

Mid-Cycle Meeting Summary

Application type and number: BL 125428/0
Product name: Hepatitis B Vaccine (Recombinant), Adjuvanted; (HEPLISAV-B)
Proposed Indication: For immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older
 [In the original BLA the indication was stated as “adults 18-70 years of age”]
Applicant: Dynavax Technologies Corporation
Meeting date & time: May 8, 2017; 1:00 pm-3:00 pm
Committee Chair: Marian Major, PhD
RPM: Katherine Berkhousen, CAPT, USPHS
 Richard Daemer, PhD
 Sudhakar Agnihothram, PhD

Attendees:

Discipline	Name	Attended meeting?
Regulatory Project Manager (RPM)	Katherine Berkhousen Lead RPM	Y
	Richard Daemer, PhD Co-RPM	Y
	Sudhakar Agnihothram, PhD Co-RPM	Y
Chair	Marian Major, PhD	Y
Clinical Reviewer	Darcie Everett, MD, MPH (safety)	Y
	Alexandra Worobec, MD (immunogenicity)	Y
CMC Reviewer	Iryna Zubkova, PhD	Y
	Brenda Baldwin, PhD (adjuvant)	Y
Animal Pharmacology Reviewer	N/A	
Clinical Pharmacology Reviewer	N/A	
Toxicology Reviewer	Andrew O’Carroll, DVM	N
Developmental Toxicology Reviewer	N/A	
OCBQ/DMPQ Reviewer	Priscilla Pastrana	Y
OCBQ/DMPQ Consult Reviewer	Ellen Huang	Y
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	N
Statistical Reviewer of Safety Data	Mridul Chowdhury, PhD	Y
	Ruoxuan Xiang, PhD	Y
Statistical Reviewer of non-clinical data	Lei Huang, PhD	Y
Postmarketing Safety Epidemiological Reviewer	Silvia PerezVilar, PharmD, PhD	Y
OCBQ/APLB Reviewer	Sonny Saini, Pharm.D.	Y
OCBQ/BIMO Reviewer	Bhanumathi Kannan	Y
OCBQ/DBSQC or OVRRLIB Reviewer	Varsha Garnepudi, M.S.	Y
	Hyesuk Kong, PhD	Y
	Lokesh Bhattacharyya, PhD	Y

Discipline	Name	Attended meeting?
	Anil Choudhary, PhD	N
	Simleen Kauer, PhD	N
	Tao Pan, PhD	N
	Alfred DeGrosso, PhD	N
	Muhammed Shahabuddin, PhD	N
	James Kenney, D.Sc.	N
Consult Reviewer(s)	N/A	
OCBQ/DMPQ/Inspectors	Priscilla Pastrana	Y
	Ellen Huang	Y
CMC Inspector	Marian Major, PhD	Y
Labeling Reviewer-Carton/Container	Daphne Stewart	N
Other Attendee(s) who attended the meeting:		
OVRP, Director	Marion Gruber, PhD	Y
OVRP, Deputy Director	Philip Krause, MD	Y
OVRP, Associate Director	Karen Farizo, MD	Y
OVRP, Regulatory Officer	Valerie Marshall, CDR	Y
OVRP/DVRPA Director	Wellington Sun, MD	Y
OVRP/DVRPA Deputy Director	Loris McVittie, PhD	Y
OVRP/DVRPA Associate Director	Douglas Pratt, MD	Y
OVRP/DVRPA Branch Chief	Elizabeth Sutkowski, PhD	Y
OVRP/DVRPA Branch Chief	Rakesh Pandey, PhD	Y
OVRP/DVRPA Branch Chief	Andrea Hulse, MD	Y
OVRP/DVRPA Team Lead	Meghan Ferris, MD, MPH	Y
OVRP/DVRPA Team Lead	Timothy Nelle, PhD	Y
OVRP/DVRPA Regulatory Health Project Manager	Darlene Martin, MS, PMP	Y
OBE/DB/VEB Branch Chief	Amelia (Dale) Horne, PhD	Y
OBE/DB/VEB Lead Mathematical Statistician	Tsai-Lien Lin, PhD	Y
OBE/DE/AEB Supervisory Medical Officer	Deepa Arya, MD	Y
OCBQ/DMPQ Deputy Director	Laurie Norwood	Y
OCBQ/DMPQ Branch Chief	Qiao Bobo, PhD	Y
OCBQ/DMPQ Team Lead	Anthony Lorenzo	Y
DBSQC	William McCormick, PhD	N
<u>Additional Attendees:</u>		
OVRP/DVRPA	Qun Wang PhD	Y

