



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

BLA REVIEW

DATE: 01-24-2013

FROM: Iryna Zubkova, PhD
SUBJECT: STN# 125428/0

Sponsor: Dynavax Technologies Corporation
Product: Hepatitis B Virus (recombinant) Vaccine [Heplisav[®]]

TO: Richard J. Daemer. PhD
Katherine Berkhausen

THROUGH: Marian Major, PhD
Robin Levis
Sara Gagneten

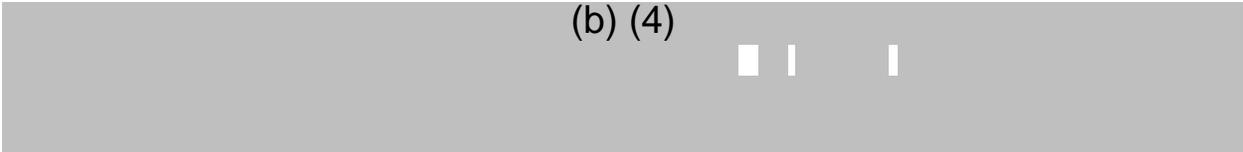
Summary: This is a review of the preparation, manufacturing process, specifications, and stability data submitted in support of a recombinant hepatitis B vaccine (HEPLISAV[™]) for active immunization against hepatitis B virus infection. It covers Sections 2.3.S.1- 2.3.S.7, 2.3.P, 2.3.A.2 (HBsAg, Drug substance), 2.3.A.2 (HEPLISAV, Solution for injection), 2.3.R (HBsAg Drug Substance and HEPLISAV Drug product), 3.2.S (HBsAg), 3.2.P.1-8, 3.2.A.2 (HBsAg and HEPLISAV) of BLA 125428.

Comments and information requests sent to the Sponsor and responses received from the Sponsor.

Comments.

Drug Substance.

(b) (4)



(b) (4)

Information Requests.

1. Information request sent on August 16, 2012

Please, explain why you use different acceptance criteria for HBsAg content in

(b) (4)
? (3.2.P.3.5. Process Validation and/or Evaluation. Table. 3.2.P.3.5-15 and 3.2.P.3.5-17)

Response (received on September 21, 2012):

(b) (4)

Response received from the Sponsor is acceptable.

2. Information Request sent on September 26, 2012.

1. CBER agrees with your proposal to remove the following tests from the stability plan for the HBsAg Drug Substance:

(b) (4)

Response: (response received on November 30, 2012)

(b) (4)

Response is acceptable.

2. CBER agrees with your proposal to remove the following tests from the stability plan for the HEPLISAV Drug Product:

(b) (4)

Response: (response received on November 30, 2012)

Dynavax will remove the tests for HBsAg (b) (4) from the stability plan for HEPLISAV Drug Product.

Response is acceptable.

3. CBER does not agree with your proposal to remove the General Safety test as a release parameter for HEPLISAV Drug Product. Please provide the method validation protocol and report for this method. If the test has been modified, please provide details on the test procedure, justification for the use of a reduced dose in guinea pigs, details on the titration studies used to determine the acceptable dose in these animals and the number of lots used for the studies. Please provide the results from all lots tested.

Response: (response received on November 30, 2012)

Dynavax acknowledged the request to maintain the General Safety test as a release parameter for HEPLISAV Drug Product. Since the test is performed according to the compendial method described in 21 CFR 610.11, no method validation was performed.

Based on dosing studies conducted to determine the maximum tolerated dose for guinea pigs and mice, the test is modified for the administered dose of HEPLISAV Drug Product in guinea pigs. The Code of Federal Regulations (21 CFR 610.11) specifies that for liquid drug products, intraperitoneal injections of the drug product drawn from its final container are to be made into each of at least 2 mice (at 0.5 mL per mouse) and into each of at least 2 guinea pigs (at 5.0 mL per guinea pig). Dosing studies have indicated that, depending on drug product dosage form, these prescribed volumes of undiluted product may exceed the maximum tolerated dose for each species, making it impossible to distinguish the impact of extraneous toxic contaminants (if present) from species-specific product toxicity.

