

Application Type	Original Application
STN	125428/0
CBER Received Date	April 26, 2012
PDUFA Goal Date	February 24, 2013
Division / Office	DVRPA /OVR
Priority Review	No
Reviewer Name(s)	Brenda Baldwin
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Dynavax Technologies Corporation
Established Name	Hepatitis B Vaccine (Recombinant)
(Proposed) Trade Name	HEPLISAV
Formulation including Adjuvants	20 mcg Hepatitis B Surface Antigen Recombinant (HBsAg; subtype <i>adw</i> ; Hansenula polymorpha; (b) (4)) with 3000 mcg CpG 1018 ISS (Immunostimulatory Sequence; Avecia Biotechnology) Adjuvant Vaccine
Dosage Form(s) and Route(s) of Administration	Sterile clear, colorless liquid in vial (0.7 ml) – excipients include (b) (4) phosphate (b) (4) , sodium (b) (4) phosphate (b) (4) , polysorbate 80, sodium chloride and (b) (4) IM administration (0.5 ml)
Dosing Regimen	2 dose – Month 0 and 1
Indication(s) and Intended Population(s)	For immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18 through 70 years of age
Cross-reference(s)	DMFs (b) (4) , and MAF ^{(b) (4)} (HBsAg DS) DMF (b) (4) (1018 ISS adjuvant) – see p. 43-44 of review DMF (b) (4) (HEPLISAV DP) No IND noted; however, this product is being studied under IND 12692 and 13332

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GLOSSARY

(b) (4)	[REDACTED]
1018 ISS	1018 Immunostimulatory Sequence; immunostimulatory phosphorothioate oligodeoxynucleotide
(b) (4)	[REDACTED]
AGU	Avecia product code
(b) (4)	[REDACTED]
AU	Absorbance Unit
BLA	Biologics License Application
BLAST	Basic Local Alignment Search Tool
(b) (4)	[REDACTED]
CoA	Certificate of Analysis
(b) (4)	[REDACTED]
CFR	Code of Federal Regulations
(b) (4)	[REDACTED]
CMC	Chemistry, Manufacturing, and Controls
CpG	Cytosine Phosphoguanosine
CpG-ODN	Cytosine Phosphoguanosine Oligodeoxynucleotide
(b) (4)	[REDACTED]
eCTD	electronic Common Technical Document
(b) (4)	[REDACTED]
DNA	Dideoxy Nucleic Acid
(b) (4)	[REDACTED]
EP	European Pharmacopoeia
FDAAA	Food and Drug Administration Amendments Act of 2007
(b) (4)	[REDACTED]
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
(b) (4)	[REDACTED]
Hr(s)	Hour(s)
ICH	International Conference on Harmonisation
(b) (4)	[REDACTED]

ID	Identification
(b) (4)	[REDACTED]
IPA	Isopropanyl Alcohol
L	Liter
(b) (4)	[REDACTED]
M	Molar
(b) (4)	[REDACTED]
Manuf	Manufactured
Min(s)	Minute(s)
Mo(s)	Month(s)
Ms	Milliseconds
MWCO	Molecular Weight Cut-off
NA	Not applicable
NaCl	Sodium Chloride
NaOH	Sodium Hydroxide
NLT	Not less than
NMT	Not more than
(b) (4)	[REDACTED]
ODN	Oligodeoxynucleotide
OH	Hydroxide
OOS	Out of Specification
PDE	Permitted Daily Exposure
(b) (4)	[REDACTED]
PI	Package Insert
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PPB	Parts per Billion
PPQ1	Process Performance Qualification 1
PPQ2	Process Performance Qualification 2
PS	Polystyrene
Psi	Pounds per square inch
PS80	Polysorbate 80
PS ODN	Phosphorothioate Oligodeoxynucleotide
RH	Relative Humidity
RMS/BLA	Regulatory Management System for the Biologics License Application
(b) (4)	[REDACTED]
RT	Room Temperature
SC	Subcutaneous
(b) (4)	[REDACTED]
Soln	Solution
Spec	Specification
(b) (4)	[REDACTED]

(b) (4)

