SUMMARY OF SAFETY AND PROBABLE BENEFIT

I.   GENERAL INFORMATION

Device Generic Name: Test, cell mediated immune response, liver and small bowel transplant/transplantation

Device Trade Name: Pleximmune™

Device Procode: PHK

Applicant's Name and Address: Plexision, Inc.

4424 Penn Avenue
Suite 202, Medical Building
Pittsburgh, PA 15224, USA

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption
(HDE) Number: HI30004

Humanitarian Use Device (HUD)

Designation Number: # 08-0206

Date of HUD Designation: June 12, 2009

Date of Notice of Approval
to Applicant: August 26, 2014

II.   INDICATIONS FOR USE

Pleximmune™ is intended to be performed at a single laboratory to measure the CD 154 expression on T-cytotoxic Memory cells (TcM) in patient's peripheral blood lymphocytes (PBL) isolated from heparinized whole blood (anticoagulant - sodium heparin). Pleximmune™ is a qualitative prognostic test intended to be used in patients less than 21 years old with liver or small bowel transplantation. The Pleximmune™ test is an aid in the evaluation of the risk of acute cellular rejection (ACR) and must be used in conjunction with biopsy, standard clinical assessment and other laboratory information.

Pleximmune™ is intended for use at the following time periods:

- Pre-transplantation period: For blood samples collected before transplantation, the test predicts the risk of transplant rejection within 60 days after transplantation.

- Early and late post-transplantation period: For blood samples collected within 60 days (early) after transplantation and for blood samples collected at 200 or more days (late) after transplantation, the test predicts the risk of transplant rejection within 60 days after sampling.

The indication for use statement is identical to that which was granted for the HUD designation.

III.   CONTRAINDICATIONS

None Known

IV.   WARNINGS AND PRECAUTIONS

The warnings and precautions, and limitations of the assay can be found in the Pleximmune™ labeling.

V.   DEVICE DESCRIPTION

Pleximmune™ is an adjunctive blood test which is intended as an aid in the evaluation of the risk of ACR of a transplant by measuring recipient inflammatory immune response toward the donor organ in children with liver or small bowel transplantation. The Pleximmune™ test system uses *in vitro* lymphocyte co-culture to elicit the inflammatory response of the recipient to the donor. This inflammatory response to donor is measured as a rejection-risk signal by quantitatively measuring the T-cytotoxic memory cells (TcM) from the recipient, which express the inflammatory marker, CD 154 (CD154$^+$TcM) using flow cytometry.

To determine if the donor specific inflammatory response is increased or decreased, a reference inflammatory response of the recipient toward "third-party" peripheral blood lymphocyte (PBL) cells is performed in parallel. Third-party PBL cells obtained from normal human subjects are dissimilar to the recipient and donor at the HLA loci. To determine similarity and dissimilarity, the HLA-A, -B, and -DR loci are compared between recipient and donors. This information is generated at the time of transplantation as a component of routine care. Additionally, because donor cells are not easily obtained from cadaveric donors, which are the major sources of liver and small bowel transplants in children, cells from normal human subjects which are antigenically similar to the donor are used. These cells are termed "surrogate donor" cells.

To characterize rejection-risk in the individual recipient, the recipient's inflammatory response to donor cells is expressed as a fraction of his/her inflammatory response to the third-party cells. This fraction or ratio is termed the immunoreactivity index (IR). If the donor-induced response exceeds the response to third-party, the individual is at increased risk for rejection. If the donor response is exceeded by the response to third-party, the individual is at decreased risk. This use of the response to third party mismatched PBL as a reference response makes test results specific for the transplant recipient and comparable between recipients. Thus, the IR value of the recipient PBL sampled prior and after the small bowel and/or liver transplantation correlates with the risk of acute cellular rejection of the transplant. The IR is intended to be used by physicians as a tool, in conjunction with all other clinical and laboratory data and biopsy, to predict the transplant patient's rejection risk level.