Therefore, for 1018 ISS drug product dosage forms, where the concentration prohibits direct injection of test animals as specified in 21 CFR 610.11, the drug product is diluted such that an injection of the prescribed volume delivers the species-specific maximum tolerated dose determined from previously documented dosing studies. The maximum tolerated dose here is defined as the dose at which no subject mortality was observed, and where, even when clinical effects were observed, animal subjects regained any body weight lost in less than 7 days.

In Dosing Study 00-122, the maximum tolerated dose of 1018 ISS in guinea pigs was determined to be (b) (4) per guinea pig (reduced dose) and in Dosing Study 00-126, the maximum tolerated dose of 1018 ISS in mice was determined to be (b) (4) per mouse, which corresponds to the dose specified in 21 CFR 610.11 (Justification of dosing for general safety and pyrogenicity testing of 1018 ISS Drug Product). Summary tables for the Dosing Studies in Guinea Pigs and Dosing Studies in Mice were provided.

Dynavax has tested (b) (4) HEPLISAV Drug Product lots; all lots tested to date have passed the General Safety test. Six of the (b) (4) batches were used in clinical studies, including phase 3 studies, and demonstrated to be safe in humans.

Results from all tested lots, including historical HEPLISAV Drug Product batches, were presented in Section 3.2.P.5.4. These data consisted of single vial presentation batches Lots (b) (4) manufactured from (b) (4))

As requested, Dynavax will maintain the General Safety test as a release parameter for HEPLISAV Drug Product.

The response is acceptable.

4. CBER does not agree with your proposal to remove the following tests from the stability plan for the HBsAg Drug Substance:

(b) (4)

Please submit a revised stability plan for the Drug Substance that includes these tests.

Response: (response received on November 30, 2012)

Dynavax acknowledged the request and committed to maintain the tests for (b) (4) for HBsAg Drug Substance stability testing. Dynavax committed to submit a revised stability plan for HBsAg Drug Substance in January 2013.

A revised stability plan for HBsAg Drug Substance was received on January 16, 2013 and has not been reviewed.

5. 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**
- (b) (4)**

Please submit a revised stability plan for the Drug Product that includes these tests.

Response: (response received on November 30, 2012)

Dynavax acknowledged the Agency's request and committed to maintain the tests for pH, particle size, 1018 ISS Adjuvant content, HBsAg concentration, and (b) (4) for HEPLISAV Drug Product stability testing. Dynavax committed to submit a revised stability plan for HEPLISAV Drug Product in December 2012.

A revised stability plan for HEPLISAV Drug product was received on December 29, 2012 and has not been reviewed.

6. Please include into the HBsAg Drug Substance Commercial Release Specification the following tests:

(b) (4)



Please submit the test procedures, method validation protocols, validation reports and SOPs to the BLA for review. Method validation may not be required if compendial method is used for the measurement of (b) (4)

Response: (response received on November 30, 2012)

Dynavax acknowledged the request and committed to include the following tests in the HBsAg Drug Substance commercial release specification:

(b) (4)



(b) (4)

The test methods for (b) (4) are validated for in-process testing but not for testing of Drug Substance. Both methods will be revalidated for HBsAg Drug Substance testing. Dynavax committed to submit the test procedures, method validation protocols and validation reports to the Agency in January 2013.

Response is incomplete. The Sponsor provided validation protocols and validation reports only for the test methods for (b) (4).

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

These documents were also reviewed by a member of DBSQC and a number of deficiencies were identified. These were communicated to the sponsor in the CR letter.

7. 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.

Response: (Response received on November 30, 2012)

Dynavax acknowledged the request and committed to include the tests for (b) (4) into the HEPLISAV Drug Product commercial release specification.

The method will be validated and Dynavax committed to submit the revised HEPLISAV Drug Product commercial release specification, the test procedure (SOP), method validation protocol, and validation report in December 2012.

(b) (4) SOP, validation protocol, and validation report were received on December 29, 2012. These documents have not been reviewed.

3. Information request sent 10/05/12

Validation reports for (b) (4) used for Drug Substance manufacturing were requested from the Sponsor

The response was received on 11/01/2012. The data submitted was found to be acceptable and is reviewed in detail on page 16 of this review under Process Validation Support Studies.

