# Pleximmune™

## Humanitarian Device Exemption (HDE) H130004

Pediatric Advisory Committee
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# Presentation Outline

- Brief Overview of In Vitro Diagnostic Devices (IVDs)
- Regulatory History
- Device Description
- Pre-Market Clinical Data
- Literature Review
- Medical Device Reporting (MDR)

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# Humanitarian Device Exemptions (HDEs)

The HDE should show the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices.

# What is an IVD?

"Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae in man. … for use in the collection, preparation, and examination of specimens from the human body." [21 CFR 809.3]

# Premarket Review

All IVDs must establish adequate:

Analytical performance

- How accurately does the test measure the analyte?
- How reliably?

Clinical performance

- How reliably does the test measure the clinical condition?

Labeling

- Adequate instructions for use
- Intended use, directions for use, warnings, limitations, interpretation of results, performance summary

# Test Effectiveness

**Sensitivity**

How likely is the test to detect the presence of a disease in someone with the disease?

**Specificity**

How likely is the test to detect the absence of a disease in someone without the disease?

**Positive Predictive Value (PPV)**

How likely is someone with a positive test result to actually have the disease?

**Negative predictive value (NPV)**

How likely is someone with a negative test result to actually not have the disease?

(PPV and NPV are highly dependent on prevalence)

# Regulatory History

June 12, 2009: Humanitarian Use Device (HUD) Designation

August 25, 2014: HDE Approval for Pleximmune

# Indications for Use (I)

The Pleximmune™ test is:

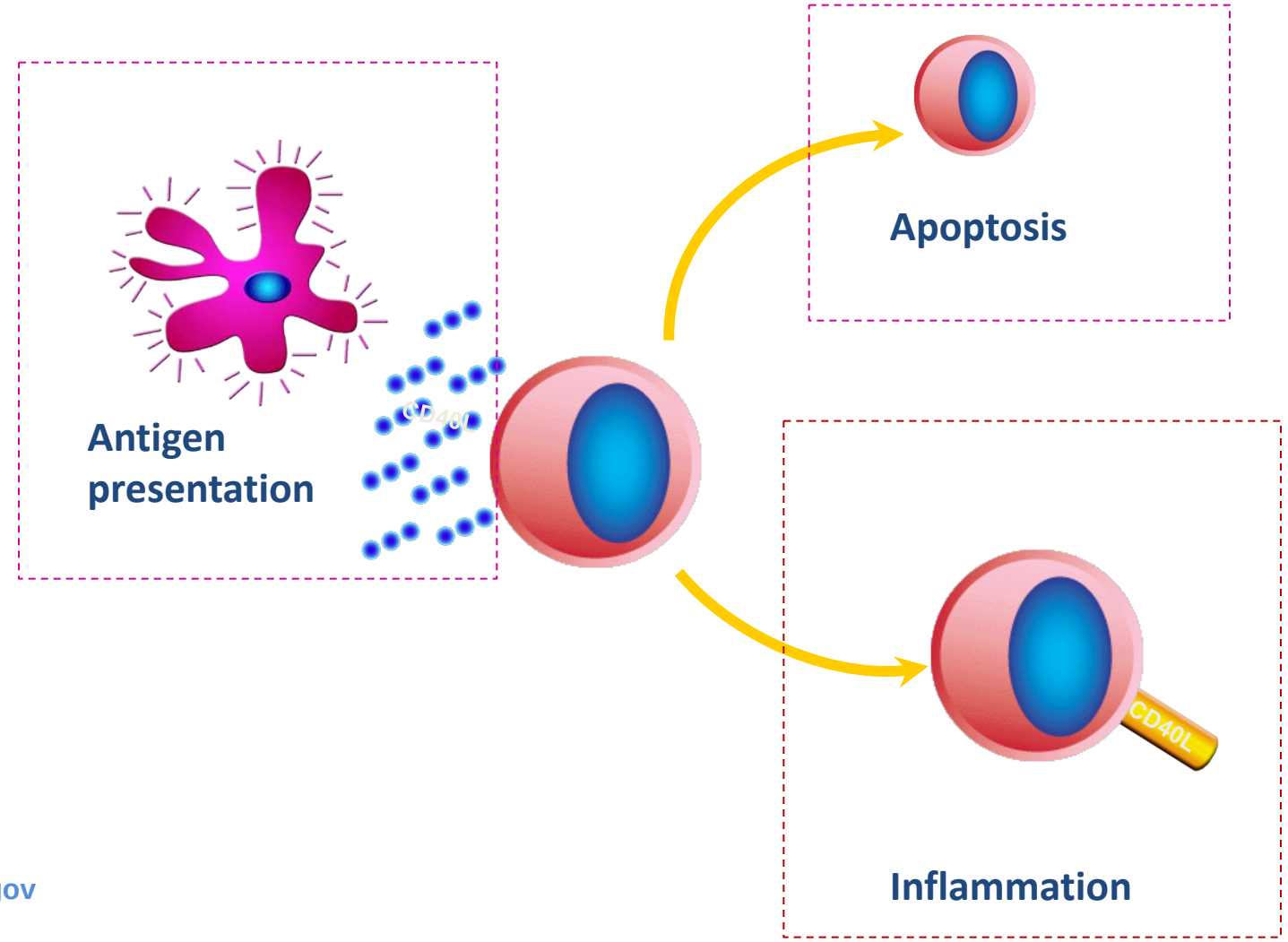
- intended to be performed at a single laboratory to measure the CD154 expression on T-cytotoxic Memory cells (TcM) in patient's peripheral blood lymphocytes.
- is a qualitative prognostic test intended to be used in patients less than 21 years old with liver or small bowel transplantation.
- is an aid 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.