Pleximmune™ Design - The Pleximmune™ test system uses four cell culture reactions as follows:

1. Negative Control - The recipient PBLs are cultured alone in culture medium which does not contain fluorochrome-labeled antibody to the inflammatory response marker, CD 154. This group of cells serves as negative control for the Flow Cytometry measurement.

2. Background - The recipient PBLs are cultured alone in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD 154. This group of cells serves as background CD154$^+$TcM cells present in the unstimulated recipient blood at the time of testing.

3. Donor Reaction - The recipient PBLs are cultured with donor or surrogate donor PBL in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD 154. This group of cells represents the immune reaction of the recipient to the donor.

4. Third-party Reaction - The recipient PBL are cultured with mismatched PBL in culture medium described in condition 2. This group of cells represents the immune reaction of the recipient to mismatched PBL. This reaction is used as a reference reaction for calculating the IR of the recipient.

Method of Operation - Transplant patient blood or blood from normal human subjects is collected and PBLs are isolated. Based on the HLA loci information of patient, surrogate donor PBL and third party PBL are selected. These PBLs are used in the four vitro cell culture reactions (as described above), incubated to elicit the immune reaction in the responder cells. The number of CD154+TcM cells is acquired by flow cytometry. These results are analyzed to calculate IR, which is used to assign the risk of rejection for the transplant patient sample.

The fluorochrome labeled antibodies used in the Pleximmune™ test to identify subsets of T lymphocytes in the recipient, donor and third party PBL are:

- Anti-CD3-FITC, for labeling CD3 expressing T lymphocytes

- anti-CD8-APC-H7, for labeling recipient CD8 expressing cytotoxic T cells

- anti-CD8-PE-Cy7, for labeling donor/surrogate donor/third party CD8 expressing cytotoxic T cells

- anti-CD45RO-APC, for labeling cytotoxic memory T (TcM) cells

- anti-CD 154-PE, for labeling CD 154 expressing TcM cells

- Viability dye 7-aminoactinomycin-D (7-AAD), stains dead cells

Interpretation of Pleximmune™ Results - The number of CD154$^+$TcM per TcM in the donor and third-party reactions are each compared with those present in the background reaction using the statistical Poisson test, (the Poisson test is recognized for a comparison of proportions between two samples). For the Pleximmune™ results to be valid for generating an IR and assigning rejection risk category (i.e., decreased or increased risk of rejection), at least one reaction must pass the Poisson test (p <0.05). If both reactions fail the Poisson test, the Pleximmune™ test is considered invalid, and IR is not reported. The IR is calculated by dividing the frequency of CD154$^+$TcM induced in the donor reaction by those induced in the third-party reaction. For post-transplant blood samples, an IR >1.1 indicates increased risk of transplant rejection, and an IR < 1.1 indicates decreased risk of transplant rejection. For pre-transplant samples, and IR >1.23 indicates increased risk of transplant rejection, and an IR <1.23 indicates decreased risk of transplant rejection.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the diagnosis of risk of liver and small intestine organ transplant rejection in children include clinical evaluation of symptoms such as fever,

diarrhea, liver function blood tests, and biopsies of the liver or small intestine. All procedures and other currently available devices used for managing this patient population have limitations.

Pre-transplant evaluation of the risk of rejection: T and B cell cross-match, donor-specific anti-HLA antibodies (DSA) and Panel reactive antibodies (PRA) maybe helpful in predicting antibody mediated rejection. These tests do not assess the risk of ACR which is the major form of rejection after organ transplantation and affects 30-40% of liver recipients and 30-60% of small bowel recipients.

Post-transplant evaluation of the risk of rejection: No laboratory test exists to measure the risk of transplant rejection objectively. The "risk of rejection" is currently assessed by several surveillance methods. These methods include clinical symptoms and signs, routine clinical and immunological laboratory tests, allograft biopsies, and molecular testing. With the exception of the biopsy, which is the gold standard, all other surveillance methods are prone to errors:

- Clinical symptoms of rejection are not specific
- Elevated liver function tests are not specific
- Anti-donor antibody tests lack sensitivity
- Other laboratory tests performed in this population provide incremental information but are not determinative of rejection prognosis.