Comments for the Complete Response (CR) letter.

Drug Substance

(b) (4)

(b) (4)

(b) (4)

Drug Product

1. After discussions concerning tests to be included in the stability plan for the HEPLISAV Drug product CBER requested that you submit a revised stability plan that included these tests for the Drug Product. This was submitted on December 29, 2012 (125428/0024) and it has not been reviewed.

Overview.

Manufacturing of HEPLISAV™ consists of the following steps:

- HBsAg Drug Substance preparation
- HBsAg Drug Product formulation.

All steps of HEPLISAV™ manufacturing, testing and storage, except Master Cell Bank and HBsAg Drug Substance Final QA Release, took place in different locations in Germany.

The Master Cell Bank was manufactured in (b) (4), but this site is no longer active. HBsAg Drug Substance Final QA Release was performed in Dynavax Technologies Corporation in USA. All facilities involved in Drug Substance testing and storage have an FDA EIN.

Manufacture HBsAg Drug Substance

(b) (4)

(b) (4)

HEPLISAV Drug Product

HEPLISAV Drug Product is a sterile, liquid dosage form that is administered as an intramuscular injection. HEPLISAV Drug Product is formulated as 6000 mcg/mL 1018 ISS Adjuvant and 40 mcg/mL HBsAg Drug Substance. The finished vial (unit) of 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. An administered dose of 0.5 mL contains 3000 mcg of 1018 ISS Adjuvant and 20 mcg of HBsAg Drug Substance in the buffered solution. Since HEPLISAV is produced as a single-dose unit, it does not contain preservatives.

HEPLISAV Drug Product is filled in sterile, single-use, 2 mL, clear borosilicate, Type ^{(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.

The review of the adjuvant (1018ISS) manufacturing process was performed by a member of DVRPA and will not be covered in this review.

During the development process the Sponsor developed 3 different formulations of HEPLISAV – Formulation 1, 2 and 3. There were several modifications within each formulation process. The proposed commercial HEPLISAV Drug Product is manufactured at Rentschler Biotechnologie GmbH (Laupheim, Germany) except Vial Labeling and Finished Product Packaging. The (b) (4) steps are performed by the (b) (4)

(b) (4)

Release and Stability testing was performed in several locations in Germany. (Table 2.3.P.3-1)

Table 2.3.P.3–1: HEPLISAV™ Drug Product Manufacturing, Testing, and Storage Sites

Facility	Responsibilit
<p>Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim Germany</p> <p>FDA Establishment Identifier: 1000291122</p>	<p>HEPLISAV Drug Product Manufacture HEPLISAV Drug Product In-process Testing Interim Bulk HEPLISAV Drug Product Storage HEPLISAV Drug Product Release Testing</p> <ul style="list-style-type: none">• Endotoxin• Sterility <p>HEPLISAV Drug Product Manufacturer's Release</p>
<p>Rhein Biotech GmbH (a wholly owned subsidiary of Dynavax Technologies Corporation) Eichsfelder Strasse 11 40595 Duesseldorf Germany</p> <p>FDA Establishment Identifier: Application submitted</p>	<p>HEPLISAV Drug Product Release Testing</p> <ul style="list-style-type: none">• Appearance• pH• 1018 ISS Adjuvant Identity• HBsAg Identity• (b) (4)• 1018 ISS Adjuvant Content• HBsAg Concentration• (b) (4)• Potency (Sample preparation (b) (4))• Extractable Volume <p>HEPLISAV Drug Product Stability Testing</p> <ul style="list-style-type: none">• Appearance• (b) (4)• (b) (4)• Potency (Sample preparation (b) (4))
<p>(b) (4)</p> <p>(b)</p>	<p>HEPLISAV Drug Product Release Testing</p> <ul style="list-style-type: none">• Sterility
<p>(b) (4)</p>	<p>HEPLISAV Drug Product Release Testing</p>

