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December 4, 2023

Jeffrey Shuren, M.D., J.D.
Director, Center for Devices and Radiological Health
U.S. Department of Health and Human Services
Food and Drug Administration

Re: Docket No. FDA-2023-N-2177 for "Medical Devices; Laboratory Developed Tests"

Dear Dr. Shuren,

The International Clinical Cytometry Society (ICCS) appreciates the opportunity to comment on the above-referenced proposed rule published in the Federal Register, Vol. 88, No. 190 on Tuesday, October 3, 2023. The ICCS is a non-profit professional organization that promotes the highest standards for the clinical applications of flow cytometry throughout the world so that patients have access to high-quality flow cytometry testing critical for diagnosis and monitoring hematologic malignancies and the immune system (http://www.cytometry.org/). It is the largest organization of its kind, and membership consists of practicing physicians, scientists, medical technologists, manufacturers of flow cytometry reagents/instruments and related medical devices, and other laboratory personnel. ICCS develops practice guidance and provides educational resources such as open access e-learning materials and practical small group, hands-on courses held throughout the world.

We look forward to ongoing engagement with the FDA regarding the proposed policy on laboratory developed tests (LDTs) and appreciate the FDA's request for comments on how it will impact patient care. We as a society take validation of LDTs in flow cytometry very seriously, as evidenced by our involvement in many published guidance documents in which we have participated (Validation of Cell-based Fluorescence Assays: Practice Guidelines from the ICSH and ICCS, Cytometry B Clin Cytom 2013 doi: 10.1002/cyto.b.21103, doi: 10.1002/cyto.b.21104, doi: 10.1002/cyto.b.21105, doi: 10.1002/cyto.b.21106, doi: 10.1002/cyto.b.21107, doi: 10.1002/cyto.b.21108). These prior guidances served as a basis for the Clinical Laboratory and Standards Institute (CLSI) document, *Validation of Assays Performed by Flow Cytometry*, 1st ed. [CLSI guideline H62 (ISBN 978-1-68440-128-4), USA 2021], which was created with both ICCS and FDA membership on the Document Development Committee (DDC); we hope that the FDA will endorse the approach articulated in this CLSI document. However, the society's biggest concern, and focus of these comments, is how patients being evaluated for hematologic malignancies will be affected by this ruling due to an anticipated decrease in access to rapid, comprehensive diagnostic flow cytometry leukemia and lymphoma immunophenotyping (i.e. "*flow cytometry L&L tests*"). We

are aware that other professional societies and stakeholders are submitting comments about the impact of the rule on pediatric patients and patients with rare diseases, including immune disorders evaluated by flow cytometry, for which commercial tests are neither available nor likely to be developed because of low-volume; we share the concerns expressed by those other stakeholders.

To substantiate our concern, we would first like to highlight the role of diagnostic flow cytometry L&L tests in patient care. A patient seeking medical attention for a hematologic malignancy is very likely to present with a life-threatening disease such as an acute leukemia (e.g. acute promyelocytic leukemia) with potential complications of tumor stasis, hemorrhage and life threatening infection (Dohner H. Blood 2022;140:1345 doi: 10.1182/blood.2022016867; Stahl M. Leuk Lymphoma 2019:60:3107 doi: 10.1080/10428194.2019.1613540; Infante J. Ann Hematol 2023;102:3031 doi: 10.1007/s00277-023-05422-z) or a high-grade lymphoma (e.g. Burkitt lymphoma) with complications such as tumor lysis syndrome and multiorgan failure (Goldman S. Best Pract Res Clin Haematol 2023;36:101463 doi: 10.1016/j.beha.2023.101463). Of the 140 hematolymphoid neoplasms defined in the most recent WHO Classification of Haematolymphoid Tumors, 5th ed. (doi: 10.1038/s41375-022-01613-1, doi: 10.1038/s41375-022-01620-2), nearly 50% of the diagnostic entities, occurring in both children and adults, are aggressive and require urgent treatment. Seamless and time-conscious coordination of the morphologic review, immunophenotypic characterization by flow cytometry, and ordering of appropriate genetic/molecular testing in large part based on flow cytometry results is essential in initial patient care to ensure that physicians can provide the most appropriate therapy as quickly as possible. For patients who are stable and desire life-extending/saving therapy, it is ideal to transfer them to a tertiary care cancer hospital with the infrastructure for definitive diagnosis and treatment of these complex groups of malignancies (Glenc EE. Oncol Ther 2023;11:145 doi: 10.1007/s40487-023-00229-4; Bhatt VR. Am J Hematol 2017;92:764 doi: 10.1002/ajh.24767; Ritter AJ. Leuk Lymphoma 2019;60:1656 doi: 10.1080/10428194.2018.1546855; Huntington SF. Cancer 2018;124:4211 doi: 101.1002/cncr.31688).

