v. List and description of investigators and other important study participants

- vi. Signatures of principal or coordinating investigators and/or your responsible medical officer indicating that the study report accurately describes the conduct and results of the study
- vii. Listings of subjects receiving test drugs/investigational products from specific batches where more than one batch was used (if applicable)
- viii. Randomization scheme and codes (subject identification and treatment assignment)
- ix. Audit certificates
- x. Discontinued subject listings (and reason for discontinuation)
- xi. Protocol deviation listings
- xii. Subjects excluded from efficacy analysis listings
- xiii. Adverse Event Listings
- xiv. Narratives of deaths, serious adverse events and other significant adverse events
- xv. Case report forms
- xvi. Cross-reference to your other applications that are related to this product
- xvii. Correspondences or meeting minutes with CBER pertaining to the submission of this BLA
- xviii. Debarment Certification
- xix. Financial Certification and Disclosure
- xx. FDA Form 3454
- xxi. Environmental analyses for your study product (Please see comment #11 for additional information.)
- xxii. References to any publications that have been based on the results of your studies for the Rubber Panel T.R.U.E. TEST
- xxiii. Please submit the electronic datasets used for your statistical analyses in SDTM format

2. Please submit the electronic Clinical Study Report and Datasets or Data Listings for “Mekos 07 29P1/2/3 401: Clinical Evaluation of T.R.U.E. TEST® Panel 1.1, 2.1, and 3.1 in Children and Adolescents” for each study site listed by individual subject number.

The clinical study report should include the following sections:

- a. Table of Contents
- b. List of Tables
- c. List of Figures
- d. Synopsis
- e. List of Abbreviations
- f. Independent ethics committee/institutional review board
- g. Ethical conduct of the trial/good clinical practice
- h. Participation information and consent
- i. Investigators and trial administrative structure, including a listing of all study sites; investigators name, addresses, and phone numbers; and the total of number of subjects enrolled at each site
- j. Introduction (also include background and rationale)
- k. Trial objectives
- l. Description of the overall trial design and investigational plan
- m. Trial plan/trial calendar
- n. Selection of trial population (i.e., eligibility criteria, contraindications, withdrawal of participants from treatment or assessment, lost to follow-up procedures, classification of subjects who discontinue the trial, follow-up of discontinuations)
- o. Trial Products (i.e., composition, preparation and administration, precautions for use, dose selection and timing, replacement doses, return of unused products, blinding and code-breaking procedures, randomization/treatment allocation procedures, treatment compliance, concomitant medication)
- p. Endpoints and assessment methods (i.e., primary, secondary, exploratory)
- q. Clinical and Data Quality Assurance
- r. Statistical Methods

- s. Trial Population (i.e., disposition of participants, data sets analyzed, demographic and baseline characteristics, concomitant medications)
- t. Efficacy Results
- u. Safety Results and Evaluation
- v. Discussion and Overall Conclusions
- w. Reference List
- x. List of appendices
- y. Analysis of safety and efficacy by study site
- z. Analysis of safety and efficacy by gender, age, race/ethnicity

3. The cover letter for your submission (dated August 19, 2014), indicates that you are seeking an indication for the Rubber Panel T.R.U.E. TEST in patients six years of age and older. However, your proposed package insert does not include this indication. In addition, no pediatric data are included in your proposed package insert.

Please submit an annotated and a clean copy of the package insert to include your proposed indication for use in pediatric subjects ages 6 to 17 years of age. Please include in your draft package insert a study summary and discussion of the pediatric effectiveness and safety data in a manner similar to the presentation of your adult data. Please do not combine the adult and pediatric data in the package insert.

4. Please submit a pharmacovigilance plan for your product. The pharmacovigilance plan should include important identified risks, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied preapproval. Routine pharmacovigilance as well as additional actions considered for important identified risks, important potential risks, and important missing information for the T.R.U.E. Test Rubber Panel should be described. The FDA guidance for industry E2E Pharmacovigilance Planning can be found at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf>
5. Please update the concentration of Thiuram mix from 25 ug/cm² to 27 ug/cm² throughout your submission and Package Insert, based on your recent approval of STN 103728/5118.
6. Please confirm the manufacturing areas used for Rubber Panel T.R.U.E. TEST are the same areas as currently licensed for T.R.U.E. TEST panels. Please provide a summary of changes and any testing performed to assess the adequacy of these changes made to the

manufacturing areas, equipment, or processes for the Rubber Panel T.R.U.E. TEST since the original submission of this material.

7. Please indicate if any changes have been made to the process flow diagrams since they were submitted as Attachment 10 in your original submission dated January 5, 2006.
8. Please provide the current procedure for the assembly and pouch packing of the Rubber Panel T.R.U.E. TEST. Information originally submitted appears to be for assembly of the original three panel T.R.U.E. TEST.
9. Please indicate if an assembling automation validation was executed for the Rubber Panel T.R.U.E. TEST. It appears that the assembling automation validation provided in the submitted materials is for one of the original T.R.U.E. TEST panels.
10. Please indicate if purchased (b) (4) water is still utilized in product manufacture.
11. Please provide an environmental assessment or a request for categorical exclusion according to 21 CFR 25.31.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*,” dated May 2009. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf> or may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER’s *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Christina Houck, at 301-796-2640.

Sincerely yours,

Wellington Sun, MD
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research