Discipline	Name	Attended meeting?
OVRR/DVRPA	Darlene Martin	Y

Background:

- HEPLISAV is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. This is the first BLA for Dynavax Technologies Corp. and the first time 1018 adjuvant is used in a vaccine.
 - Data from two pivotal Phase 3 trials (HBV-16 and -10) including 4,864 randomized subjects (HEPLISAV: N=3,777, active comparator ENGERIX-B: N=1,087), ages 18 – 70 years, were submitted in the BLA. The BLA also contains data from eight supportive trials.
 - The sponsor was asked to remove the superiority claims in their label.
 - The initial prelicensure facility inspection (PLI) was done August 16 – 23, 2012, for the drug substance. A 13-point 483 was issued.
 - PeRC held on October 3, 2012. A full PREA waiver was granted for birth through age 17 years.
 - A VRBPAC meeting was held November 15, 2012, in which a majority of the committee Members voted that the safety database was too small to consider licensure at that time, as the vaccine contains a novel adjuvant. VRBPAC recommended a larger safety database.
 - A Complete Response (CR) Letter was issued on February 22, 2013.
 - A Type C Meeting was held May 8, 2013 to discuss the path forward and design of the additional required pre-licensure safety study
 - Dynavax submitted a complete CR on March 16, 2016, which included data from the additional pivotal safety study HBV-23 (N= 8,374 subjects), along with immunogenicity data for the subgroup with type 2 diabetes mellitus, and revised clinical study reports for pivotal phase 3 studies HBV-16 and -10.
 - A Major Amendment letter was issued on April 18, 2016, due to a substantial amount of clinical data not previously reviewed or submitted to the application.
 - Second PLI was performed on June 8-16, 2016. Five observations were issued in a Form FDA 483. Dynavax responded to these observations July 2016.
 - A CR was issued on November 10, 2016. The first 25 items in the CR were information requests that had recently been submitted by Dynavax to CBER, to address a potential cardiac concern, but were of such volume that it was not reviewable under the remaining review clock.
 - A Type A Meeting was held via telephone with the applicant on January 10, 2017 to clarify specific CR items.
 - Dynavax submitted a Complete Response on February 8, 2017. The Action Due Date will be August 10, 2017.
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- A number of IRs have been sent to Dynavax, and responses were received. CBER is waiting on submission of the revised Lot Release Protocol Template as a response to the IR dated 5/3/17 (requested by Varsha) and a clinical request dated 4/24/17 (requested by Darcie/Bhanu). An IR from the Pharmacovigilance Team was sent out on 5/8/17. Response is awaited.

- Two telecons have been held with Dynavax: 1) to discuss the impact of shipping procedures on the quality of the Heplisav drug product. 2) To discuss the discrepancies observed between CBER and Dynavax in the (b) (4) Endotoxin (b) (4) Testing process for post licensure lot release.

Report and Discussion:

As a quick overview, Dynavax responded to the CR Letter, (issued on Nov 10, 2016) on Feb 8, 2017 resulting in an action due date of August 10, 2017. Dynavax provided a complete response to the CR items as follows: BIMO and clinical (CRL items # 1-44), manufacturing (CRL item # 45), CMC adjuvant testing (CRL item #46), quality control testing (CRL items # 47-49), and pharmacovigilance post-marketing (CRL items #50-52).

We are in the 3rd cycle review and the discussions will focus on those discipline reviews related to the CRL items and issues that may prevent licensure.

