Date: January 15, 2012

From: Charles M. Maplethorpe M.D., Ph.D., Chair of the Review Committee

BLA/ STN#: 125035/162

Applicant Name: Cangene Corporation

Date of Submission: March 17, 2011

PDUFA Goal Date: January 15, 2012

Proprietary Name/ Established Name: HepaGam B/Hepatitis B Immune Globulin (Human)

Indication: Prevention of hepatitis B recurrence following liver transplantation, in HBsAg-positive liver transplant patients

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

□ I concur with the summary review.

□ I concur with the summary review and include a separate review to add further analysis.

□ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date	
Clinical Review	January 9, 2011, clinical review memo of Charles Maplethorpe, M.D., Ph.D.
Clinical Pharmacology Review	N/A
Statistical Review	N/A
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Biomonitoring Review	December 22, 2011, memo of Shannon Aldrich, FDA/CBER/OCBQ

Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Other (list) APLB review memo	September 28, 2011, APLB memo of Alpita Popat, PharmD, MBA

1. Introduction

   - The purpose of submission STN125235/125 [same submission as STN125035/162] is to update the labeling of HepaGam B® to include the final study results for study HB-005, the licensure study for the indication for prevention of hepatitis B recurrence in patients undergoing orthotopic liver transplantation.
   - HepaGam B® is plasma-derived Hepatitis B Immune Globulin (HBIG).
   - HepaGam B was first licensed in 2006 for Hepatitis B Virus (HBV) post-exposure immunoprophylaxis.
   - On April 6, 2007, HepaGam B received the indication for prevention of hepatitis B recurrence following liver transplantation in HBsAg-positive liver transplant patients after an interim analysis of a historically controlled open-label study of HBIG as monotherapy (prophylaxis) in subjects with a low risk of HBV recurrence [$HBsAg^+/HBeAg^-$].
   - Orphan product designation for the HBV-OLT indication was granted on March 24, 2008; therefore, the Pediatric Research Equity Act (PREA) does not apply.

2. Background

   HBIG products have been used as standard-of-care for patients undergoing HBV-related orthotopic liver transplantation (OLT) since the early 1990's. In the late 1990's, the nucleoside analogue lamivudine was added to HBV-OLT treatment regimens to further suppress the rate of HBV recurrence in liver grafts. New anti-HBV drugs are often added to HBV-OLT treatment regimens when they become available. Anti-HBV drugs are approved initially for the treatment of HBV chronic hepatitis and, to date, they are not approved for HBV-OLT, although they often become standard-of-care for this purpose.

   As concomitant use of anti-HBV antiviral drug products has become standard of care, it becomes difficult to evaluate the safety and efficacy of HBIG products for the HBV-OLT indication compared to historical controls when antiviral drugs were not avialable . CBER recognizes the difficulty in meeting regulatory requirements for clinical trial designs that can demonstrate the individual contributions of HBIG products to safety and efficacy in the HBV-OLT setting. In response to proposals from individual sponsors, CBER has allowed the use of data from studies published prior to the introduction of anti-HBV antiviral drugs in attempts to obtain the HBV-OLT indication. This approach has not been successful due to large gaps in the retrospectively collected monitoring databases, including insufficient information on the actual HBIG dosing that was used.

Another complication for attempts to gain the HBV-OLT indication has been ascertainment of the appropriate primary endpoint for the clinical studies. Among the categories for the primary endpoint considered by CBER in discussions with sponsors are the following:

- Mortality and/or graft survival
- Graft function
- Graft re-infection by HBV as shown by liver biopsy
- HBV recurrence as shown by serological assays
- Maintenance of anti-HBs levels above a pre-determined threshold level

Another issue that complicates trial design is the appropriate study length and the uncertainties about outcome rate estimates as influenced by baseline risk factors (subject- or virus-associated risk factors, concomitant medical care risk factors).

The most difficult challenge for the attainment of the HBV-OLT indication has been identification of the appropriate control group.

To address these clinical trial design issues, CBER brought these questions to the March 2004 Blood Products Advisory Committee (BPAC). The BPAC recommended the following:

- HBsAg seronegativity is an acceptable primary endpoint to determine absence of recurrence of HBV graft infection.
- Clinical trials for HBIG monotherapy (i.e. no concomitant anti-HBV antiviral drugs) should be of at least one year's duration.
- Clinical trials for HBIG combination therapy with lamivudine should be at least two year's duration in order to capture delayed lamivudine resistant revertants.

CBER agreed with BPAC's recommendation.

3. Chemistry Manufacturing and Controls (CMC)

   N/A [HepaGam B is a licensed product.]

4. Nonclinical Pharmacology/Toxicology

   N/A [HBIG is used off-label as standard-of-care for this indication.]

5. Clinical Pharmacology

General clinical pharmacology: There was no formal pharmacokinetics study in the HBV-OLT patient population. The protocol was designed to maintain anti-HBs levels above 500

IU/L, based upon published claims for the ability of this dosing strategy to maintain HBsAg seronegativity [Hepatology 32(6): 1189-95 (2000)]. The dose schedule used in study HB-005 resulted in trough anti-HBs levels that are reported in the medical literature to be more than adequate for this use.