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SUMMARY OF PRE- AND POST-SUBMISSION REGULATORY ACTIVITY RELATED TO THE SUBMISSION

A preBLA meeting was held with Dynavax on January 25, 2012. Discussions concerning CpG 1018 ISS adjuvant included:

1. Need for validation reports for all analytical methods
 - Validation reports were provided to the BLA and will be reviewed by OMPQ/DBSQC.
2. 3 lots of 1018 ISS adjuvant will need to be available on request for testing in support of licensure by CBER
 - These lots will be tested by DBSQC
3. Master Batch records pertaining to the lot consistency Trial DV2-HBV-16 should be submitted (lot (b) (4))
 - Lot (b) (4) was submitted as part of the BLA.
 - Batch records for the requested lots were submitted on November 23, 2012.
4. A description, justification and discussion of the specifications including the (b) (4) (versus sterility) for the adjuvant should be provided
 - See section II.F.2 of this review.
5. The adjuvant manufacturing facility (Avecia) information will need to be supplied as either a MF or as part of the BLA
 - Information was supplied as part of the BLA and will be reviewed by DMPQ.

FDA request: On 10/12/12, Dynavax was asked the following question by e-mail. As requested in the preBLA meeting, please provide the master batch records for the lots of 1018 ISS used in the lot consistency trial DV2-HBV-16 (lots (b) (4)). Please also provide the Certificate of Analysis for the 3 lots of 1018 ISS adjuvant used in the lot consistency trial.

Dynavax's response: On 11/26/12 (Serial 21), Dynavax submitted the batch records for the 3 requested lots.

FDA Reviewer comment: Response was acceptable.

BACKGROUND INFORMATION

This is a review of the CMC information regarding the manufacturing and testing of the starting materials for CpG and the final container of CpG adjuvant included in the BLA STN 125428 from Dynavax Technologies for Human Hepatitis B virus (HBV) Vaccine, CpG 1018 ISS Adjuvant, as titled in RMS-BLA. Throughout this review, the adjuvanted vaccine may be referred to as HEPLISAV.

The antigen in this vaccine, Recombinant HBsAg (rHBsAg), is a 22 nm particle containing the *adv* subtype of the HBV S protein and lipids, and is produced in *Hansenula polymorpha* yeast cells. This particle resembles the noninfectious, HBsAg-containing particles that are secreted by human hepatocytes during natural HBV

infection. The intended biological activity of HBsAg is to generate antibodies to the alpha determinant of the S protein (amino acids 124 to 147).