(b) (4)	HEPLISAV Drug Product Release Testing <ul style="list-style-type: none"> General Safety Test
(b) (4)	HEPLISAV Drug Product Release Testing <ul style="list-style-type: none"> Particulate Contamination: Subvisible Particles/Particulate Matter HEPLISAV Drug Product Stability Testing <ul style="list-style-type: none"> Container Closure Integrity
(b) (4)	HEPLISAV Drug Product Release Testing <ul style="list-style-type: none"> Potency (In vivo study) HEPLISAV Drug Product Stability Testing HEPLISAV Drug Product Stability Testing <ul style="list-style-type: none"> Potency (In vivo study)
Dynavax Technologies Corporation 2929 Seventh Street, Suite 100 Berkeley, CA 94710 USA FDA Establishment Identifier: Application submitted	HEPLISAV Drug Product Final QA Release
(b) (4)	Bulk HEPLISAV Drug Product Storage HEPLISAV Drug Product Secondary Labeling and Packaging Finished HEPLISAV Drug Product Storage

All organizations involved in the manufacturing, testing and storage sites associated with the HEPLISAV Drug Product production except Rhein Biotech GmbH (Germany), Dynavax Technologies Corporation (USA), and (b) (4) have an FDA EIN. Rhein Biotech GmbH (Germany) and Dynavax Technologies Corporation (USA) had submitted an EIN application at the time of the BLA submission.

From information provided by the Sponsor on September 13, 2012, FDA EINs were received for the following sites:

1. Rhein Biotech GmbH (a wholly owned subsidiary of Dynavax Technologies Corporation) Eichsfelder Strasse 11
40595 Duesseldorf
Germany

EIN 1000350748

2. Dynavax Technologies Corporation
2929 Seventh Street, Suite 100
Berkeley, CA 94710
USA
EIN 3003212117

Manufacturing

The manufacturing process consists of the following steps:

(b) (4)

(b) (4)

	[REDACTED]	(b) (4)
E	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
E	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
E	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Process Validation Support Studies.

In order to support the Process Validation program the Sponsor performed Process Validation Support Studies, which included hold time studies, mixing studies, final filtration qualification, and shipping validation.

Formulation Buffer Hold Studies

(b) (4)

Shipping Validation

The validation of the HEPLISAV Drug Product bulk unlabeled vials shipping procedure was executed by Dynavax Technologies, California, USA, in order to demonstrate that the defined shipping method is capable of maintaining the desired storage conditions ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ with no controlled humidity) during an extended period of time and is capable of maintaining the integrity of the packaged HEPLISAV Drug Product during transit.

The Report of shipping validation was provided. The results demonstrate that the shipping configuration and method for bulk unlabelled 1018 ISS-HBsAg Drug Product vials is capable of maintaining the required storage temperature of $5 \pm 3^{\circ}\text{C}$ for the shipment duration of (b) (4), and maintaining product integrity of all vials during the entire duration of shipment. Therefore the shipping configuration and method defined in Rentschler SOP DYN-VS-001 for transporting bulk unlabelled 1018 ISS-HBsAg Drug Product vials from the manufacturing site, Rentschler Biotechnologie GmbH, Laupheim, Germany to the packaging, labeling and storage site at (b) (4) is acceptable.

Process Performance Qualification

(b) (4)

(b) (4)

[Redacted text block]

Control of Excipients [HEPLISAV, Solution for Injection]

(b) (4)

All excipients are non-human and non-animal origin. All excipients are compendial. No novel excipients are used.

Final Container Closure

The container closure system for HEPLISAV Drug Product is a 2 mL clear borosilicate Type (b) (4) glass vial by (b) (4) with a 13 mm finish. A gray 13 mm (b) (4) -coated chlorobutyl rubber stopper (b) (4) is used to stopper the filled vial. A white 13 mm (b) (4) aluminum seal (b) (4) is used as the final seal for the vial and stopper for the proposed commercial product.

Integrity testing of the HEPLISAV Drug Product container closure system was performed at Rentschler Biotechnologie (Laupheim, Germany) using a microbial challenge test which (b) (4)

The results of the (b) (4) tests were presented in Table 3.2.P.2.4–1 and in (b) (4) /Challenge Report. The test results demonstrated that no contamination could be detected in this container closure system. The positive controls indicated (b) (4) for all vials, and that the (b) (4) was sufficient for the test.