Biopsies: Biopsies can exclude or confirm rejection but can cause bleeding and perforation of abdominal organs.

Pleximmune™ is a first of a kind device.

VII.   MARKETING HISTORY

Pleximmune™ has not been marketed in the United States or any foreign country.

VIII.   POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The risks associated with the use of Pleximmune™ arise from false positive or false negative results, and from blood sampling. The potential adverse effects of the device on health are as follows:

A falsely elevated Pleximmune™ test result could potentially lead to a medical decision that causes unnecessary diagnostic workup for transplant rejection and subsequent unnecessary treatment.

A falsely low Pleximmune™ test result could potentially lead to a medical decision depriving patients of necessary diagnostic workup and subsequent timely treatment for transplant rejection.

Blood sampling could cause complications such as bleeding, infection, or fainting. These risks are minimized by using experienced phlebotomists to draw blood samples in CLIA-certified or hospital-based laboratories. The amount of blood sample needed from children is 3.0 to 5.0 mL and unlikely to pose a risk.

Pleximmune™ is a prognostic test, and is not indicated as the sole diagnostic tool in assessing the risk of liver or small bowel transplant rejection in children; it should be used in conjunction with the information from a complete clinical evaluation including

clinical signs and symptoms, other laboratory test results, and biopsy.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX.   SUMMARY OF PRECLINICAL STUDIES

The purpose of the non-clinical laboratory studies was to assess the analytical performance of the standardized format for Pleximmune™. For these studies, normal human samples were used since clinical samples were difficult to get from the intended population of children with liver and small bowel transplant. A single antigenically dissimilar stimulator was used to stimulate PBL from normal human subjects.

Each assay consists of three cell culture reactions:

- Negative control - responder PBL without anti-CD 154-PE in culture medium

- Background - responder PBL with anti-CD 154-PE in culture medium; and

- Stimulated - responder and stimulator PBL with anti-CD 154-PE in culture medium. Stimulator PBL is antigenically dissimilar to responder PBL at all three HLA loci.

Non-clinical Laboratory Studies:

1)   Characterization of Pleximmune™:

   a)   Specificity of antibodies in reagent cocktail - Pleximmune™ employs six different fluorophores and dyes with overlapping emission spectra. The study to demonstrate the specificity of individual antibodies in the reagent cocktail was conducted by adding saturating concentrations of the various antibodies and the effect on the frequency of a reference T cell subpopulation, CD8$^+$ cells labeled with anti-CD8-APCH7 was evaluated. With the exception of anti-CD 154-PE, each antibody/7-AAD was first added singly, and then in combination to PBL from three normal human subjects. The frequency of CD8+ cells labeled with various combinations of antibodies showed variations (%CV) of 4.9%, 12.2%, and 3.5% in respective PBL from three normal human subjects. The results met the sponsor's acceptance criteria.

   b)   Effect of Anti-CD154-PE on Assay - The effect of adding anti-CD154-PE on the frequency of CD8 cells labeled with anti-CD8-APCH7 was evaluated in the presence of all other antibodies/7-AAD. To stimulate CD 154 expression, three overnight co-cultures were performed using three different pairs of HLA-mismatched responder and stimulator PBL from normal human subjects, with and without anti-CD 154-PE in culture medium. Mismatches existed at all alleles at the HLA-HLA-B and HLA-DR loci. These co-cultures between PBL from normal human subjects simulated the conditions of the Pleximmune™ test system. All antibodies/7 AAD were added at saturating concentrations. The results of this study demonstrated that CD8 cell frequencies varied within an acceptable range with addition of anti-CD 154-PE to the remaining antibodies/7 AAD. The coefficient of variation (%CV) ranged from 1.04-5.9%. The results met the sponsor's acceptance criteria.