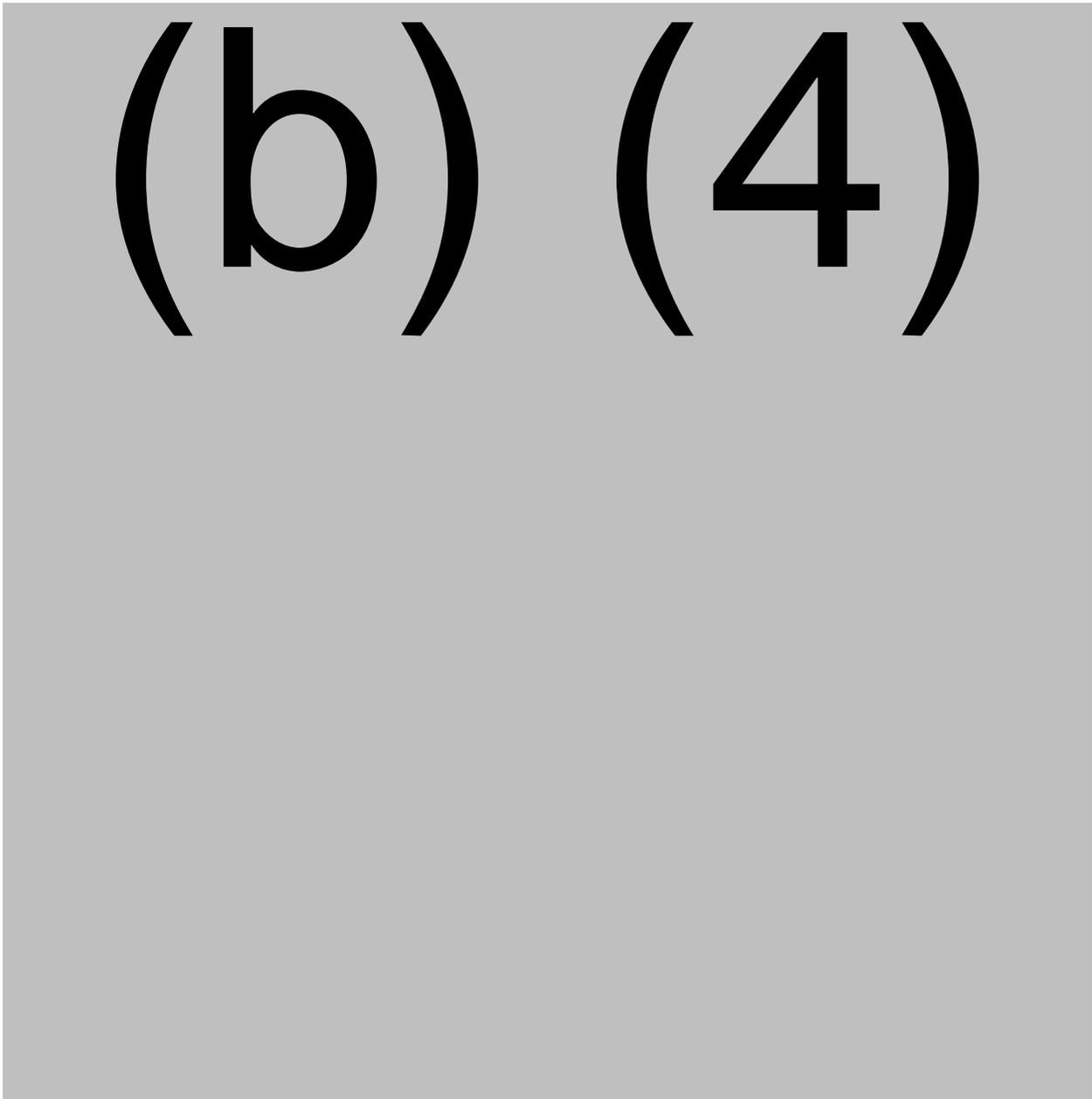
The CpG 1018 ISS adjuvant (also referred to as 1018 ISS adjuvant, 1018 ISS, AGU or the adjuvant in this review) is a 22-mer phosphorothioate linked oligonucleotide (natural DNA has a phosphodiester linkage) with a molecular mass of (b) (4) that is produced by (b) (4). The sequence of the 1018 ISS Adjuvant is 5' TGA CTG TGA ACG TTC GAG ATG A 3'. The molecular formula of the 1018 ISS adjuvant free acid is (b) (4). The 1018 ISS adjuvant was selected from a large panel of oligodeoxynucleotides for immunostimulatory activity *in vitro* and *in vivo* and for activity in both human cells and important animal species. The 1018 ISS adjuvant sequence has been demonstrated to be immunostimulatory *in vivo* in mice, rabbits, dogs, baboons, and cynomolgus monkeys and *in vitro* in human peripheral blood cells.

Human DNA sequence databases were searched to evaluate the extent to which 1018 ISS Adjuvant had homology with sequences of known human genes and transcripts. Results from the search indicate that there were no homologies with 1018 ISS Adjuvant in any stretch of 16 to 22 contiguous nucleotides. The 2 sequences with 15 nucleotides of contiguous homology found in genomic DNA were both within introns of their respective genes. At the level of 14 contiguous nucleotides, 21 homologous sequences were identified and all were found within introns or intergenic regions. Homology to such intronic sequences is not anticipated to have off-target effects.