1. Reviewer Reports.

Reviewer	Role	Final Report TBC	Notes
Marian Major, PhD	Chair		Roll call and Introduction Opening Remarks CRL Items # 1-44 are Clinical and will be discussed towards the end.
Priscilla Pastrana and Ellen Huang	Facilities	May 2017 (Tentative)	CRL Items # 45.a and #45.b. <i>Shipping Validation of Drug Product to Labeling and Packaging Facilities in the</i> (b) (4) . The firm’s response to the CR item and subsequent IR questions appear acceptable. Additional information was provided regarding (b) (4) of the DP vials during (b) (4) transportation, a comparison of the (b) (4) transportation, and shipping duration. The DMPQ review memo associated with the Second CRL is under the review by DMPQ BR 2 management. The EIR associated with the second PLI conducted at Dynavax GmbH in Düsseldorf, Germany, from June 8-16, 2016 is under review. <u>No substantive issues which could</u>

			<u>prevent approval and impact the review timelines were reported during this meeting</u>
Brenda Baldwin, PhD	CMC/Adjuvant	May 31, 2017	<p>CRL Item #46 <i>Purity of 1018</i> (b) (4)</p> <p>Review completed, with supervisor. The information and data related to the adjuvant appears acceptable; reviewer's questions have been adequately addressed. In addition, adjuvant reviewer in consultation with DBSQC concurred with the addition of sterility testing as a part of post-licensure testing for Heplisav.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting</u></p>
Hyesuk Kong, PhD	DBSQC Product Testing	Review Memo completed on 7/9/16. (b) (4) Endotoxin licensing support testing is ongoing with t-con held on April 20, 2017.	<p>CRL Item #47 (b) (4) <i>Endotoxin Licensing Support Testing</i></p> <p>During (b) (4) endotoxin in-support testing, CBER experienced 50% more enhancement in Positive Product Control (PPC) recoveries as compared to Dynavax. The unusual difference observed in PPC enhancement by CBER is not significant enough to impact the BLA process; it is only a potential concern for confirmatory lot release. CBER, in a telecon on 4/20/17, discussed the potential issues that might contribute to the observed difference. During the mid-point meeting, the reviewer updated that the issue regarding the difference observed in PPC enhancement by CBER has been resolved.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Lei Huang, PhD	Stats -Bioassay	Review	CRL Item #48 <i>In-vivo potency assay</i>

		completed	<p>In response to 45 # a, Dynavax provided an explanation of how the two-sided 95% confidence interval was computed. In response to 45 # b, Dynavax indicated that the reference lots had the same theoretical potencies as validation samples used in their assay. The responses were acceptable. No outstanding issues.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Lokesh Bhattacharyya, PhD	DBSQC QC Testing and Validation	July 10 2017	<p>CRL Item #49 <i>Quality Control Tests and Method Validations</i></p> <p>In response to 49 a, Dynavax submitted information demonstrating that the (b) (4) could detect impurities. In response to 49b, Dynavax clarified the laboratory sites in which the tests were performed.</p> <p>The responses were deemed as acceptable.</p> <p>More validation data came in on 5/3/17 as a response to IR dated 4/6/17 and review of that is ongoing. The reviewer indicated that if there were any additional questions, an IR will be sent.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Varsha Garnepudi	DBSQC Testing Plan and Lot Release Protocol template	N/A	<p>Dynavax submitted another revised Lot Release template. The review is complete and an IR was sent on 5/4/2017.</p> <p>Review of the testing plan <i>draft</i> is complete:</p> <ul style="list-style-type: none"> • Decisions about release tests have been made. • Post licensure testing has been determined.

			<ul style="list-style-type: none"> Need final LRP template and labeling to be completed. <p>The reviewer updated that the Post Licensing Testing Proposal includes a testing frequency of (b) (4) for the first (b) (4) lots followed by (b) (4) for rest of the lots. The reviewer also indicated that the draft testing plan has been circulated for review.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Bhanu Kannan	BIMO	Mid May 2017	<p>CRL Item # 41-42 <i>Lost to Follow-Up subjects and protocol deviations</i> BIMO reviewed the sponsor response dated February 8, 2017 to CRL items #41 and #42. Sponsor's response to CR item #42, use of an excel table with inadequate access control to capture protocol deviations, is acceptable. Sponsor responded on May 1, 2017 to the IR (April 6, 2017) regarding Item #41 discrepant data in lost to follow-up subjects who were reengaged. Preliminary review of the response finds the response to be acceptable.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Alexandra Worobec, MD (Ruoxuan Xiang Ph.D.- statistical support to clinical team)	Clinical- Immunogenicity Statistical Review	15 June 2017 Ruoxuan's review will be completed 5/26/17.	<p>The reviewers concurred with the following updates. Dynavax submitted responses to CRL items 23, 24 and 25. The review of these responses clarified the right number of subjects included and excluded in the study. A statistical review was performed on the primary immunogenicity endpoints. Immunogenicity data from DV2-HBV-</p>

