November 10, 2016

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave., Bldg. 1, Rm. 2217
Silver Spring, MD 20993

Dear Commissioner Califf:

The Pan American Society for Clinical Virology (PASCV) and American Society for Microbiology (ASM) are worldwide organizations with expertise in clinical and diagnostic virology. Our organizations appreciate the Food and Drug Administration's (FDA) commitment to protecting patients, and we share this common goal. PASCV and ASM have closely followed the agency's discussions regarding classification of quantitative nucleic acid amplification tests (qNAATs) for the measurement of virus DNA levels in transplant-associated infections, specifically the possible reclassification of quantitative cytomegalovirus (CMV) qNAAT devices from Class III to II, and the initial classification of qNAAT devices for Epstein-Barr virus (EBV), BK virus, JC virus, human herpes virus 6 (HHV-6), and adenovirus as Class II devices.

As has been well documented by over two decades of clinical use and publication in the peer-reviewed literature, measurement of viral DNA levels in peripheral blood is essential for the diagnosis and management of viral infections described above. The use of these tests is recommended in numerous practice guidelines, highlighting their importance and reliable performance in the routine clinical care of transplant recipients. Both PASCV and ASM recognize the integral role these assays play in patient care and the necessity for accurate and reliable qNAATs. Therefore, we would ask that the FDA consider qNAATs for CMV, EBV, BK virus, JC virus, HHV-6 and adenovirus as Class II devices for the following reasons:

1. ***Historically, qNAATs have been used safely and effectively, and provide reliable results.***

   qNAATs have been used for over two decades to diagnose and monitor infections in transplant recipients and immunocompromised hosts. Their performance has been thoroughly studied, with >1,000 peer-reviewed publications on their use and interpretation. An important indicator of the quality and reliability of viral load assays is

their performance on proficiency testing surveys, such as those distributed by the College of American Pathologists (CAP). The most recent CAP Viral Load survey (VLS-B 2016) completed by participating laboratories in June 2016 demonstrates the robustness of these tests, with greater than 98% of laboratories obtaining the expected results for most panel members (Table, Appendix).

2. ***Class II device designation of qNAATs for transplant-associated viral infections will increase their accessibility, allowing for the achievement of further gains in result standardization.***

   Due to the high cost and significant regulatory requirements associated with Pre-Market Approval (PMA) submissions, many device manufacturers opt to defer the development and commercialization of certain products, including viral qNAATs. The incidence of disease caused by EBV, HHV-6, JC virus and adenovirus in transplant patients and immunocompromised hosts may not justify the resources required to fulfill a PMA submission. Therefore, clinical laboratories must use laboratory developed tests (LDTs) or modified commercial assays to provide this essential diagnostic service. Although we are confident that this approach yields accurate and reliable test results, we would advocate for increased qNAAT commercialization, in an effort to enhance standardization, which has improved markedly for some viral qNAATs with the availability of international reference preparations for use in calibration. We are confident that establishing qNAATs as Class II devices would encourage manufacturers to develop these products, which ultimately, would provide the FDA an opportunity to play an important role in the review and approval of a large group of diagnostic test devices.

We appreciate the FDA's continued commitment to patient safety and the opportunity to comment on this important topic. Thank you for taking the time to review our request. As you consider this matter, please contact us if additional information or clarification would be helpful.

Sincerely,

Alexandra Valsamakis, M.D., Ph.D.

President, Pan American Society for Clinical Virology

Susan E. Sharp, Ph.D., D(ABMM)

President, American Society for Microbiology

Appendix

Table - Summary of the CAP VLS-B 2016 Viral Load Survey

Analyte	Sample ID (Expected Result)	No. Participants	Concordance with Expected Result (%)	Mean Viral Load[a]	S.D.
BK virus	VLS2-11 (Positive)	175	**99.4**	5.75	0.54
	VLS2-12 (Negative)	176	**98.9**	NA	NA
CMV	VLS2-13 (Negative)	262	**99.2**	NA	NA
	VLS2-14 (Positive)	256	**99.6**	3.73 (IU/mL)	0.44
EBV	VLS2-15 (Positive)[b]	173	**74.0**	2.39 (IU/mL)	0.66
	VLS2-16 (Negative)	174	**99.4**	3.63 (IU/mL)	0.39
Adenovirus	VLS2-17 (Positive)	43	**100.0**	6.08	1.13
	VLS2-18 (Negative)	42	**100.0**	NA	NA
HHV-6	VLS2-19 (Positive)	35	**100.0**	4.17	0.73
	VLS2-20 (Positive)	35	**100.0**	4.85	0.66

[a] Results are given in copies/mL unless indicated in parentheses

[b] This sample contained analyte that was at or below the limit of detection of the assay used by 26% of participants