Dynavax did evaluate for the potential antigenicity (induction for antibodies to both ss-DNA (in mice) and ds-DNA (in mice and baboons)) of the adjuvant component using samples from an immunogenicity study in mice (Study 99-0086) and a study in baboons (Study 99-0089). Mice immunized with 46 mcg 1018 ISS Adjuvant plus 0.84 mcg HBsAg developed measurable antibody to ss-DNA, but not to ds-DNA. Antibodies to ds-DNA are associated with certain autoimmune diseases, including systemic lupus erythematosus and Sjögren's syndrome. In 1/5 baboons that received 2 injections of HEPLISAV (human dose) a ds-DNA antibody mean value very slightly above antibody levels considered normal (22 IU/mL compared to the upper boundary of the normal range, 20 IU/mL) was found. In the conclusion, the report states that no clinical signs or symptoms associated with autoimmune disease were observed in this baboon.

Reviewer comment: *It was noted in the clinical section, that Dynavax analyzed for anti-ds-DNA antibodies at baseline and at the end of the trial for subjects in DV2-HBV-10 (efficacy trial), DV2-HBV-14, HBV001, DV2-HBV-03 and DV2-HBV-05 using a qualitative (b) (4) and for DV2-HBV-16 (lot consistency trial) using a quantitative assay. About 1-1.5% of individuals had positive results at baseline and about 1.5-1.8% of individuals had positive results at the end of the trial, depending on the tier/formulation. Findings were essentially the same for the HEPLISAV group as they were in the Engerix-B group and raised no clinical concerns (see safety review by clinical reviewer).*

Hybridon Specialty Products was the original site for 1018 ISS Adjuvant manufacturing, and the adjuvant produced was used to make the original reference standard, nonclinical, and clinical materials (2 batches were manufactured in (b) (4)). The Hybridon Specialty Products facility changed ownership in 2001 when it was purchased by Avecia Biotechnology. The 1018 ISS Adjuvant was manufactured at (b) (4). The commercial batch scale is targeted to (b) (4), but they state that it may vary within pre-determined ranges depending on the loading of the (b) (4) support. There were (b) (4) major process variations used in the manufacture of 1018 ISS Adjuvant throughout development and (b) (4). 1018 ISS Adjuvant Lot (b) (4) was the first batch to use (b) (4) (b) (4). See table below for information on the manufacturing and scale differences.



The lot used in the pivotal efficacy trial DV2-HBV-10 was under Process ^{(b) (4)} with differences from the current ^{(b) (4)} process of: (b) (4)

The commercial lots will be made by Process ^{(b) (4)}.

HEPLISAV has not been approved in any country. At this time it is under review by the EMA in Europe.

Dynavax is asking for a Categorical Exclusion from the requirement for an Environmental Assessment of the CpG adjuvant component because although BLA approval would increase the use of this specific CpG ODN, the estimated concentration of the 1018 ISS adjuvant at the point of entry into the aquatic environment will be below 1 part per billion (determined using CBER guidance for industry – 1998 titled “Environmental Assessment of Human Drug and Biologic Applications”; $A \times B \times C \times D = \text{EIC} - \text{Aquatic (ppb)}$).

(b) (4)

Reviewers comment: *According to the guidance, this exclusion is acceptable since it meets the criteria that the concentration of 1018 ISS manufactured per year will be below 1 part per billion at the point of entry into the aquatic environment.*

SUBMISSION QUALITY AND COMPLETENESS

The submission was adequately organized and integrated to accommodate the conduct of a CMC review of the 1018 ISS adjuvant without unreasonable difficulty. Although it was well organized, several documents were not present and needed to be requested as noted in the comments below.

FDA REVIEWER’S OVERALL SUMMARY AND CONCLUSION

Information submitted regarding manufacturing of the 1018 ISS adjuvant and tests including adjuvant ^{(b) (4)} and concentration in the HEPLISAV vaccine final container are unacceptable and/or inadequate at this time. A CR is recommended. Comments and requests for information to be conveyed to Dynavax are provided throughout this review and are italicized.

CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

I. INTRODUCTION

(b) (4)

V. HEPLISAV DRUG PRODUCT

The finished vial (unit) of HEPLISAV Drug Product contains 4200 mcg of 1018 ISS Adjuvant and 28 mcg of HBsAg Drug Substance formulated in 0.7 mL of 8 mM sodium phosphate, 154 mM sodium chloride, 0.01% w/w polysorbate 80, pH 7.0 buffer. To account for (b) (4)

HEPLISAV Drug Product is filled in sterile, single-use, 2 mL, clear borosilicate, (b) (4) glass vials (b) (4) and sealed with a 13 mm gray chlorobutyl rubber stopper with (b) (4) coating on the side in contact with Drug Product. The stopper is capped with a 13 mm flip-off, aluminum seal with a white button.