<p>Darcie Everett, MD</p>	<p>Clinical- <i>safety</i> See Appendix 1 for the <i>safety</i> <i>discussion</i></p>	<p>N/A</p>	<p>10 and -16 will be used to support the effectiveness of this vaccine product to demonstrate non-inferiority to Engerix. Immunogenicity data will not be reviewed for Study DV2-HBV-23 in the context of this CR response. Immunogenicity was reviewed for DV2 HBV-23 during the last review cycle.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p> <p>There is an imbalance in events of acute MI observed in DV2-HBV-23. The Applicant has submitted their detailed analysis of major adverse cardiovascular events, a composite endpoint of cardiac deaths, MIs, and stroke, adjudicated in a blinded fashion. This analysis demonstrates a significant/near-significant increased risk of MI in the Heplisav group in DV2-HBV-23 (RR = 6.97, 95% exact CI 1.00, 184.9), with risk of cardiovascular death and stroke trending in the same direction.</p> <p>An unfavorable imbalance was not observed in prior, smaller studies of Heplisav that enrolled individuals with fewer risk factors for cardiac disease. The Applicant concludes 1) the imbalance in MIs was due to lower than expected events in the Engerix-B group. An internal cardiology consultation offered critique of the analysis, but agreed that the Applicant’s conclusions are plausible. Two external cardiology consults are pending.</p> <p>In studies DV2-HBV-16 and DV2-HBV-23, the studies that utilized a safety adjudication committee, there was an imbalance in adjudicated new-onset AESIs with no alternative plausible cause (14 subjects who</p>
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<p>(Mridul Chowdhury PhD-statistical support to clinical team)</p>			<p>received Heplisav (0.19%) and one subject who received Engerix-B (0.03%). Two of the subjects in the Heplisav group reported rare granulomatous vasculitides.</p> <p>These imbalances remain concerning for overall risk benefit profile of a preventive vaccine.</p> <p>The Clinical Reviewer summarized the review of data, safety concerns and risk benefits via a power point presentation. The Presentation is attached as Appendix #1.</p> <p><u>In conclusion, the Clinical reviewer indicated that their current recommendation is that the risk benefit balance is not in favor of approving the licensure of this vaccine.</u></p> <p>Statistical reviewer indicated AMI rate (due to 14:1 split of SAEs) remains a concern, despite CDER Consult's report.</p> <p>The Statistical reviewers concerns were summarized in a document that's attached as Appendix #2.</p> <p><u>The statistical reviewer indicated that the statistical approaches used by the sponsor were questionable, and that the statistical team will be performing revised statistical analysis of the data, and their recommendations regarding the approval of Heplisav will be based upon the outcome of this analysis.</u></p>
<p>Siliva PerezVilar, PharmD, PhD</p>	<p>Pharmacovigilance</p>	<p>June 2017</p>	<p>Upon review of the safety data, PV group will be providing inputs on whether the submitted studies will be a PMC/PMR.</p> <p>Issues that need to be discussed include:</p> <p>a) A potential post marketing</p>

			<p>study aimed to follow up on cardiac events, immune-mediated diseases, and/or additional adverse events.</p> <p>b) A pregnancy registry.</p> <p>c) Inclusion of the class effects of PS ODNs as potential risks in the pharmacovigilance Plan).</p> <p>An information request was submitted to the sponsor on May 8. The request asked for confirmation in regard to post-marketing plans (mentioned in the PVP) for events identified by the sponsor as important missing information.</p> <p><u>No substantive issues which could prevent approval and impact the review timelines were reported during this meeting.</u></p>
Andrew O'Carroll	Toxicology		The toxicology review was completed by a joint effort between S. Kunder and C. Wrzesinski in 2013 as part of the original submission. No new toxicology data submitted. PLLR language currently under review.
Sonny Saini, Pharm. D.	APLB		Review pending. Labeling discussions to begin June 19 th
Iryna Zubkova, PhD	CMC/Product		CMC review is completed. There are no significant changes in manufacturing process.
Anil Choudhary, PhD Tao Pan, PhD Alfred DeGrosso, PhD	DBSQC		Reviews completed