Extractables and Leachables

A risk assessment was performed to evaluate the potential of components used in the final HEPLISAV Drug Product container closure system to contribute leachable compounds to the product that could impact product quality or stability. The

extractable/leachable risk assessment considered long-term storage of the HEPLISAV Drug Product. Based on the Risk Assessment, both of the container closure system components, glass vial and 13mm rubber stopper, were considered at risk for leachables and were further analyzed in an extractables study. The aluminum seal with white cap is used to maintain the closure of the final container, and does not come in contact with the Drug Product solution directly.

The extractables study used (b) (4). The extractables study and report were submitted in the BLA. The toxicological evaluation of the extractables study indicated (b) (4) safety threshold as leachables in the HEPLISAV Drug Product. The HEPLISAV Drug Product is formulated in an aqueous buffer, and given the hydrophobic and water insoluble nature of all the potential leachables, it was concluded that there is a very low probability that these compounds will leach at any significant level into the Drug Product. There was an absence of any extractables above the analytical threshold in the aqueous extracts, which supports this conclusion.

Adventitious Agents Safety Evaluation for HEPLISAV Drug Product.

The Sponsor evaluated the proposed commercial Drug Product manufacturing process for potential contamination by adventitious agents. HEPLISAV Drug Product is (b) (4) sterile filtered (b) (4), and sterility testing is a requisite for release, which results in an extremely low risk of contamination by (b) (4).

In addition, the raw materials for Drug Product manufacture are not of human or animal origin, thereby obviating the risk of viral contamination.

Accordingly, the evaluation focused on the risk of contamination by transmissible spongiform encephalopathy agents of (1) raw materials and (2) components that are in direct contact with the Drug Product process stream, including container closure components. The results of this assessment indicate that the risk of introducing BSE/TSE contamination into the HEPLISAV Drug Product during manufacture is extremely low.

List of the Raw Materials used to manufacture HEPLISAV Drug Product

Ingredient/Raw Material	Function	Manufacturer/ Supplier	Origin	BSE/TSE Risk
1018 ISS Adjuvant	Adjuvant	Avecia Biotechnology	Not of animal origin (refer to 1018 ISS Adjuvant)	Low
HBsAg Drug Substance	API	Rhein Biotech	HBsAg is prepared with non-animal material, except for animal components that have been processed accordingly (refer to HBsAg Drug Substance)	Low

Sodium Phosphate, (b) (4)	(b) (4)	(b) (4)	Inorganic Salt (Not of animal origin)	Low
Sodium Phosphate, (b) (4)	(b) (4)	(b) (4)	Inorganic Salt (Not of animal origin)	Low
Polysorbate 80	(b) (4)	(b) (4)	(b) (4) origin (Not of animal origin)	Low
Sodium Chloride	(b) (4)	(b) (4)	Inorganic Salt (Not of animal origin)	Low
(b) (4)	(b) (4)	Rentschler Biotechnologie	Not of animal origin	Low

API = active pharmaceutical ingredient; BSE = bovine spongiform encephalopathy; TSE = transmissible spongiform encephalopathies.

The product-contact components including the container closure system for the HEPLISAV Drug Product manufacturing process were evaluated for TSE risk. (b) (4) are all non animal origin and therefore are at extremely low risk of BSE/TSE contamination.

There are two components of Container Closer System of animal origin:

- (b) (4)
- (b) (4)

(b) (4)

Lot Release and Stability Specifications.

The Sponsor presented Commercial Lot Release and Stability Specification based on manufacturing and clinical experience, pharmacopoeial standards, and stability studies (Tables 3.2.P.5.1-1 and 3.2.P.5.1.-2)

These specifications are used to ensure the identity, potency, purity, and safety are maintained throughout the proposed shelf-life period.