Three formulations of the HEPLISAV drug product have been manufactured due to changes in HBsAg.

Manufacturing of the Drug Product (process (b) (4)) is performed at Rentschler Biotechnologie GmbH, located on Erwin-Rentschler-Strasse 21 in 88471 Laupheim, Germany. The 1018 ISS adjuvant is removed from storage at (b) (4)

Release tests regarding the 1018 ISS adjuvant: (b) (4)

FDA request: On 9/26/12, Dynavax was conveyed the following by e-mail. CBER does not agree with your proposal to remove the following tests from the stability plan for the HEPLISAV Drug Product: pH, Particle size, 1018 ISS adjuvant content, HBsAg concentration, HBsAg (b) (4) Please submit a revised stability plan for the Drug Product that includes these tests.

Dynavax's response: On 11/30/12 (Serial 23), Dynavax commits to maintain the tests. The revised stability plan will be provided in December 2012.

FDA reviewer comment: Response is acceptable; however, the revised stability plan has not been submitted.

FDA request: On 11/2/12, Dynavax was asked the following question by e-mail. The specification of confirmed is not adequate for the 1018 ISS adjuvant identity in the HEPLISAV drug product commercial release tests and specifications. Please provide a numerical value to the specification to include (b) (4) Please provide the method validation protocol and report for this analytical method used for the release of the HEPLISAV drug product. Additionally the identity of the 1018 ISS adjuvant should also be confirmed by sequence analysis, please add this as a HEPLISAV drug product release test.

Dynavax's response: On 11/21/12 (Serial 20), Dynavax proposed the specification limit of (b) (4), but did not agree to note the (b) (4) Thy stated that the "confirmed" test method applies a (b) (4)

FDA Reviewer comment: Response is not acceptable, comment is provided in the CR letter sent on 2/22/13 as comment #53: In your November 20, 2012, response to the November 2, 2012, CBER Information Request regarding release tests for the final product, you proposed the release specification limit of (b) (4) of 1018 ISS adjuvant by (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted, and you stated that you do not agree to include the (b) (4). We note that the release test specification for the 1018 ISS adjuvant alone (bulk) is (b) (4) Please incorporate a release specification of (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted drug product or explain why

you would need to have a lower limit for the (b) (4) in the final product than that for (b) (4) in the 1018 ISS adjuvant bulk. Regarding the (b) (4) test specification of “confirmed” we will allow it to remain; however, you will also need to state the (b) (4) as previously requested by CBER. Please provide the method validation protocol and report for the revised (b) (4) test method using the (b) (4) and revised (b) (4) of 1018 ISS adjuvant proposed for the release of the Hepatitis B Vaccine (Recombinant), Adjuvanted drug product and include data from the analysis of several lots of drug product via the revised test to support your specification limits.

FDA request: On 11/2/12, Dynavax was conveyed the following by e-mail. Please perform sequencing on each batch of 1018 ISS adjuvant upon receipt at the Rentschler manufacturing facility and include this information in the Heplisav drug product batch records. Alternatively, you may perform sequence analysis on the 1018 ISS adjuvant as part of the Heplisav drug product release tests. Please provide the validation protocol and report for the sequencing method implemented.

Dynavax’s response: On 11/21/12 (Serial 20), Dynavax stated that they will perform (b) (4) of each 1018 ISS Adjuvant batch upon receipt (by (b) (4)) at the Rentschler manufacturing facility and they will include this information in the HEPLISAV Drug Product batch records. They state the validation report and protocol are valid for the procedure performed in Rentschler.

FDA reviewer comment: Response is acceptable; however, Dynavax will need to submit the revised batch record template.

FDA request: On 9/26/12, Dynavax was conveyed the following by e-mail. Please include into the HEPLISAV Drug Product Commercial Release Specification the following test: (b) (4) . Please submit the test procedure, method validation protocol, validation report and SOP to the BLA for review.

