COLLEGE of AMERICAN PATHOLOGISTS

April 21, 2022

Robert M. Califf MD, MACC
FDA Commissioner
US Food and Drug Administration
10903 New Hampshire Ave, Silver Spring, MD 20993

Re: Medical Devices; Immunology and Microbiology Devices; Classification of Human Leukocyte, Neutrophil and Platelet Antigen and Antibody Tests (FDA-2021-N-0851)

Dear Dr. Califf,

The College of American Pathologists (CAP) appreciates the opportunity to provide comments to the Food and Drug Administration (FDA) on the proposed rule to classify Human Leukocyte Antigen (HLA), Human Platelet Antigen (HPA), and Human Neutrophil Antigen (HNA) devices, as a generic type of device, into class II (special controls). As the world's largest organization of Board-certified pathologists and the leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating for excellence in the practice of pathology and laboratory medicine worldwide. The CAP shares the FDA's goal of ensuring safe testing for patient care by educating our CAP members and the histocompatibility and identity testing communities on best practices and regulatory guidance for new and emerging issues, practices, and technologies.

The reclassification of HLA, HPA, and NHA devices into class II with special controls is proposed as a necessary measure to prevent risk from medical device malfunction in the transplantation and transfusion setting. As evidence, the proposed rule cites 37 class I, 19 class II, and 18 class III adverse events related to device failure in a review period prior to May 1, 2017. While it is worthwhile to attempt to limit any risk for device-related adverse events, the proposal does not acknowledge the total number of potential events in the reviewed time period, which would provide important context for assessing the risk of these diagnostics as currently existing. While the total numbers of tests potentially affected by these changes are difficult to ascertain, the 74 reported diagnostic device-related are in the context of > 9,000 allogeneic stem cell transplants, > 40,000 solid organ transplants, and > 17 million blood product transfusions each year in the United States. Furthermore, it is difficult to evaluate how the proposed classification change would prevent these device failures, as the specifics for the adverse events was not fully described. This is particularly relevant in the realm of HLA diagnostics, as technology in

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this field had moved rapidly, and information prior to 2017 is likely to not recognize advances in the field such as the widespread implementation of next-generation DNA sequencing for HLA genotyping. We propose that this information is essential in attempting to consider the costs and benefits of this reclassification.

The FDA is proposing to classify HLA, HPA, and HNA devices, a generic type of device, into class II with special controls. Also, the FDA is also giving notice that they do not intend to exempt these device types from premarket notification requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The CAP is concerned with the FDA's proposal to reclassify Human Leukocyte Antigen (HLA), Human Platelet Antigen (HPA), and Human Neutrophil Antigen (HNA) devices from general controls into Class II with special controls. While we recognize the HLA, HPA and HNA testing market is expected to significantly grow due to an increasing number of organ transplantation, this reclassification may have an impact on the availability of HLA, HPA, and HNA clinical testing because of the limited number of methods available. Currently, most high-resolution HLA typing are done by next-generation sequencing (NGS), which are research use only (RUO) kits. Given the market size, it is unclear if manufacturers of these kits have the resources to invest in 510K clearance. There is also concern about testing availability while the community awaits these clearances.

From our experiences, the one manufacturer of an FDA cleared Sanger sequencing platform provides outdated information because this manufacturer is not able to update their software without obtaining FDA clearance for these software updates as the new HLA nomenclature becomes available. The IPD-IMGT/HLA Database for sequences of human major histocompatibility complex (MHC) and the official sequences named by the WHO Nomenclature Committee for Factors of the HLA System provide new HLA updates every six months[1]. The IPD-IMGT/HLA Database has provided a repository for information regarding polymorphism in genes of the immune system since 1998 when the first release of the database had 964 allelic variants. Currently, the IPD-IMGT/HLA Database now contains over 24,009 distinct allele variants.

We understand the purpose of developing such guidance for the manufacturers of these tests is to ensure safe and effective HLA, HPA, and HNA testing. As proposed, this rule will likely negatively influence the use and availability of these devices and possibly raise questions of medical liability.

In conclusion, the CAP recommends that HLA, HPA, and HNA platforms NOT be placed into the Class II designation.

We look forward to discussing this issue with you.

[1] Robinson J, Halliwell JA, Hayhurst JH, Flicek P, Parham P, Marsh SGE The IPD and IMGT/HLA database: allele variant databases *Nucleic Acids Research* (2015) **43**:D423-431

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Sincerely,

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