2)   Lot to lot variation of reagents used in the assay - A lot to lot variation study was conducted using two lots of reagents, and three normal control assays were performed in duplicate. Combinations of all antibodies in previous and new lots were used

for each replicate and %CD154$^+$TcM compared. The results showed variation (%CV) ranging from 0.9-15.3% for the subset measured by respective antibody between duplicate assays. The results met the sponsor's acceptance criteria.

3) Precision testing - Run to run, operator to operator, three instrument/three operator and day to day imprecision studies were conducted using normal blood samples stimulated with a single HLA mismatched stimulator. The assay readout was read as %CD154$^+$TcM, and the assay imprecision was measured in %CV.

- Run to run and between run imprecision studies were conducted at Plexision's laboratory site by a single operator using twenty pairs of HLA-mismatched PBL from normal human subjects. Assays were performed in duplicate in each of two runs that were separated by 60-90 minutes on the same day. The background frequency of %CD154$^+$TcM ranged from mean 0.24-0.3%, and stimulated frequency of %CD154$^+$TcM ranged from mean (SD) 24.1 (10.8) to 25.2 (11.3) in the various runs. For stimulated reaction, the mean %CV (SD) for duplicates within runs and for all replicates in both runs ranged from 5.2% (4.9) to 6.0% (3.1). For the background reaction, mean %CV (SD) are higher, ranging from 38.9% (47.2) to 61.3% (39.3). The results met the sponsor's acceptance criteria.

- Operator to operator imprecision study was conducted at Plexision's laboratory by two operators on the same day using five pairs of HLA-mismatched PBL from normal human subjects. The samples were blinded and each sample was tested by two operators on the same day and the % CV determined for % CD154$^+$TcM in background and stimulated reactions. The variation (%CV) between technicians for each sample ranged from 1.8-8.4%, and mean variation (%CV) between technicians for all five samples ranged was 4.8%. The results met the sponsor's acceptance criteria.

- Three instrument/three operator variation testing was conducted on three independent instruments by three independent operators who could perform the Pleximmune™ test as well as acquire results by flow cytometry. Three operators assayed one of the three aliquots of each of the 21 normal human samples on the same day. A single HLA-mismatched normal human sample was used for the stimulation reaction. Three-operator, three-instrument same-day testing demonstrated mean stimulated frequency of CD154$^+$TcM ranging from 22.8-24.5% with mean %CV of 8.2%, and a mean background frequency of CD154$^+$TcM ranging from 4.0-5.8% with mean %CV of 34.3% for same day testing between operators/instruments. The results met the sponsor's acceptance criteria.

  Day to day variation testing - Samples are expected to arrive at Plexision in a manner that allows for testing on the day of sampling if received before 10AM, or the day after sampling if received after 10AM on day of sampling, or on the day after sampling if shipped overnight. Therefore, a day to day precision study was conducted to demonstrate that samples can be tested with acceptable variation up to 24 hours after retrieval and storage at ambient temperature in Plexision's laboratory or after a 24 hour shipment at ambient temperature. The study included testing of five normal human samples by one operator at one site. Each sample was divided into three aliquots for same day testing, testing after 24 hour storage at ambient temperature in Plexision's laboratory, and testing after overnight shipment at ambient temperature. The frequency of CD154$^+$TcM was read and compared between aliquots. The variation between aliquots for each sample ranged from 0 to 6.67%CV, and %CV of mean %CD154$^+$TcM between three conditions of storage/shipment for five samples was 3.2%. The results met the sponsor's acceptance criteria.

4) Sample storage stability study - A cryopreservation precision study was conducted to demonstrate that the Pleximmune™ test performance is consistent with either fresh or frozen PBL samples. Cell function under the most ideal (fresh stimulator and responder) and the least ideal (cryopreserved stimulator and responder) combination of stimulator and responder cells was compared. Cell function was measured by %CD154$^+$TcM. The frequency of CD154$^+$TcM induced by stimulation with HLA-mismatched PBL was compared in twenty normal human samples tested before and after 30 days of cryopreservation. Fresh stimulator and responder cells were used in samples tested before cryopreservation. Cryopreserved stimulator and responder cells were used in samples tested after 30 day cryopreservation. The results show that the variation in %CD154$^+$TcM measured as mean %CV before and after 30-day cryopreservation was 8.9%. The results met the sponsor's acceptance criteria.