Dynavax’s response: On 11/30/12 (Serial 23), Dynavax commits to include the test. The test will be validated and the report will be provided in December 2012.

FDA reviewer comment: Response is acceptable; however, Dynavax has not submitted the report which will include this test. Of note, this test was not previously included in any of the drug substance or drug product release tests.

MECHANISM OF ACTION

The intended biologic activity of the CpG Adjuvant is to enhance antibody generation by activating the innate immune system via Toll-like receptor 9 (TLR9). They also note that the CpG 1018 ISS adjuvant component of HEPLISAV is thought to have the following effects: (1) activate pDCs through the pattern recognition receptor TLR9; (2) differentiate pDCs into activated dendritic cells that present the processed HBsAg component of HEPLISAV to CD4+ T cells; and, (3) promote Th1 T-cell differentiation through the

production of IFN-alpha and IL-12. References to published papers are provided in the application (section 2.4).

Furthermore Dynavax states the following: intravenous (IV) or subcutaneous (SC) administration, in general, phosphorothioate oligonucleotides (PS ODNs) as a class are rapidly absorbed and detected in the plasma (1-2 hrs). They bind non-specifically and reversibly to plasma proteins. Distribution from the plasma into the tissues is rapid. PS ODNs primarily distribute into the kidney, liver, lymph nodes, spleen, adipose tissue, and bone marrow, and have minimal distribution to heart, lung, and skeletal muscle and do not cross the blood-brain barrier. ODNs are usually not degenerative in nature; however, in high dose levels degeneration in the proximal tubular kidney and single-cell necrosis in the liver has been described. Hepatic Kupffer cells are activated (reflecting an acute phase response) and extramedullary hematopoiesis in rodents is evidenced as noted in bone marrow cell maturation resulting in peripheral anemia, thrombocytopenia and neutropenia (may be due to the broader expression of TLR9). The half-life of PS ODNs in plasma is on the order of hours, whereas the half-life in tissues is on the order of days to weeks. PS ODNs are metabolized by exonucleases into shorter oligonucleotides which ultimately lose biological activity and protein-binding capacity. These shorter ODNs are primarily filtered through the glomeruli and excreted in the urine. A Polyanion effect (interaction of ODN with cationic site on blood proteins) is evidenced in that inhibition of the coagulation cascade (prolongation of activated partial thromboplastine time [APTT]) and activation of alternative complement pathway (plasma levels of split products) is seen. PS ODNs have not been reported to have any interaction with the cytochrome P450 system. References to the above information can be found in section 2.6.4.1.1. Studies were performed specifically with 1018 ISS to determine bioavailability following SC administration in rats and monkeys (distribution, metabolism and excretion not performed). See review by Haiyan Qin for more information.

FDA request: On 10/12/12, Dynavax was asked the following question by e-mail. You have provided information on the bioavailability of 1018 ISS adjuvant with HBsAg delivered subcutaneously. Please provide a rationale for not performing a bioavailability study following intramuscular administration of the 1018 ISS with and without HBsAg, or submit such data if available.

- Dynavax's response: On 11/26/12 (Serial 21), Dynavax provided their response.*
- They state that the WHO Guidance on Nonclinical Testing of Vaccines and the Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines state that determination of serum concentration of antigen (HBsAg) is not required for vaccines as part of the nonclinical program.*
 - The PK profile of 1018 ISS Adjuvant following IM injection of HEPLISAV was evaluated during the clinical development of a 3-dose regimen of HEPLISAV for adults with chronic kidney disease (Study DV2-HBV-09). In this phase 1 trial, the C_{max} was observed 1 hour after injection, and no 1018 ISS adjuvant was detectable 24 hrs after injection. Single compartment volume of distribution (V_d) ranged*

from 0.42 to 1.31 L/kg in the 1500/10 group and from 0.46 to 0.79 L/kg in the 3000/20 group, which is similar to findings in clinical studies of other PS ODNs.

