AMERICAN SOCIETY FOR HISTOCOMPATIBILITY & IMMUNOGENETICS

15000 Commerce Parkway • Suite C • Mt. Laurel, NJ 08054
Phone: 856.638.0428 • Fax: 856.439.0525 • Web site: www.ashi-hla.org • E-mail: info@ashi-hla.org

Monday, February 3, 2014

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-1358 - **Draft Guidance for Industry: Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Transfusion and Transplantation**

To whom it may concern:

The American Society for Histocompatibility and Immunogenetics (ASHI) is an international society of professionals dedicated to advancing the science, education, and application of immunogenetics and transplant immunology. The purpose of this letter is to express our concerns about one of the proposed guidelines that will significantly delay the use of newly available HLA allele information in transplant decision making.

We support the proposed guideline for the intent of producing reliable and accurate HLA typing results in newly submitted Traditional 510(k) applications. However, section G of the proposed guideline - Additional Consideration: changes to the device (page 9 and 10) - raises concerns about the ability of manufacturers to provide critical reagent upgrades and/or new versions of kits in a timely manner, so that HLA laboratories can provide their transplant physicians with the most current and accurate molecular typing results.

Manufacturers regularly update molecular HLA typing kits based on:

i) additions or changes in the WHO nomenclature listing of recognized HLA alleles
ii) new typing ambiguities resulting from the WHO nomenclature updates (typing ambiguities occur when multiple alleles share key sequences; manufacturers aim to reduce typing ambiguities by adding or modifying primers and/or probes),
iii) feedback from the users on the performance of the probes and primers, and
iv) new ambiguities found in specific populations.

For these updates, the manufacturers follow the FDA published guideline "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" (Ref 7 on Page 11) in making the determination of whether to resubmit a 510(k) with FDA. Since there are no significant changes for these updates per the guidelines, they don't usually resubmit a 510(k) to the FDA. Based on the new proposed guideline, they would have to file a Special 510(k), which includes all the steps needed for a Traditional 510(k) except for outside clinical testing.

Currently, when producing a new kit for an already FDA cleared family of products (e.g. to add new alleles) using the exact same technology and manufacturing processes, the FDA guideline "Replacement Reagent and Instrument Family Policy" (link) is followed without having to resubmit a 510(k) with the FDA. All required verification and validation of these kits is completed and documented internally.

Under the new proposed guideline, however, a new Traditional 510(k) would have to be submitted. It is estimated that these new submission requirements will delay the availability of new lots and/or kits from six (6) months to one (1) year. By the time the new lots or kits are available, they may already be outdated. The additional cost associated with the preparation for a 510(k) submission will ultimately increase the cost of health care as both the manufacturers and laboratories will have to recover the costs associated with the 510(k) submissions. The only alternative to prevent manufacturing delays and substantial cost increases would be to stop or greatly reduce the updates of molecular typing kits. **This possibility could have dire consequences if critical HLA mismatches between donors and recipients are not recognized**.

The ASHI accreditation program is deemed by CMS for CLIA. Thus, ASHI-accredited HLA laboratories are strictly regulated to ensure quality of the tests performed and are required to remain current with the continuously evolving HLA molecular information. In performing high-complexity testing, HLA laboratories are required by ASHI standards to test each new shipment and lot of reagents for precision and accuracy. Laboratories also must subscribe to proficiency testing for each method. This proficiency testing accomplishes several of the FDA suggested quality control requirements in these guidelines, e.g.:

> "The study should use nationally or internationally recognized well-characterized DNA samples that represent the most prevalent HLA alleles, and, if possible, also include rare alleles."
>
> "The repeatability estimate can be captured using data from an internal study or by combining results collected at multiple sites in a reproducibility study. A reproducibility study should be performed at multiple sites using multiple operators with skill levels similar to those of your intended users."

The additional requirements mentioned above will duplicate quality control testing already required by ASHI and will hamper our ability to test patient samples using the most up-to-date reagents.

We trust that the FDA will reconsider section G of the proposed guideline and allow manufacturers of these reagents to continue following the FDA guideline "Replacement Reagent and Instrument Family Policy without having to resubmit a 510(k) with the FDA when producing a new kit for an already FDA cleared family of products." Thank you for taking the time to consider our response.

Sincerely,

Amy B. Hahn, PhD, D(ABHI)
National Clinical Affairs Committee
Senior Co-Chair

John A. Gerlach, PhD, D(ABHI)
ASHI President