# Indications for Use (II)

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

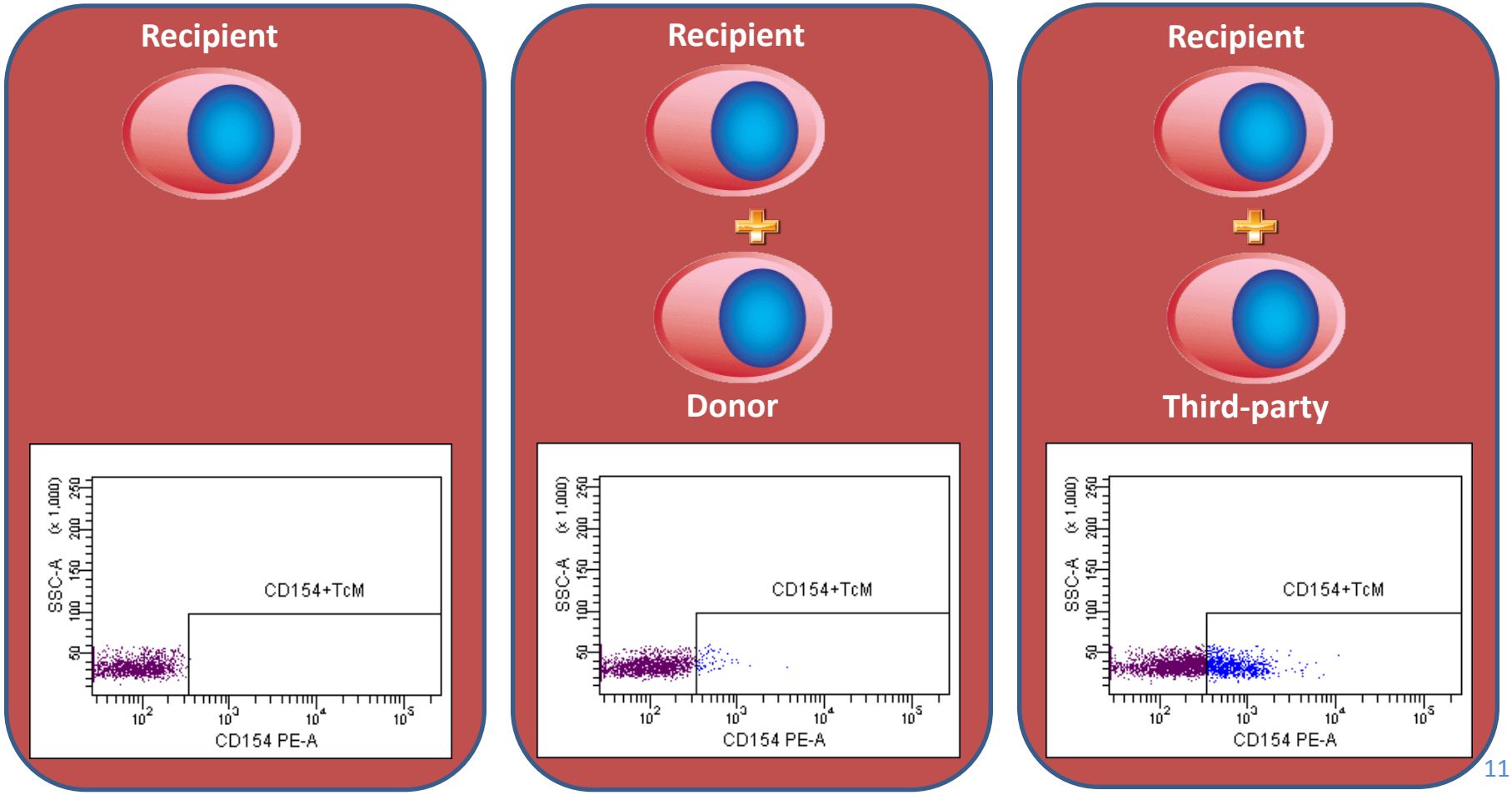
- Pre-transplantation period: the test predicts the risk of transplant rejection within 60 days after transplantation.
- Early and late post-transplantation period: For blood samples collected within 60 days (early) after transplantation and for blood samples collected at 200 or more days (late) after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