X. SUMMARY OF CLINICAL INFORMATION

The Sponsor performed a clinical validation to determine the safety and probable benefit, sensitivity, specificity, and positive and negative predictive values (PPV, NPV) of Pleximmune™ for predicting rejection.

A total of 122 specimens from 87 individual transplant patients were enrolled in the clinical validation study. Of these, 97 samples consisting of 33 pre-transplant (IRO), 64 post-transplant (30 IRl and 34 IRx) samples from 72 subjects were analyzable because 16 specimens failed to generate signal and 9 specimens had inadequate cell count.

Using the post-transplant rejection-risk cutoff threshold of 1.10, the sensitivity, specificity, PPV and NPV were 84%, 80%, 64% and 92%, respectively (AUC 0.791) when applied to 64 post-transplant samples in the validation study. Using the pre-transplant rejection-risk cutoff threshold of 1.23, the sensitivity, specificity, PPV and NPV were 57%, 89%, 80%, 74%, respectively (AUC 0.842), when applied to 33 IRO samples in the validation study. The results are shown in the table below:

Cohort	AUC	Sensitivity [n] (95% CI)	Specificity [n] (95% CI)	PPV [n] (95% CI)	NPV [n] (95% CI)
IRO set (n=33)	0.842	**57%** [8/14] (30%-81%)	**89%** [17/19] (65% - 98%)	**80%** [8/10] (44% - 96%)	**74%** [17/23] (51%-89%)
IRl+IRx set (n=64)	0.791	**84%** [16/19] (60% - 96%)	**80%** [36/45] (65% - 90%)	**64%** [16/25] (43%-81%)	**92%** [36/39] (78% - 98%)

Gender Bias:

The study population consisted of approximately 60% male and 40% female subjects.

Subgroup analysis of available limited clinical data by gender did not indicate any significant differences in the Pleximmune™ performance, and hence in the safety and probable benefit of the device based on gender.

To address the possibility of gender based differences in the performance of Pleximmune™test, following statement will be included under the 'Warning and Precautions' section of the Pleximmune™ labeling:

"Pleximmune™performance may be affected by gender- and ethnicity-related effects. However, the sample size limitations imposed by the rarity of the clinical condition addressed by the Pleximmune™ test (i.e., solid organ transplantation in pediatric patients) did not allow for a comprehensive evaluation of possible gender- and ethnicity-related effects on the test's performance"

XI.   FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one clinical investigator. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII.   RISK PROBABLE BENEFIT ANALYSIS

Clinical Need for a Predictive Test for Estimation of Risk of Transplant Rejection

In transplantation, under-immunosuppression may lead to rejection with consequent possible graft loss and over-immunosuppression may lead to opportunistic infections, malignancies, and other adverse events. The desired goal in transplantation is to achieve the optimum level of immunosuppression customized to each patient's risk level. Currently no tool exists for risk based customization of immunosuppression, and immunosuppression is managed by clinical judgment based on the type of organ transplanted, baseline immunologic risk level of the patient, and a variety of clinical/laboratory findings.

Biopsy, which is the current gold standard for the diagnosis of rejection, cannot be used as a predictive tool and is an invasive procedure. Biopsies may result in bleeding or perforation (in the case of small bowel) with subsequent requirement for surgical treatment which will add to the existing high morbidity and mortality in the patient population of pediatric recipients of liver and/or small bowel transplants.

A prognostic tool, and especially a non-invasive tool, may help the clinician intervene before an acute rejection develops by implementing a relatively small increase in maintenance immunosuppression compared to the amount of additional immunosuppression required to treat rejection once it occurs. Alternatively, in a patient with a low risk of rejection, unnecessary increase of immunosuppression could be avoided.

