Association of Medical Diagnostics Manufacturers

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Recommendations for Premarket Notification Submissions for Nucleic Acid-Based HLA Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation

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Products Regulated by DRB

- Blood Grouping Reagents (BGR)
- Reagent Red Blood Cells (RRBC)
- Anti-Human Globulin (AHG)
- Human Leukocyte Antigen(HLA), Human Neutrophil Antigen (HNA), Human Platelet Antigen and Antibody test kits (HPA)
- Red Blood Cell Genotyping Test Systems
- Hemoglobin and Hematocrit measuring devices
- Blood warming and thawing devices
- Blood Establishment Computer Software (BECS)
- Software contained in medical devices (instrument operation and interpretative software)

HLA Guidance

- "Recommendations for Premarket Notification Submissions (510(k)) for Nucleic Acid-Based HLA Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation – July 2015"
  - Draft guidance – November 2013 (78 69693, November 20, 2013)
  - Changes made to address public comments
  - Final Guidance – July 2015 (80 FR 46032, August 3, 2015)

HLA Background

- Most cells of the body bear human leukocyte antigens
- Role of the HLA system is to allow the human immune system to distinguish the body's own blood, organs, and tissues from foreign substances
- Clinical complications, such as graft rejection or graft-versus-host disease, may occur if the immune system recognizes transplanted cells, tissues, or organs as foreign

HLA Background (2)

- There are significant and unique challenges to develop and design studies that validate the accuracy of these HLA kits because HLA is one of the most polymorphic systems found in humans
- FDA's expectation for analytical and clinical studies focus on identifying potential risks to patients if the kits fail to perform as expected
- Performance of the kits is critical for ensuring precise and successful matching between donors and recipients

Intended Use

- We recommend the following statement be included in the intended use statement for HLA test kits:

"To be used to determine {*indicate HLA locus or loci*}, to aid in transfusion and transplantation donor and recipient matching."

Please consult CBER for specific guidance regarding HLA test kits that have a different intended use than the one mentioned above!

Device Design

- Describe the elements and provide applicable studies for the design of your HLA test kits. Examples:
  - Test platform (e.g. flow cytometry, instrumentation for multiplex test systems)
  - Methods used for attaching capture or probe material to a solid surface
  - Assay components
  - Sample preparation and type of sample
  - Controls
  - Stability

Performance Studies

Performance studies should demonstrate with a high level of confidence that the test kit performs within established specifications

- Accuracy Studies
- Precision Studies (Reproducibility and Repeatability)
- Clinical Comparison Studies

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Accuracy Studies

Should address all probes and/or primers included in the test kit, however, due to the large number of polymorphisms it may be impractical to individually measure the accuracy of each polymorphism.

Accuracy Studies (2)

- Samples - use nationally or internationally recognized well-characterized DNA samples that represent the most prevalent HLA alleles
- Sample Size – Use a sufficient number to demonstrate that the one-sided 95% lower confidence limit of overall agreement exceeds 0.95 for each locus
- Concordant if one pair of the reported alleles is the same as the typing results of the well-characterized DNA sample

Precision Studies

Precision studies should capture possible sources of variation including within run, run-to-run, day-to-day, operator-to-operator, instrument-to-instrument, site-to-site and lot-to-lot variation.

You may choose to combine the repeatability study and the reproducibility study into a single study.

Precision Studies (2)

Recommended Study Design:

- Three study sites, at least two external sites
- Two operators at each site performing two runs per day
- Run sample in duplicate (for repeatability), on five nonconsecutive days over 20 days using one lot of the test kit
- Lot-to-lot studies may be conducted in-house
- Use the instruments for which you are seeking clearance
- Operator training is an important consideration – training program for the use of the test kit should be the same for the end-users once the product is marketed

Precision Studies (3)

- Precision Panel:
  - Should be blinded and should consist of well-characterized DNA samples representing significant diversity of the alleles represented in the test kit
  - Use lowest DNA concentration outlined in the test kit instructions for use
  - Use the same panel for all precision studies

Precision Studies (4)

- Concordance Description:
  - Concordant if one pair of the reported alleles is the same as the typing results of the well-characterized DNA sample
  - Uncertainty in the typing assignment (list of the ambiguities) should be compared between operators, sites, runs, repeats, and days
  - In general, complete agreement should be expected between all variables and the panel sample results. Provide justification if there is disagreement

Clinical Comparison Studies

Clinical comparison studies evaluate the proposed device's performance in a clinical setting compared to a device legally marketed in the U.S. or to results obtained by bi-directional sequencing

Clinical Comparison Studies (2)

We recommend the following study design:

- Use three sites, at least two external site of which at least one is in the U.S. The sites should cover different geographic regions and include a representation of major ethnic groups found in the U.S. in order to increase the probability of covering the many genotype variants found in the U.S. population
- Sample size – sufficient number of samples to establish that the one-sided 95% lower confidence limit for the overall agreement with the comparison device exceeds 0.95 for each HLA locus

Clinical Comparison Studies (3)

- Discordant results should be investigated, however, the statistical analysis should be performed on the original results
- Sample types – Use blinded random samples
- Concordance – Results are concordant with the results from the comparison device if at least one pair of alleles at a specific locus is the same between the two devices

Software

FDA guidance documents:

- "General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 11, 2002"

- "Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005"

Validation of Instrumentation

- Include instrument validation data in the 510(k)
- If the instrument is submitted in a separate 510(k) submission (stand-alone instrument) the HLA test kit and the instrument are reviewed at the same time

Labeling

- Subject to labeling requirements under 21 CFR Part 809 (In Vitro Diagnostic Products for Human Use)

- Should also include the following statement in your labeling:

"Should not be used as the sole basis for making a clinical decision."

Changes to the Device

- Section 807.81(a)(3) requires a new 510(k) for any change or modification that could significantly affect either the safety or effectiveness of a device
- See FDA Guidance: "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997"
- For the addition of a new test kit locus, submit a traditional 510(k)

Summary

- The HLA guidance should be used as an aid to determine the types of studies that should be included in your premarket notification (510(k)) submission
- The HLA guidance is specific to nucleic acid-based HLA test kits used for the matching of donors and recipients in transfusion and transplantation
- See FDA Guidance: "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff, February 18, 2014"