- TK studies of 1018 ISS adjuvant alone (at doses up to 272X the clinical dose for HEPLISAV (mg/kg basis) were conducted in rats and monkeys (Studies 00-158 and 00-157, respectively) using the SC route. The TK evaluations confirmed a consistent pattern of elimination for 1018 ISS from plasma as reported for many other PS ODNs. Results from these studies showed measureable plasma concentrations at 1 to 2 hrs after SC injection of 1018 ISS (primarily at 2.5 and 12.5 mg/kg), with lower or undetectable plasma levels at 4 to 24 hrs.

FDA reviewer comment: Rationale is acceptable.

BLA DOCUMENTS THAT SERVE AS THE BASIS FOR THE ADJUVANT CMC REVIEW

The CMC information and data related to the Antigen Drug Substance (HBsAg antigen) and the Adjuvanted Vaccine Drug Product (HEPLISAV) have been reviewed by Iryena Zubkova in a separate document.

The CMC information and data reviewed in this document include the following: data on the manufacture, characterization, control of drug substance, reference standards, container closure system and stability of 1) the 1018 ISS drug substance (presented in Module 3.2.S); and 2) the Control of Drug Product as part of the Heparisav Hepatitis B vaccine (presented in Module 3.2.P.5). The 1018 ISS relevant appendices including information on the Adventitious Agents Safety Evaluation (Module 3.2.A.2 – 1018 ISS), and Regional Information (Module 3.2.R – Batch records and validation reports of 1018 ISS) were also reviewed. In addition, the summary of all of the above data (provided in Module 2.3) was reviewed.

Itemized List of Amendments and Sections Reviewed:

Biologic License Application (BLA)/STN 125428/0 Original Application (Amendment 0)/26-APR-2012:

- Quality Overall Summary Module 2.3
- Nonclinical Overview of 1018 ISS adjuvant human sequence homology and anti-DNA antibody analysis as presented in Module 2.4
- CMC information and data as presented in Module 3.2.S 1018-ISS Avecia on General Information (3.2.S.1), Manufacture (3.2.S.2), Characterization (3.2.S.3), Control of Drug Substance (3.2.S.4.1 and 3.2.S.4.4), Reference Standards and Materials (3.2.S.5), Container Closure System (3.2.S.6) and Stability (3.2.S.7) of the 1018 ISS adjuvanted
- CMC information and data on the HEPLISAV drug product: Description and Composition of the Drug Product (3.2.P.1)

- Adventitious Agents Safety Evaluation as presented in Module 3.2.A.2 – 1018 ISS, and Regional Information as presented in Module 3.2.R – Batch records and validation reports of 1018 ISS

Amendment to BLA/STN 125428/Seq. 20 (amendment 21)/Received November 21, 2012:

CMC responses to FDA's request for information received by Dynavax via email on November 2, 2012 regarding 5 comments related to (b) (4), new part numbers, Heplisav release specifications and sequencing of the adjuvant upon receipt at the Rentschler facility.

Amendment to BLA/STN 125428/Seq. 21 (amendment 22)/Received November 26, 2012:

CMC responses to FDA's request for information received by Dynavax via email on October 12, 2012 regarding 20 comments related to many different aspects of the adjuvant manufacturing process.

Amendment to BLA/STN 125428/Seq. 23 (amendment 24)/Received November 30, 2012:

CMC responses to FDA's request for information received by Dynavax via email on September 26, 2012 regarding release tests and specifications for both the 1018 ISS adjuvant and the Heplisav drug product.

LITERATURE REVIEWED

1. Sterilizing Filtration of Liquids – Technical Report No. 26, PDA Journal of Pharmaceutical Science and Technology, 1998 Supplement, Volume 52, Number S1
2. Points to Consider for the Submission of CMC Information in Oligonucleotide-Based Therapeutic Drug Applications – Powerpoint by Rao V.B. Kambhampati for the DIA Industry and Health Authority Conference on Oligonucleotide-based Therapeutics, 4-20-0
3. ICH Harmonised Tripartite Guideline – Impurities: Guideline for Residual Solvents Q3C (R4) – February 2009