2. For PDUFA V Program submissions:

N/A

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

VRBPAC scheduled for July 28, 2017. VRBPAC voting members are being vetted. An update will be provided by Valerie Marshall at the Mid-Cycle Meeting regarding the status of inclusion of SGE's in VRBPAC.

4. Determine whether Post marketing Requirements (PMRs), Post marketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

An Initial discussion was held between DVRPA and OBE on 4/17/17 to discuss the proposed Pharmacovigilance plan. A second follow up meeting is being scheduled on 5/10/17 to finalize the decision. Meanwhile, PV and clinical team will provide an update on the course of action.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

Partial NDC code was submitted - only the labeler code. The sponsor will need to provide the entire NDC for our review. Label review is scheduled to begin in June.

6. Proper naming convention.

Proprietary: **HEPLISAV-B**

Non-proprietary: **Hepatitis B Vaccine (Recombinant), Adjuvanted**

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

GMP PLI:

- Second PLI of Dynavax GmbH in Düsseldorf, Germany, was conducted from June 8-16, 2016. Inspectors: Marian Major/Priscilla Pastrana/Ellen Huang.
- PLI of the following facilities in support for the manufacture and testing of HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] or Drug Product *were waived*:

(b) (4) [Redacted]

8. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Mid-point Meeting	May 8, 2017
PMC/PMR/SWG Determination:	June 9, 2017
Draft Reviews to Supervisor	June 12, 2017
VRBPAC Briefing Doc to Div andIOD	June 13, 2017
PMC/PMR/SWG Notify applicant	July 11, 2017
Reviewers Final Reviews	

....Signed/Uploaded Due: July 11, 2017

Press Release –contact M. Hess	June 26, 2017
Labeling Meetings:	June 19, 2017
Labeling Comments to Applicant:	July 11, 2017 (T-30)
Late-Cycle Briefing Package*:	N/A
Late-Cycle Meeting*:	N/A

9. Establish a labeling review plan and agree on future labeling meeting activities.

Dynavax will need to be notified to revise their PI by removing all superiority claims. This will make a better starting point to review the PI. Time point for this notification is to be determined. The first internal labeling meeting is scheduled for June 19, 2017.

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

DVRAPA has communicated with the BITS-ABC data abstractors and provided information for the components table. No additional requests will be made to the sponsor.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*.

This has been completed (May 2016).

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

Details of tests to be included in the lot release testing plan have been finalized by DBSQC and agreed upon by the Product Team. The frequency for the planned testing will be (b) (4) for the first (b) (4) lots and then (b) (4) of the lots.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.

The submitted Heplisav-B SPL already contains UNII codes minus the adjuvant code. We worked closely with the UNII code team and now have a UNII code for the adjuvant and the antigen.

Adjuvant: H0E71D85ZS Description: DNA, D(P-THIO)(T-G-A-C-T-G-T-G-A-A-C-G-T-T-C-G-A-G-A-T-G-A), sodium salt. The adjuvant reviewer indicated that this UNICODE would be the most appropriate one to use for the adjuvant.

HBsAg Antigen: XL4HLC6JH6

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

N/A

PeRC Discussion: 10/3/2012

PREA- Full Waiver as the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

15. Additional Discussion Items:

The clinical reviewers presented a summary of the safety review to date. Concerns regarding the cardiac autoimmune safety issues were discussed followed by a short discussion on the CDER consult report from Dr. Sheri Targum, MD. The clinical reviewer also indicated their plans of sending an IR to obtain clarification on adjudication of safety events.

16. Action Items:

- A follow up meeting to be scheduled within 2-3 week time frame (week of 29 May 2017,) to discuss the recommendation on licensure of this vaccine.
- An Clinical IR requesting clarification on the adjudication of the safety issues will be sent to the applicant.