SUMMARY BASIS FOR APPROVAL

I. GENERAL INFORMATION

Licensed Product Name:	Hepatitis B Immune Globulin (Human)
Trade Name:	HepaGam B™
Name and Address of Sponsor	Cangene Corporation Winnipeg, Canada US License No. 1201

Biologics License Application (BLA) Tracking Number: STN 125035

II. INDICATIONS FOR USE

Hepatitis B Immune Globulin (Human), HepaGam B™ (NP-002), is indicated for the treatment of acute exposure to blood containing hepatitis B surface antigen (HBsAg), perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg positive persons, and household exposure to persons with acute hepatitis B virus (HBV) infection in the following settings:

- Acute Exposure to Blood Containing HBsAg
  Following either parenteral exposure (needlestick, bite, sharps), direct mucous membrane contact (accidental splash), or oral ingestion (pipetting accident), involving HBsAg-positive materials such as blood, plasma or serum.

- Perinatal Exposure of Infants Born to HBsAg-positive Mothers
  Infants born to mothers positive for HBsAg with or without hepatitis 'e' antigen (HBeAg).

- Sexual Exposure to HBsAg-positive Persons
  Sexual partners of HBsAg-positive persons.

- Household Exposure to Persons with Acute HBV Infection
  Infants less than 12 months old whose mother or primary caregiver is positive for HBsAg. Other household contacts with an identifiable blood exposure to the index patient.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION & RECOMMENDED DOSAGE

A. Dosage Form

Hepatitis B Immune Globulin (Human), HepaGam B™, is a sterile solution of the purified gamma globulin (IgG) fraction of human plasma containing antibodies to hepatitis B surface antigen (anti-HBs). HepaGam B™ is formulated as a 5% (50 mg/mL) protein solution with 10% maltose and 0.03% polysorbate 80 at pH 5.6. It is available in 1 mL and 5 mL single-dose vials. The product appears as a clear to opalescent liquid. It contains no preservatives and is intended for single use by the intramuscular route only.

The product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) standard Hepatitis B Immune Globulin. Each vial contains greater than 312 IU/mL. The potency of each vial of HepaGam B™ exceeds the potency of anti-HBs in the U.S. reference hepatitis B immune globulin (FDA). The U.S. reference has been tested against the WHO standard and found to be equal to 220 IU/mL.

B. Route of Administration

For post-exposure prophylaxis, this product must be administered intramuscularly. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration; if these are seen, the vial should not be used.

It is important to use a separate vial, sterile syringe, and needle for each individual patient, in order to prevent transmission of infectious agents from one person to another. Any vial of HepaGam B™ that has been entered should be used promptly. Do not reuse or save for future use. This product contains no preservative; therefore, partially used vials should be discarded immediately.

Hepatitis B Immune Globulin (Human)) may be administered at the same time (but at a different site), or up to one month preceding hepatitis B vaccination without impairing the active immune response to Hepatitis B Vaccine.

C. Recommended Dosage

Acute Exposure to Blood Containing HBsAg

Table 1 summarizes prophylaxis for percutaneous (needlestick, bite, sharps), ocular, or mucous membrane exposure to blood according to the source of exposure and vaccination status of the exposed person. For greatest effectiveness, passive prophylaxis with Hepatitis B Immune Globulin (Human) should be given as soon as possible after exposure, as its value after seven days following exposure is unclear. An injection of 0.06 mL/kg of body weight should be administered intramuscularly as soon as possible after exposure, and within 24 hours if possible. Consult the Hepatitis B Vaccine package insert for dosage information regarding the vaccine.

For persons who refuse Hepatitis B Vaccine or are known non-responders to vaccine, a second dose of Hepatitis B Immune Globulin (Human) should be given one month after the first dose.

