

## Telecon memorandum

**Date:** February 12, 2013

**Time:** 1:00 pm

**Participants:** CBER/OVRR: Marion Gruber, PhD, Phil Krause, MD

Dynavax: Tyler Martin, MD

**Background:** Dr. Martin contacted me by email on February 11, 2013 requesting a t-con to follow-up on a conversation he had on February 7, 2013 with Dr. Sun (Division Director, DVRPA) and Dr. Major, Chair, Heplisav BLA). During that t-con Drs. Sun and Major had provided Dynavax with a status update (requested by Dynavax in an email to me dated February 5, 2013) regarding their BLA for Heplisav, a vaccine for immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18 – 70 years of age).

**Discussion:** Dr. Martin thanked me for arranging the t-con between Dynavax and Drs. Sun and Major but expressed disappointment with the “likely conclusion of a Complete Response letter with a requirement for an additional safety study pre-licensure.” Dr. Martin provided his summary of the t-con of February 7, stating that Dr. Sun had reiterated concerns stated by CBER during the December 19th face-to-face meeting with Dynavax, i.e., outstanding concerns with the safety of Heplisav based on a) the case of cavernous sinus syndrome/Tolosa-Hunt syndrome, b) the general risk of autoimmune disease and c) the VRBPAC vote on safety. Dynavax continues to have serious concerns about the reasoning for each of these items. In addition, they understand from the discussion with Drs. Sun and Major that a modification of the indication that Dynavax proposed in an email dated January 4, 2013 is not being considered. Dr. Martin indicated that in light of the comments made at VRBPAC regarding the safety database and at-risk populations, Dynavax believes that the proposal is a reasonable approach and the company is not clear as to why the revised indication is not acceptable.

From the t-con with Dr. Sun, Dr. Martin understands that the presumed case of Tolosa-Hunt/cavernous sinus syndrome remains of fundamental concern to the agency. However, Dynavax’ consultant, a senior professor of neuro-ophthalmology at (b) (4), essentially excluded the potential diagnosis of Tolosa-Hunt syndrome. Dr. Sun had indicated that CBER has engaged its own expert consultants to assess this case and the original case of Wegener’s granulomatosis and results are pending. Therefore, Dr. Martin suggested that CBER classify the submitted materials regarding the potential Tolosa-Hunt case as a major amendment and delay the action due date by 90 days to get clarity on these 2 potential cases (Wegener’s and Tolosa-Hunt) before sending a CR letter. Dr. Martin stated that such a delay was important enough that Dynavax would be willing to wait to begin addressing the outstanding CMC concerns until after receipt of a delayed letter. Dr. Martin also stated that the company is not in the position to meet expectations for an additional large pre-licensure safety study, based on an estimated cost of (b) (4) for such a study.

We stated that a regulatory action considers information, assessments and recommendations from all disciplines including CMC and facilities information and that it is our understanding, after consulting with the review team, that there are numerous outstanding CMC and facilities issues to be resolved in

addition to the safety concerns raised. The proposed indication submitted to the BLA is for immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18 to 70 years old. Two potentially related rare diagnoses (Wegener's Granulomatosis and potential Tolosa-Hunt syndrome) were found in a safety data base of approximately 4000 subject. CBER would need to further evaluate the material submitted recently by Dynavax related to these diagnoses before a determination regarding the required pre-licensure safety data base to support an indication for this vaccine for use in 18-70 year olds could be made. However, we stressed that the safety data required to support licensure of a vaccine is determined in context of the proposed indication. Thus, if Dynavax would consider a more restricted population, such as persons with underlying disease or hypo-responders to currently licensed hepatitis B vaccine, the safety data required to support an approval would be different as the risk/benefit ratio would change.

Dr. Martin indicated that this was encouraging. He then referred to the VRBPAC discussion and that there was some confusion regarding the term "persons at risk". In this context, he wanted to understand why the agency did not accept Dynavax' revised indication sent per email on January 4, 2013. We stated that this revised indication was not formally submitted to the BLA but noted that it would not have been acceptable because it did not change anything regarding the population for whom the vaccine would be indicated, and thus did not represent a narrowing of the indication in a way that would alter a benefit-risk calculation. Universal hepatitis B vaccination is only recommended for children. Hepisav would be indicated for persons 18-70 years of age and older, and the vaccine recommendations as posted by CDC are essentially identical to Dynavax' proposed revised indication, e.g. persons at risk for sexual exposure, international travelers to regions of endemic HBV infection, settings in which hepatitis B vaccination is recommended for all adults and all other persons seeking protection from HBV infection, and thus it did not seem that this revised indication would limit use beyond that originally contemplated by the review team or the advisory committee in their deliberations.

We reiterated our recommendations made at the face-to-face meeting on December 19 with Dynavax , namely for Dynavax to consider an indication that would differ from the currently proposed indication in a meaningful way. For example, use of this product in subsets of persons with underlying disease such as ESRD patients or those who do not respond to currently licensed hepatitis B vaccine could be considered if also supported by effectiveness studies.

Dr. Martin indicated that the company has internally discussed several different potential approaches for a revised indication a) persons > 40 years of age who are at risk from hepatitis B infection, and b) persons who do not respond to currently licensed hepatitis B vaccine (non-responders). Dr. Martin indicated that they have data from one study in non-responders but the study was underpowered and results not statistically significant. Dr. Martin asked whether, as part, of a major amendment, Dynavax and the agency could agree on a revised indication for either of these populations. Dr. Martin suggested the option of an orphan drug indication for hypo-responders. The company would be able to conduct a single arm study in about 100 persons to generate supportive immunogenicity data. We indicated that it is unlikely that we can address the suggested approaches in the current review cycle but would be happy to further discuss various approaches with the company.

Dr. Martin indicated that Dynavax' board felt that all along, the company followed the agency's advice, and yet they find themselves in a situation of not getting the product approved. He reiterated the question whether the agency could consider a major amendment in order to discuss additional potential indications in these 90 additional days. We indicated that there are not only concerns regarding the clinical issues but also CMC and facility issues and that these issues cannot be addressed within 90 days.

Moreover, we explored with Dr. Martin his specific concerns regarding the receipt of a CR letter. He indicated that he was not concerned about delaying a complete action letter per se, but that his major concern was that the letter could foreclose options other than obtaining a substantial additional safety database prior to licensure. He also was concerned that the requirements as outlined in a CR letter might be less restrictive if the letter were drafted after CBER had completed its evaluation of the recently-submitted data on the potential Tolosa-Hunt case. We reassured Dr. Martin that any letter would not presuppose any specific outcome of that analysis, and that any letter would not delineate an immutable request for additional safety data, since the amount of safety data that would be required would depend upon the indication and the assessment of benefit/risk associated with that indication, and we would be open to further discussion of product indication.

We also suggested that we could include in the CR letter language on potential paths forward, and a statement that FDA would continue to work with the company to revise the indication for Heplisav to target a more restricted at risk population. Dr. Martin indicated that Dynavax would consider a more focused labeling and indicated that it would be helpful to include into the action letter language as suggested by us.

Dr. Martin stressed that the survival of the company is at stake and maintained that comments and discussions at the VRBPAC had prevented a more favorable outcome of the committee's vote. Also, the FDA briefing document did not point out any safety concerns. We acknowledged the latter but pointed out that at the time the briefing document was due to the committee the BLA review was still ongoing and did not capture the complete review.

We closed the conference call by assuring Dr. Martin that the agency would continue working with Dynavax on a path forward and encouraged him to contact OVRR leadership if he had additional questions.