Table 3.2.P.5.1–1: HEPLISAV Drug Product Commercial Release Specifications

Parameter	Method Type	Specification	Method Summary
Appearance	(b) (4)	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles	Section 3.2.P.5.2.1.1
pH	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.2
1018 ISS Adjuvant Identity	(b) (4)	Confirmed	Section 3.2.P.5.2.1.3
HBsAg Identity	(b) (4)	Confirmed	Section 3.2.P.5.2.1.4
1018 ISS Adjuvant Content	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.5
HBsAg Concentration	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.6
HBsAg (b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.4
HBsAg (b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.7
Potency	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.8
Particulate Contamination: Sub- visible Particles/	(b) (4)	(b) (4)	Section 3.2.P.5.2.1.9

Endotoxin	(b) (4)		Section 3.2.P.5.2.1.10
Sterility	(b) (4)	Sterile, no growth	Section 3.2.P.5.2.1.11
Extractable Volume	(b) (4)	≥ 0.5 mL	Section 3.2.P.5.2.1.12

(b) (4); NLT = not less than; NMT = not more than; (b) (4)
 (b) (4) SOP = standard operating
 procedure; UCL
 = upper confidence limit; (b) (4)

Table 3.2.P.5.1–2: HEPLISAV Drug Product Commercial Stability Specifications

Parameter	Method Type	Specification	Method Summary Location
Appearance	(b) (4)	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles	Section 3.2.P.5.2.2.1
HBsAg (b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2.2.2
1018 ISS Adjuvant (b) (4)	(b) (4)		Section 3.2.P.5.2.2.3
Potency	(b) (4)		Section 3.2.P.5.2.2.4
Container Closure Integrity	(b) (4)	(b) (4)	Section 3.2.P.5.2.2.5

(b) (4) NLT = not less than; NMT = not more than (b) (4)
 ; SOP = standard
 operating procedure; UCL = upper confidence limit.

^a Test method adjusted for single-use vials; (b) (4) for test.

Justification of Specification

The Sponsor provided justification for the Commercial Release Specifications and Commercial Stability Specifications.

Commercial Release Specification

Appearance

The parameter appearance includes 3 attributes: color, opalescence, and visible particles.

The specification is set based on historical data. The color and opalescence specifications are set in reference to color and opalescence standard solutions defined in (b) (4).

The specification for visible particles is set in compliance with (b) (4)

pH

Proposed commercial release specification: (b) (4) The proposed specification defines the pH range that is acceptable for HEPLISAV Drug Product given the lack of susceptibility of the components to the range of pH covered in this specification.

1018 ISS Adjuvant Identity

Proposed commercial release specification: Confirmed. Identity of 1018 ISS Adjuvant in HEPLISAV Drug Product must be confirmed.

HBsAg Identity

Proposed commercial release specification: Confirmed. Identity of HBsAg, the active pharmaceutical ingredient, used the in HEPLISAV Drug Product must be confirmed.

1018 ISS Adjuvant Content

Proposed commercial release specification: (b) (4) The proposed commercial specification is statistically derived. Stability data from both long-term and accelerated stability studies for (b) (4) lots of HEPLISAV Drug Product (b) (4) were analyzed by linear regression. The proposed 1018 ISS Adjuvant content commercial release specification of (b) (4) replaces the current release specification of (b) (4)

HBsAg Concentration

Proposed commercial release specification: (b) (4). The HBsAg protein concentration specification limits for lot release are supported by HBsAg protein concentration data for HEPLISAV Drug Product lots that have shown to be safe and immunogenic in clinical studies.

The upper limit is supported by HBsAg protein concentration data for Lot TDG010, used in clinical Study DV2-HBV-16, a phase 3 clinical studies. The lower limit is supported by HBsAg protein concentration data for Lot TDG003, which was used in clinical Studies DV2-HBV-10, DV2-HBV-11, and DV2-HBV-14.

The upper specification limit of (b) (4) is supported by Lot TDG010, which showed the highest HBsAg protein concentration results among all clinical lots of HEPLISAV Drug Product. HBsAg protein concentration long-term stability results for TDG010 are available through 18 months. The long-term stability results for TDG010 at 2 time points are (b) (4) but no result exceeds (b) (4).

(b) (4)

(b) (4)

Potency

Proposed commercial release specification: The upper confidence limit ($P = 0.95$) of the estimated relative potency is (b) (4)

The specification is stipulated by the (b) (4). Potency specification is linked to the potency of the reference material. The characteristics of the reference material are defined by the (b) (4). Specifically, the reference should be at least as immunogenic in an animal assay as a lot that has demonstrated clinical immunogenicity.