Table 1 Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure

Source	Unvaccinated Exposed Person	Vaccinated Exposed Person
HBsAg-positive	1. Hepatitis B Immune Globulin (Human) x 1 immediately* 2. Initiate HB vaccine series†	1. Test exposed person for anti-HBs 2. If inadequate antibody‡, Hepatitis B Immune Globulin (Human) x 1 immediately plus HB vaccine booster dose, or 2 doses of HBIG*, one as soon as possible after exposure and the second 1 month later§
Known Source – High Risk for HBsAg-positive	1. Initiate HB vaccine series 2. Test source of HBsAg. If positive, Hepatitis B immune Globulin (Human) x 1	1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give Hepatitis B Immune Globulin (Human) x 1 immediately plus HB vaccine booster dose, or 2 doses of HBIG*, one as soon as possible after exposure and the second 1 month later§
Known Source – Low Risk for HBsAg-positive	Initiate HB vaccine series	Nothing required
Unknown Source	Initiate HB vaccine series	Nothing required

* Hepatitis B Immune Globulin (Human) dose of 0.06 mL/kg IM.
† See manufacturers' recommendation for appropriate dose.
‡ Less than 10 mIU/mL anti-HBs by radioimmunoassay or enzyme immunoassay.
§ Two doses of Hepatitis B Immune Globulin (Human) is preferred if no response after at least four doses of vaccine.

Prophylaxis of Infants Born to Mothers who are Positive for HBsAg with or without HBeAg

Table 2 contains the recommended schedule of Hepatitis B prophylaxis for infants born to mothers that are either known to be positive for HBsAg or have not been screened. Infants born to mothers known to be HBsAg-positive should receive 0.5 mL Hepatitis B Immune Globulin (Human) after physiologic stabilization of the infant and preferably within 12 hours of birth. The Hepatitis B Vaccine series should be initiated simultaneously, if not contraindicated, with the first dose of the vaccine given concurrently with the Hepatitis B Immune Globulin (Human), but at a different site. Subsequent doses of the vaccine should be administered in accordance with the recommendations of the manufacturer.

Women admitted for delivery, who were not screened for HBsAg during the prenatal period, should be tested. While test results are pending, the newborn infant should receive Hepatitis B Vaccine within 12 hours of birth (see manufacturers' recommendations for dose). If the mother is later found to be HBsAg-positive, the infant should receive 0.5 mL Hepatitis B Immune Globulin (Human) as soon as possible and within seven days of birth; however, the efficacy of Hepatitis B Immune Globulin (Human) administered after 48 hours of age is not known. Testing for HBsAg and anti-HBs is recommended at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Table 2 Recommended Schedule of Hepatitis B Immunoprophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus Infection

Administer	**Age of Infant** **Infant born to mother known to be HBsAg-positive**	**Age of Infant** **Infant born to mother not screened for HBsAg**
First Vaccination* Hepatitis B Immune Globulin (Human)†	Birth (within 12 hours) Birth (within 12 hours)	Birth (within 12 hours) If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second Vaccination*	1 month	1-2 months
Third Vaccination*	6 months‡	6 months‡

* See manufacturers' recommendations for appropriate dose.
† 0.5 mL administered IM at a site different from that used for the vaccine.
‡ See ACIP recommendation.

Sexual Exposure to HBsAg-positive Persons
All susceptible persons whose sexual partners have acute hepatitis B infection should receive a single dose of Hepatitis B Immune Globulin (Human) (0.06 mL/kg) and should begin the Hepatitis B Vaccine series, if not contraindicated, within 14 days of the last sexual contact or if sexual contact with the infected person will continue. Administering the vaccine with Hepatitis B Immune Globulin (Human) may improve the efficacy of post exposure treatment. The vaccine has the added advantage of conferring long-lasting protection.

Household Exposure to Persons with Acute HBV Infection
Prophylaxis of an infant less than 12 months of age with 0.5 mL Hepatitis B Immune Globulin (Human) and Hepatitis B Vaccine is indicated if the mother or primary caregiver has acute HBV infection. Prophylaxis of other household contacts of persons with acute HBV infection is not indicated unless they had an identifiable blood exposure to the index patient, such as by sharing toothbrushes or razors. Such exposures should be treated like sexual exposures. If the index patient becomes an HBV carrier, all household contacts should receive Hepatitis B Vaccine.

IV. MANUFACTURING AND CONTROLS

A. Manufacturing

HepaGam B™ is manufactured from plasma collected from healthy, screened donors with high titers of anti-HBs (meeting minimum potency specifications) that is purified by an anion-exchange column chromatography method. Each plasma donation used for the manufacture of Hepatitis B Immune Globulin (Human) is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency viruses-1/2 (HIV-1/2) and hepatitis C virus (HCV) using FDA-licensed serological tests. In addition, plasma used in the manufacture of this product has been tested by FDA licensed Nucleic Acid testing (NAT) for HIV-1 and HCV and found to be negative. An investigational NAT for HBV is performed on all Source Plasma

used, and found to be negative. Plasma also has been tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) via minipool testing and the limit for B19 in the manufacturing pool is set not to exceed 10^4 IU of B19 DNA per mL.