Based on the above paragraph, we hope we have made it clear that patients with hematological malignancies should have rapid access to comprehensive diagnostic flow cytometry L&L tests. However, the proposed phaseout for the general enforcement discretion approach to LDTs, as it is now, will disrupt the availability of rapid results for these tests. The vast majority of diagnostic flow cytometry L&L tests are LDTs. We are concerned that these diagnostic flow cytometry L&L LDTs may be considered at least moderate clinical risk assays and alarmed that, according to the proposed rule, submission of validation documentation may be required for 510(k)/De Novo/Pre-Market Approval by the FDA (or its designees) for (1) all existing, (2) all newly developed and (3) all modifications to flow cytometry L&L LDTs. In contrast to industry, clinical laboratories have many fewer individuals knowledgeable of the regulatory submission process and such staff will be difficult to find and hire. Although front line laboratory staff are unlikely to be primarily involved with managing the required documents for FDA submissions, they will be needed to coordinate with the regulatory specialists and inevitably pulled away from their current work. The difficulty of hiring specialized laboratory personnel and the time constraints impacting this workforce is highlighted by two recent ICCS surveys. According to a recent ICCS Cost of Labor Survey (May 2023), 88% of flow cytometry laboratory (i.e. flow lab) respondents indicated that recruitment for flow cytometry technologists is either "difficult" or "very difficult." Furthermore, in a separate ICCS Workload Survey (January 2023), 60% of flow lab respondents stated that "staff number" and 78% stated that "lack of staff or time dedicated for new assay development" were the major barriers for test development when considering these and all other barriers including staff experience, specimen types/numbers and financial resources (manuscript in preparation). In addition, please realize that there are a minimum of 400 clinical flow labs in the U.S. that would likely need to submit their validation documentation to the FDA for approval, based on the 548 laboratories (>75% from the U.S.) subscribed in 2017 to the College of American Pathologists (CAP) FL3 Survey for "characterization of leukemia/lymphoma" (Hupp MM. Arch Pathol Lab Med 2021;145:336 doi: 10.5858/arpa.2019-0493-CP).

Although we are unable at this time to say with certainty how many existing diagnostic flow cytometry L&L LDTs would require FDA submissions, a snapshot based on 13 clinical flow labs in the U.S. associated with ICCS Leadership Council and ICCS Advocacy Committee members (mostly tertiary care cancer centers) reveals a median of 20 unique laboratory-validated marker sets (i.e. "tubes" of markers) with the 25th-75th percentile spanning 14-25 tubes. Even if the median number were closer to 10 diagnostic flow cytometry L&L LDTs per lab, based on a larger lab survey and better understanding of how the proposed rule would be applied, the process of

FDA submissions for 4000 existing diagnostic flow cytometry L&L LDTs along with all such newly developed and modified LDTs would be insurmountable for clinical flow labs based on the proposed phaseout requirements. With requirements of the proposed rule as it is, some laboratories will permanently cease offering diagnostic flow cytometry L&L tests due to the inability to hire the additional workforce needed to meet the requirements. Other laboratories will work toward managing the new requirements but will fall short and also end up sending out testing. Sending out flow cytometry testing will delay initiation of definitive treatment for patients with hematologic malignancies. Importantly, the barrier "lack of staff time" in our surveys was specifically associated with labs that do higher numbers of flow cytometry L&L tests, including tertiary care cancer hospitals where patients with aggressive, life-threatening hematologic malignancies are referred for definitive diagnosis and treatment.