LABELING REVIEW AND RECOMMENDATIONS

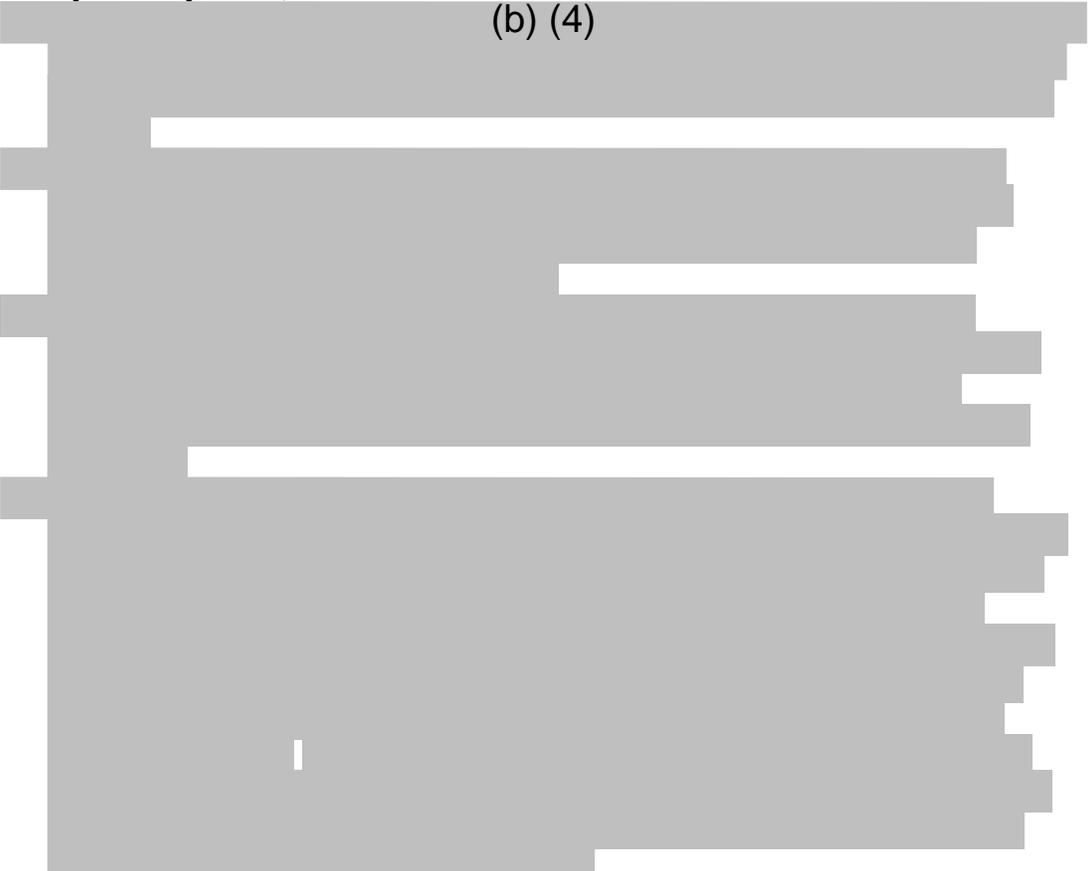
Recommendations will be provided when a response to the CR is provided and discussions regarding the labeling will commence.

RECOMMENDATIONS ON REGULATORY ACTIONS

At this time a CR is recommended.

Outstanding Issues as of the date of the CR issuance (comments in bold still need to be conveyed to Dynavax):

(b) (4)



5. Dynavax stated that they would develop a specification for Assay by (b) (4) and would submit the specification to the Agency in January 2013. Dynavax will need to provide the new assay protocol and validation report for our review. The validation protocol and report provided in this amendment will be reviewed by DBSQC.
6. Dynavax committed to keep the (b) (4) for product impurities, (b) (4) to calculate the amount of 1018 ISS relative to reference, (b) (4) tests in the stability plan and stated they would submit the revised plan in January 2013. This plan has yet to be submitted and reviewed.

7. Dynavax committed to include the (b) (4) test as part of the HEPLISAV drug product release and stated that the test will be validated and the report will be provided in December 2012. This plan has yet to be submitted and reviewed.