A prognostic tool such as the Pleximmune™, which may provide additional information to the clinician about the patient's immunologic risk level, would be valuable in the management of transplant patients. The value of a prognostic tool for rejection risk assessment will be even higher in life sustaining organ transplantations such as liver and /or small bowel (compared for example to kidney transplants) since there is no alternative way of sustaining life (e.g. hemodialysis) if the graft is lost. An effective noninvasive prognostic tool could decrease the requirement for graft biopsies due to timely adjustment of immunosuppression with fewer rejection episodes and graft loses or unnecessary over-immunosuppression with consequent opportunistic infections and malignancies.

Use ofPleximmune™ in Conjunction with other Clinical Information including Biopsy

Transplant physicians generally rely on a wide range of clinical, laboratory and histopathologic data in the differential diagnosis of rejection and when making decisions about the level of immunosuppression for each patient. Although biopsies are considered to be the gold standard for the diagnosis of rejection, a correlation with clinical aspects such as the original disease, current immunosuppression, liver function tests, viral serology, immunology, and radiologic findings must be made in the interpretation of the transplant liver biopsies.[1] Reliance on the biopsy alone or the liver function tests alone without consideration of all the available clinical and laboratory information may be misleading. A systematic review of 15 studies including 1566 liver transplant recipients showed that 32% of the patients had histologic acute cellular rejection (ACR) on protocol biopsy without associated biochemical graft dysfunction; without additional treatment, only 14% of these patients subsequently developed biochemical graft dysfunction.[1]

Similarly in small bowel transplantation it is essential to interpret biopsy findings in the appropriate clinical context including history, clinical symptoms and abnormal laboratory values.[2]

Therefore, it is anticipated that transplant physicians will not solely rely on the Pleximmune™ results for clinical decision making and will use it as an adjunctive tool, similar to the utilization of other diagnostic tools such as biopsy, liver function tests and other laboratory or clinical data consistent with the proposed device label.

The data provided by the Sponsor which mainly reflects the Pittsburg Transplant Center's experience with Pleximmune™ supports the fact that the assay can be safely used in conjunction with other clinical information in the management of pediatric recipients of liver and/or small bowel transplantations.

If used as an adjunctive prognostic tool as recommended in the device label, the risks associated with false positive and false negative results ofPleximmune™ appear to be adequately mitigated.

Assessment of the Probable Benefits ofPleximmune™

The probable benefit ofPleximmune™ is the prediction of the risk of transplant rejection in pediatric recipients of liver and/or small bowel transplantation and the consequent provisional risk-based adjustment of immunosuppression.

According to the intended use of the assay, in case of a "high rejection risk" as determined by the assay results (in conjunction with other clinical and laboratory parameters), the immunosuppression level is either increased or any plan to taper immunosuppression is postponed. Alternatively in case of a "low rejection risk," again as determined by the assay results (in conjunction with other clinical and laboratory parameters), the immunosuppression can be tapered as generally practiced since the goal is to optimize immunosuppression to prevent rejection without over-immunosuppressing the patient.

The probable benefit of "risk based optimization" of immunosuppression in transplant patients is very important due to the known adverse consequences of both under- and over-immunosuppression (see risks below). Currently immunosuppression is managed by clinical judgment based on the type of organ transplanted, baseline immunologic risk level of the patient and a variety of clinical/laboratory findings. A tool for objective method of risk assessment, which is not currently available, with acceptable predictive value would be an important contribution to the management of transplant patients.

Assessment of Risks ofPleximmune™

The possible risks associated with Pleximmune™ are related to blood draws and

inappropriate treatment based on undetected false positive or false negative results.

Risks associated with the blood draws for the assay: Transplant patients require blood draws for a variety of laboratory tests including concentrations of immunosuppressive drugs, biochemistry parameters and blood counts. Blood draws occur daily in the early post-transplant period and become less frequent over time. The risks associated with blood draws such as infection and hematoma are infrequent and may be considered negligible in a patient population already requiring frequent blood draws as part of their standard care.