The pooled plasma is treated with ---------- for ----------and then ---------- applied to an anion-exchange chromatography column, which purifies the IgG from the remaining plasma proteins.

The purified IgG is applied to a nanofilter (Planova 35N), which is effective for removal of viruses with sizes greater than or near the nominal pore size of 35 nanometers. The nanofiltered IgG is then concentrated by ----------

Solvent and detergent (SD) reagents are added to the concentrated IgG, to final concentrations of ------- tri-n-butyl phosphate (solvent) and ----- Triton X-100 (detergent). The SD reagents and plasma are mixed to ensure ---------- and then ---------- to ensure ---------- which may harbor potential viruses. The IgG and SD reagents are ---------- and applied to a ---------- SD reagents. The virally inactivated product is ---------- concentration and potency. The product is adjusted to pH 5.6 and formulated to10% maltose and 0.03% polysorbate 80. The formulated product is ---------- into a sterile ----- and held until confirmed for release. The released product is sterile-filtered into the filling suite, and aseptically filled into the appropriately sized ---------- vials. The vials are then stoppered and capped.

Final product release tests are performed on every lot HepaGam B™. The finished product release tests are: Hepatitis B Antibody Potency by ---------- Total Protein; pH; ---------- Appearance; General Safety; ---------- Bulk and Final Product Sterility; ----------

All final container lots meet the established specifications for HepaGam B™.

B. Validation

1. Validation of Systems, Processes, and Equipment

The facility, utilities, manufacturing equipment, manufacturing processes and cleaning operations used in the production of Hepatitis B Immune Globulin (Human), HepaGam B™, have been validated according to pre-approved, written procedures (validation protocols). Preventative maintenance procedures are in place to ensure regular maintenance of the equipment. In addition, regular monitoring of the environmental conditions within the production facilities is carried out according to a pre-defined schedule.

The analytical methodologies used in the testing of HepaGam B™ have been validated according to pre-approved written procedures (validation protocols).

2. Viral Inactivation/Removal Studies

Two specific viral clearance steps are incorporated in the manufacturing process to increase viral safety of the final product:

Solvent and Detergent (SD) Treatment: The SD step is a well-established virus clearance step, and is highly effective for the inactivation of enveloped viruses, such as HIV, HBV and HCV.

Nanofiltration: Nanofiltration is a physical method of virus removal, employing size exclusion. The nanofiltration step does not distinguish between enveloped or non-enveloped viruses, but removes viruses based on the virus size. The process employs a Planova 35N virus filter, which is capable of effective removal of viruses at or above the nominal pore size of 35 nm. The nanofiltration step is therefore effective for all of the above viruses, which range in size from 50 – 460 nm.

The virus panel used for the validation of the hyperimmune process was selected to represent those viruses that are potential contaminants for the product, and to represent a wide range of physico-chemical properties, in order to challenge the manufacturing process ability for viral clearance in general. The virus panel included the following characteristics: DNA and RNA genomes; enveloped and non-enveloped; large, intermediate and small sizes; easily inactivated to very resistant; and relevant, specific model, and non-specific model viruses. Table 3 summarizes the viral reduction values obtained through validation studies.

Table 3 Virus reduction values obtained through validation studies

Virus used in validation	HIV-1	BVDV	PRV	Poliovirus	HAV	MMV
Genome Envelope Size (nm)	RNA Yes 80-100	RNA Yes 50-70	DNA Yes 120-200	RNA No 24 –30	RNA No 25-30	DNA No 20-25
Anion Exchange Chromatography	Not evaluated	Not evaluated	Not evaluated	Not evaluated	2.3	3.4
35 N Nanofiltration	≥ 6.0	4.4 to ≥ 6.4[1]	≥6.8	4.25	≥ 4.3	Not evaluated
Solvent/Detergent Step	≥ 4.7	≥ 6.6	≥ 5.0	Not applicable	Not applicable	Not applicable
Total Reduction (log_{10})	≥ 10.7	≥ 11.0	≥ 11.8	4.25	≥ 6.6	3.4