Particulate Contamination: Sub-visible Particles/Particulate Matter

Proposed commercial release specification: (b) (4)

The proposed specification for the attribute of particulate contamination: sub-visible particles/particulate matter is set in compliance with (b) (4) is applied and the specification is set with respect to this method.

(b) (4)

Potency

The proposed stability specification for potency is the same as the proposed commercial release specification.

Container Closure Integrity

Proposed commercial stability specification: (b) (4)

Sterility is a pharmacopeial requirement for parenteral articles throughout its entire shelf life.

Sterility of HEPLISAV Drug Product during storage is ensured by the container closure integrity test performed in lieu of a sterility test at the end of stability program.

Comments:

These comments were communicated to the sponsor in an information request dated September 26, 2012. The review of these responses is included under “Comments” at the beginning of this review. The sponsor agreed to retain all tests that we determined could not be removed at this time.

1. The Sponsor requested to exclude the General Safety Test from Commercial Release Specifications. General safety is tested only at release of HEPLISAV Drug Product. The general safety test for the detection of extraneous toxic contaminants is required by 21 CFR § 610.11 for all biological products intended for administration to humans.

I do not recommend removing General Safety Test from Commercial Release Specifications at this time. Further data in support of this is required.

2. I do not recommend removing from the Commercial Stability Specification the following methods:

pH
HBsAg Concentration
(b) (4)
1018 Adjuvant Content
Particle Size

Even though the product demonstrated stability under accelerated storage conditions; during the Forced Degradation study the following methods revealed changes in HEPLISAV Drug Product characteristics. Therefore the methods mentioned above will be useful to monitor product stability and therefore quality of HEPLISAV Drug Product.

3. The Sponsor can remove from the Commercial Stability Specification the following methods:

(b) (4)

Stability data

The proposed storage condition for HEPLISAV Drug Product is $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.
The following lots of HEPLISAV Drug Product lots were placed on stability study:

(b) (4)

Stability studies for HEPLISAV Drug Product were performed at long-term ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) conditions for up to 36 months and accelerated (b) (4) conditions for up to (b) (4) months according to International Conference on Harmonization (ICH) Guideline Q1A(R2), Stability Testing of New Drug Substances and Drug Products.

The Sponsor presented completed stability studies (up to 36 month of long-term at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) for HEPLISAV Drug Product lots:

(b) (4)

Also the Sponsor presented completed accelerated studies (b) (4) through (b) (4) months for HEPLISAV Drug Product:

(b) (4)

The Sponsor provided data for ongoing long-term stability at recommended conditions for HEPLISAV Drug Product Lots (b) (4). These three batches were subjected to the additional test attribute:

(b) (4), Particle size by (b) (4).

Based on the results of stability studies the Sponsor calculated for commercial HEPLISAV Drug Product a 24 month shelf life.

Stability data under accelerated conditions (b) (4) demonstrated no significant changes for HEPLISAV Drug product were observed except for Lot (b) (4). At (b) (4) months (b) (4) data for the Lot (b) (4) fell below the lower limit of specification. This was at the end of the study point and no further testing was performed.

The Sponsor performed the (b) (4)

The Stress Stability study was performed by exposing HEPLISAV Drug product to (b) (4) cycles:

- HEPLISAV Drug Product was (b) (4)
- HEPLISAV Drug Product was exposed to (b) (4)

The Stress study demonstrated that HEPLISAV Drug Product is considered stable to (b) (4). Potency is stable for at least (b) (4).

and (b) (4) months when stored at (b) (4). No significant trend is apparent in the long-term stability data at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ through 18 months.

No stability data for (b) (4) are yet available. The Sponsor committed to perform reevaluation of (b) (4) in 12-months.

Batch analysis.

The current HEPLISAV Drug Product formulation was used for (b) (4) and all subsequent batches. All batches meet specifications.

Conclusion.

During the review of BLA 125428/0 submitted by Dynavax several issues were identified. In order to address these issues two Information Requests were sent to the Sponsor. Some documents from the information request from September 26, 2012 have not yet been received. Therefore, at this time, this application cannot be recommended for approval.