Risks due to the false positive and false negative results of the assay: A false positive result means that the assay indicates an increased risk of rejection when the risk is actually low. In this situation, the physician may defer tapering of immunosuppression or may increase immunosuppression in an effort to prevent rejection. In this scenario the patient may receive more immunosuppression than is needed, but is considered to be a lower degree of risk than in the case of a false negative result.

A false negative result means that the assay indicates no increased risk of rejection when the risk is actually high. In this situation, the clinician may decide to taper the patient's immunosuppression and precipitate an episode of rejection necessitating treatment with additional immunosuppression in an effort to reverse the rejection. The amount of increased immunosuppression that a patient may receive in order to treat an episode of rejection is much greater than that described above in the case of a false positive result.

The risks associated with under-immunosuppression are acute and chronic rejection which may or may not be responsive to treatment. Ongoing rejection may result in the loss of the graft and/or patient.

The risks of over-immunosuppression include an increased risk of opportunistic infections and malignancies. Risks associated with the use of particular immunosuppressive agents include bone marrow suppression including leukopenia, anemia and thrombocytopenia (proliferation signal inhibitors, such as Thymoglobulin), nephrotoxicity and neurotoxicity (calcineurin inhibitors, such as cyclosporine and tacrolimus), and diabetes (corticosteroids).

The risk of a false positive or a false negative test may be mitigated by the fact that the test is not being used alone; the physician will continue to collect biopsy samples, monitor signs, symptoms, lab tests, etc. to assess the patient's risk of transplant rejection.

Additional Factors in the Assessment of the Probable Benefits and Risks of Pleximmune™

The sponsor states that CMV, EBV and other opportunistic infections may confound test results. Graft versus host disease (GVHD) and ischemia reperfusion injury (in the early post-transplantation period) may also confound the results.

As required by the HDE regulations (21 CFR 814.104), the proposed device label contains the following statement:

"Humanitarian Device. Authorized by Federal Law for use as an aid in the evaluation of the immunological risk for Acute Cellular Rejection (ACR) in children with liver or small bowel transplantation. The effectiveness of this device for this use has not been demonstrated. "

This adjunctive nature of the assay is also stated in the proposed label:

"Pleximmune™ is a qualitative prognostic test intended to be used in patients less than 21 years old with liver or small bowel transplantation. The Pleximmune™ test is an aid in the evaluation of the risk of acute cellular rejection (ACR) and must be used in

conjunction with biopsy, standard clinical assessment and other laboratory information.".

Physicians who are already familiar with the care of transplant recipients will not be likely to solely rely on the Pleximmune™ results to make their immunosuppressive management decisions, but will primarily rely on other clinical and laboratory evaluations in addition to the assay results.

Therefore, if used as an adjunct prognostic tool as recommended in the label, the risks associated with false positive and false negative results of the Pleximmune™ test appear to be adequately mitigated.

Therefore, it is reasonable to conclude that the probable benefit to health from using Pleximmune™ for the target population outweighs the risk of illness or injury, taking into accounts the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII.   PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Clinical Chemistry and Toxicology Devices panel because it was determined that the clinical issues raised by the HDE did not require panel review for the proposed indications.

XIV.   CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Pleximmune™ will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on August 26, 2014.

The final conditions of approval are cited in the approval order.

The applicant's manufacturing facility has been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV.   APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.

XVI.   REFERENCES

[1]Marco Carbone and James Neuberger (2011). Role of Liver Biopsy After Liver Transplantation, Liver Biopsy in Modern Medicine, Dr. Yoshiaki Mizuguchi (Ed.), ISBN: 978-953-307-883-0, InTech, Available from: http://www.intechopen.com/books/liver-biopsy-in-modern-medicine/role-of-liver-biopsy-after-livertransplantation
[2]Remotti H, Subramanian S, Martinez M, Kato T, Magid MS. Small-bowel allograft biopsies in the management of small-intestinal and multi visceral transplant recipients: histopathologic review and clinical correlations. Arch Pathol Lab Med. 2012 Jul;136(7):761-71.