[1] The lower value was used for calculation of the total reduction factor. The range obtained was for the validation of the process robustness.
HIV-1: relevant virus for human immunodeficiency virus-1 and model for HIV-2
BVDV: bovine viral diarrhea virus; model virus for HCV and West Nile virus (WNV)
PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes
Poliovirus: model for HAV and small non-enveloped viruses in general
HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general
MMV: murine minute virus; model for Parvovirus B19 and small non-enveloped viruses in general

In addition to the validated reduction values for enveloped viruses, two steps were identified as contributing to the overall viral clearance capacity for small, non- enveloped viruses: 1) The anion-exchange chromatographic step yielded a clearance of 3.4 log_{10} of murine minute virus (MMV), which is a model for parvovirus B19, and a clearance of 2.3 log_{10} for the relevant virus, HAV. 2) The 35N virus filtration step yielded a clearance of 4.25 log_{10} of poliovirus, a model for HAV, and > 4.3 log $_{10}$ of the relevant virus, HAV.

C. Stability

The sterile bulk material can be stored in the ---------- for up to --------- at 2-8 °C from the date of sterile filtration.

A total of 5 conformance lots of each dosage size have been monitored at the recommended storage conditions 2-8 °C according to the stability program. To date these lots have met the required specifications including the first three lots of the 1 mL and 5 mL final container product, with 36 months of real time data completed. In addition, all lots have been evaluated under accelerated conditions ------ for ---------- ---------- The studies have concluded that the product is stable for ---------- when stored at ----------

On the basis of real time data accumulated to date, when analyzed by regression analysis using a 95% confidence level, a shelf life of 36 months from the date of manufacture has been demonstrated for the 1 mL and 5 mL dosage sizes with storage at 2-8 °C. ---------- ---------- The final container lots are intended to be stored at 2-8 °C for maintaining long-term stability of the product.

D. Labeling

The labeling for HepaGam B™ is comprised of a product information insert (package insert), and a vial and shelf carton label for the 1 mL and 5 mL containers. The labeling has been reviewed as part of the BLA and is in compliance with 21 CFR Part 201 Subparts A and B, and 21 CFR Part 610 Subpart G. The Trade Name, HepaGam B™, is not known to be in conflict with or easily confused with the trademark of any other licensed pharmaceutical product.

E. Establishment

A pre-licensing inspection of the Cangene facility in Winnipeg, Manitoba, Canada, was conducted between April 23 –26, 2002. A form FDA-483 was issued at the conclusion of the inspection. Cangene responded to all FDA-483 observations and the corrective actions have been found to be adequate and complete. The establishment was found to be in compliance with current Good Manufacturing Practices.

F. Environmental Assessment

A categorical exclusion from the requirement to prepare an Environmental Assessment was requested and granted according to 21 CFR 25.31 (c).

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Nonclinical pharmacology studies have not been performed with Hepatitis B Immune Globulin (Human) as there is broad experience in humans with intravenous and intramuscular administration of immune globulin products. Since the product is of human origin, immunogenicity is expected when administered to animals.

Formal toxicity studies were not conducted for HepaGam B™ or its components. The active ingredient of HepaGam B™ is human immune globulin, a physiological constituent of human plasma, and thus is not expected to have toxic effects. The safety profile of non-active components is well established in the literature. There is no evidence of mutagenicity/genotoxicity associated with non-active components of HepaGam B™.

VI. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

In two 84-day pharmacokinetics studies, 70 volunteers were administered HepaGam B™. The mean peak concentrations (C_{max}) in both studies were comparable and occurred within 4-5 days of administration. Both studies demonstrated mean elimination half-lives ($t_{½}$) following IM administration of 22 to 25 days. The mean clearance rate was 0.21 to 0.24 L/day and the volume of distribution was approximately 7.5 L. Thus, HepaGam B™ demonstrates pharmacokinetic parameters similar to those reported for other licensed Hepatitis B Immune Globulin (Human) products when compared in the two pharmacokinetic trials, HB-002 and ---------- as described below.