6. Clinical/ Statistical

a) Clinical Program

- Cangene Corporation conducted a clinical trial for use of HepaGam B as monotherapy for anti-HBV immunoprophylaxis in subjects undergoing HBV-related OLT, and who are at low risk for HBV recurrence due to their HBV serostatus ($HBsAg^+/HBeAg^-$).
- The open-label clinical trial was conducted at sites that used HBIG monotherapy after HBV-OLT based on the low risk serostatus ($HBsAg^+/HBeAg^-$). There were two sites in Turkey and one site in California.
- A historical control was identified from the medical records of past patients treated at the clinical sites using eligibility criteria that were pre-specified to ensure comparability to the prospectively enrolled treated population. These patients were $HBeAg^-$ and did not receive HBIG immunoprophylaxis.
- The two-sided 95% exact binomial confidence interval for the HBV recurrence rate for the treatment arm was to be compared with the historical recurrence rate of 0.8 from a meta-analysis of the historical control group, which is equivalent to a one-sample two-sided exact binomial test at alpha level 0.05.
- After 14 subjects were enrolled, a planned interim analysis was performed that demonstrated statistically significant efficacy after controlling type I error using the O'Brien and Fleming group sequential plan. As a result, CBER licensed HepaGam B for the HBV-OLT indication on April 6, 2007, and permitted the sponsor to truncate the sample size from an original 50 planned subjects to approximately 25 subjects. The final sample size was 27 subjects.
- In study HB-005, one subject seroconverted to $HBsAg^+$ (primary endpoint), and one subject unexpectedly seroconverted to $HBeAg^+$ (a marker for HBV replication) while maintaining HBsAg seronegativity. Both subjects were considered efficacy failures for primary efficacy analysis purposes.

The following table summarizes the efficacy results of study HB-005:

Comparison of the proportion of subjects with HBV recurrence* (HBsAg or HBeAg)

Study group	**Proportion (%)**	**95% Confidence Interval**	**P-value****
Active Treatment (NP-002)	8.3	(1.0; 27.0)	< 0.001
Retrospective Untreated Control	85.7	(57.2; 98.2)	

*HBV recurrence is defined as a positive HBsAg or HBeAg result between 4 weeks post-OLT and the last study visit.
**Fisher's Exact Test
Source: Study HB-005 Clinical Report, page 57 of 273

- As part of the April 6, 2007, licensure for the HBV-OLT indication, the sponsor accepted a post-marketing commitment to complete study HB-005, although with a reduced sample size (decreased to 25 subjects from the originally planned 50 subjects). This commitment has been fulfilled.
- The bioresearch monitoring inspection did not reveal unacceptable protocol violations.

b) Pediatrics

- PREA does not apply because HepaGam B received orphan product designation on March 24, 2008.
- Study HB-005 enrolled only adults (age range: 31 to 65 years).

7. Safety

- The treatment emergent adverse events were expected for this seriously ill patient population. There were four deaths during the study, attributed to the underlying medical situation and not to the product. The causes of death were septic shock, lung cancer metastasis, fungal sepsis, and myocardial reperfusion injury. There were 26 serious adverse event reports, none judged related to the product (see section 6.1.12.4 of the clinical review memo). The complete list of adverse events by body system and preferred term is given in appendix 3 of the clinical review memo.

- A notable safety event was the apparent infection of one subject (enrolled at a Turkey site) with hepatitis C during study HB-005. The sponsor attributed this possibly to a blood transfusion. After consideration of the viral removal/inactivation validation of the HepaGam B manufacturing process, and the lack of hepatitis C infection of subjects who also received the same product lots as did the HCV infected subject, it was concluded that the HCV infection was locally-acquired.

8. Advisory Committee Meeting

- There were no safety or efficacy concerns in study HB-005 that warranted presentation of the clinical trial results before BPAC.

9. Other Relevant Regulatory Issues

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

10. Labeling

- The label was reviewed together with the APLB reviewer. The clinical reviewer and the APLB reviewer agreed on the majority of items. The APLB reviewer recommended that the frequency histogram showing anti-HBs trough levels be replaced with a briefer statistical presentation of these data; however, the clinical reviewer thought the frequency histogram gives a fuller presentation of the data, and that some physicians may find this useful. The histogram remains in the present label.
- CBER had considerable discussions on how to label potency on the product vials. Traditionally, HBIG products have been labeled with minimum product specification for the vial content of anti-HBs (IU/milliliter). The minimum anti-HBs content was set for manufacturing purposes, and it was usually greatly exceeded, in practice. This discrepancy between the labeled vial contents and the actual vial contents did not have much clinical significance when the labeled indication was for HBV post-exposure prophylaxis. However, for the HBV-OLT indication, many physicians have a desired anti-HBs target level in mind, and knowledge of the actual vial

contents was thought to be of clinical importance. It was decided to ask manufacturers of HBIG products to label their products with the actual vial contents, as well as with the minimum anti-HBs product specification.

11. Recommendations and Risk/ Benefit Assessment

- CBER does not have additional concerns at this time based upon the results of study HB-005.