# Pleximmune measures the recipient's immune response



# Device Description

## Flow cytometric monitoring of the immune response



# Test interpretation

- 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 acute cellular rejection (ACR).
- Pre-transplant rejection-risk cutoff threshold = 1.23
- Post-transplant rejection-risk cutoff threshold = 1.10

# Clinical validation study

- A total of 122 specimens were evaluated from 87 individual pediatric transplant patients enrolled in the clinical validation study.
- Of these, 97 samples consisting of 33 pediatric pre-transplant (IRO) subjects and 64 post-transplant (30 IR1 and 34 IRx) samples from 72 pediatric subjects were analyzable
- IR1 = samples collected 1-60 days post-transplant
- IRx = samples collected 200 – 6226 days post-transplant

# Study results

| Cohort | AUC | Sensitivity [n] (95% CI) | Specificity [n] (95% CI) | PPV [n] (95% CI) | NPV [n] (95% CI) |
|---|---|---|---|---|---|
| Pre-transplant 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%) |
| Post-transplant 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%) |

# Study results summary for pre-transplant samples

A summary of the results obtained for pre-transplant samples:

- The test predicted correctly the increased risk of ACR 80% of time (8/10 samples analyzed), and gave 20% false positive results (2/10 samples analyzed).
- The test predicted correctly decreased risk of ACR 74% of time (17/23 samples analyzed), and gave 26% false negative results (6/23 samples analyzed).

# Study results summary for post-transplant samples

A summary of the results obtained for post-transplant samples (IR1+IRx combined):

- The test predicted correctly the increased risk of ACR 64% of time (16/25 samples analyzed), and gave 36% false positive results (9/25 samples analyzed).
- The test predicted correctly decreased risk of ACR 92% of time (36/39 samples analyzed), and gave 8% false negative results (3/39 samples analyzed).

# Annual Distribution Number (ADN)

HDE: H130004 – Pleximmune

The annual distribution number (ADN) for this device is 4000 tests total per year.

# Actual Device Distribution

- During the period between June 1, 2015 to May 31, 2016, Plexision, Inc. performed a total of 254 Pleximmune™ tests for a total of 210 patients at Plexision's CLIA-approved laboratory.
- All specimens were post-transplant samples. No pre-transplant specimens were tested.
- Among the 210 patients, there are 106 males and 104 females.
- The average age of these patients is 10.4 years with an age range from 4 months to 20.95 years old.
- 156 had liver transplants, 14 had intestine transplants, and 40 had both liver and intestine transplants.

# Literature Review

**Method**: A search on the internet was performed using the Web of Science, Embase, PubMed, ECRI and Google Scholar sites for "Pleximmune™".

**Results**: There is no literature published from June 1, 2015 – May 31, 2016 includes any safety-related information for the Pleximmune test.

# Medical Device Reporting (MDR)

1. **MAUDE** (**M**anufacturer **A**nd **U**ser Facility **D**evice **E**xperience) and **PRIMO** (**P**harmacovigilance **R**eport **I**ntake and **M**anaged **O**utput) **Databases**

**MDR Search Criteria:**

Brand Name: Pleximmune

Product Code: PHK, Test, Cell mediated immune response, liver and small bowel transplant/transplantation

Date range for review: June 1, 2015 to May 31, 2016

**Search Result: 0 MDRs**

# Medical Device Reporting (MDR)

2. **Reported postmarket issues shared by Plexision**

   **Result:** No adverse events or complaints reported to Plexision by patients or physicians from June 1, 2015 – May 31, 2016.

# FDA Conclusions

- From June 1, 2015 – May 31, 2016, Plexision, Inc. performed a total of 254 Pleximmune™ tests for a total of 210 patients at Plexision's CLIA-approved laboratory.
- Our review of the published literature and MDRs since the time of approval has not identified any new or unexpected risks for the pediatric population when compared to the premarket data.
- FDA concludes that the benefit/risk profile of the Pleximmune for its Indication for Use continues to support the HDE for which the exemption was granted.

# FDA Recommendations and Question to the PAC

- FDA recommends continued surveillance and will report the following to the PAC in 2017:
  - Annual distribution number
  - Literature review
  - MDR review

**Question: Does the Committee agree with FDA's conclusions and recommendations?**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