The first study, HB-002, assessed the safety and pharmacokinetics of HepaGam B™ and ---------- in healthy adult volunteers. Each group of subjects (30 subjects per arm) received 0.06 mL/kg of either HepaGam B™ or ---------- administered intramuscularly under fasting conditions. Pharmacokinetic samples were collected at defined time points for a period of 84 days (3 half-lives of the product) and analyzed using the quantitative AUSAB anti-HBs immunoassay. Pharmacokinetic analyses were performed on the anti-HBs levels and the parameters are summarized in Table 4 below. HepaGam B™ had a similar pharmacokinetic and safety profile as the comparator and other immune globulin products.

Table 4 Pharmacokinetic parameters for HepaGam B™, study HB-002

Parameter	HepaGam B™ Results	
AUC_{0-T} (mIU·d/mL)	7356.73 7521.34 (20.60)	Geometric Mean Arithmetic Mean (CV,%)
AUC_{0-inf} (mIU·d/mL)	8253.94 8477.42 (22.85)	Geometric Mean Arithmetic Mean (CV,%)
C_{max} (mIU/mL)	211.63 215.6 (19.1)	Geometric Mean Arithmetic Mean (CV,%)
T_{max} (d)	5.40 (43.93)	Arithmetic Mean (CV,%)
---------	----------	Arithmetic Mean (CV,%)
t ½ (d)	24.53 (18.86)	Arithmetic Mean (CV,%)

VII. CLINICAL SUMMARY

A. Overview

Hepatitis B Immune Globulin (Human) products provide passive immunization for individuals exposed to the hepatitis B virus and reduce the infection rate of hepatitis B. Historical clinical studies with hepatitis B immune globulins similar to HepaGam B™ demonstrated the advantage of simultaneous administration of Hepatitis B Vaccine and Hepatitis B Immune Globulin (Human) to prevent hepatitis B after exposure to HBV.

Comparability of pharmacokinetics between HepaGam B™ and one commercially available hepatitis B immune globulin product indicates that similar efficacy of HepaGam B™ should be inferred.

B. Safety

Seventy healthy male and female volunteers received HepaGam B™ intramuscularly in clinical trials. Seventeen subjects reported 30 adverse events with the use of HepaGam B™. The most frequently reported adverse events included 4 subjects (6%) who experienced headache, 7 subjects (10%) who had cold symptoms or flu and 2 subjects (3%) who experienced lightheadedness/fainted. The majority of events were reported as

mild. One adverse event, an episode of nausea, was considered to be drug-related. There were no serious adverse events reported. A similar number of subjects in the comparator groups reported adverse events. Occasionally, the following adverse events may occur after IM administration of immune globulin products: chills, fever, headache, vomiting, allergic reaction, nausea, arthralgia, and moderate low back pain.

No anaphylactic reactions with HepaGam B™ have been reported. However, these reactions, although rare, have been reported following the injection of human immune globulins.

C. Efficacy

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) advises that the combination prophylaxis of Hepatitis B Immune Globulin (Human) and the Hepatitis B Vaccine series should be provided following certain instances of hepatitis B exposure. These recommendations are based on clinical studies conducted in the 1970's and 1980's, with hepatitis B immune globulin products like HepaGam B™.

The efficacy of HepaGam B™ for the post-exposure prophylaxis of HBV is inferred from the bioequivalence to another licensed hepatitis B immune globulin product.

VIII. ORPHAN DRUG CONSIDERATION

Not Applicable

IX. MARKETING HISTORY

HepaGam B™ has not been commercially marketed.

Mei-ying W. Yu, Ph.D. (Scientific Lead)	Date	Charles Maplethorpe, M.D. Ph.D. (Clinical)	Date
Jessica Kim, Ph.D. (Statistic Evaluation)	Date	Martin D. Green, Ph.D. (Pharmacokinetics)	Date
Mahmood Farshid, Ph.D. (CMC/Product)	Date	Douglas J. Frazier (CMC/Product)	Date
Laurie Norwood (CMC/Establishment)	Date	Mary Padgett (CMC/Establishment)	Date
Debbie Nadel (Regulatory Manager)	Date	Yongkai Weng, Ph.D. (Proprietary Name)	Date
Basil Golding, M.D. (Director, Division of Hematology)	Date	Dorothy Scott, M.D. (Chief, Lab. of Plasma Derivatives/DH)	Date