Finally, it is imperative to acknowledge that there is no evidence that diagnostic flow cytometry L&L LDTs are unsafe. The case reports that the FDA gave as examples of LDTs that raise public health concerns (FDA-2023-N2177-0076) relate to LDTs in early cancer or cancer diagnosis detected by proteomics and genetics, LDTs in cancer risk assessment detected by proteomics and genetics, LDTs in cancer prognosis by genetics, LDTs to inform treatment eligibility or treatment options by genetics, and LDTs to quantify minimal residual disease or changes in tumor burden. None of the examples relate to concerns about diagnostic flow cytometry L&L LDTs. Importantly, although flow cytometry L&L LDTs are a crucial contribution for arriving at a specific diagnosis of hematologic malignancy, any risk of an incorrect result associated with these tests is low because (1) specific diagnoses are made in conjunction with the clinical evaluation of the patient, the morphologic evaluation including immunohistochemistry and cytochemistry, and genetic evaluation of patient tissues, and (2) flow cytometry panels are comprehensive and built to include redundancy with multiple markers of each potential lineage.

We therefore request that the FDA consider and comment on applying further enforcement discretion and waive the requirement for some or all QS requirements and premarket review for all diagnostic flow cytometry L&L LDTs when they are designed, validated, and used in a single laboratory certified under CLIA that meets requirements to perform high-complexity testing. In summary, the request is based on (1) the role of such testing in patient healthcare, including urgent life-saving situations for patients with hematologic malignancies (discussed in detail above), (2) the inevitable degradation of patient access to such testing under the proposed rule as is, (3) consideration that flow cytometry L&L LDTs are similar to immunohistochemistry tests (i.e. "1976-Type LDTs") because flow cytometry too relies on manual interpretation of visual patterns by trained experts, albeit in a different medium, and (4) the lack of any evidence that diagnostic flow cytometry L&L LDTs are unsafe. *However, the ICCS does support the FDA's plan to require listing of LDTs by year 2. We agree that there is a lack of transparency about what LDTs are offered where and that providers, patients and even other laboratories can benefit from such information.*

Should the FDA not agree to continue enforcement discretion for all diagnostic flow cytometry L&L LDTs, then we ask the FDA to consider and comment on applying enforcement discretion (i.e. grandfathering) with respect to premarket review and some or all QS requirements for all existing diagnostic flow cytometry L&L LDTs being offered as of the date of issuance of this proposed rule. As noted, these tests are an integral part of the workup of patients with leukemia and lymphoma and, as employed as an adjunct to diagnosis, have performed well. The risk that labs will choose to stop offering these tests, thereby compromising access to rapid diagnosis that allows very sick patients to be treated appropriately far outweighs the risk of issuing an incorrect result, especially given the lack of known significant safety concerns for these LDTs. This approach would at least permit clinical flow labs and the FDA to focus on premarket review and QS requirements for new tests and modified tests.

We also ask the FDA to consider and comment on a longer phaseout period for all diagnostic flow cytometry L&L tests. Clinical laboratories in general have little experience dealing with the FDA, and submissions for L&L LDTs are likely to be complex. Thus, labs will need guidance in this process. This is especially true for leukemia and lymphoma phenotyping because it can be challenging to adapt qualitative cell-

based assays to the standard metrics that the FDA typically requires for quantitative, or quasi-quantitative submissions (thus, our strong interest in having the FDA endorse the CLSI H62 guidelines). We therefore request that rather than having the 3 ½ to 4 year phaseout for premarket submission be measured from the time of the final rule, but rather from the time of issuance of final guidance documents. The work for labs is likely to be considerable and, as noted above, developing the infrastructure needed to do submissions will be a challenge. It is neither in the laboratories' nor the FDA's interest to have submissions rejected because initial ones were prepared before labs were clear on what was needed or before they were adequately staffed to do high quality submissions.

We thank you for the opportunity to provide constructive comments on the proposed LDT rule for "Medical Devices; Laboratory Developed Tests." The ICCS has a wealth of experience and expertise related to clinical flow cytometry. We look forward to working together with the FDA on future versions of this proposed rule or other related regulation or legislation pertaining to LDTs. Please do not hesitate to contact any of us for clarification or assistance regarding this letter.

Sincerely,

SA Wang, MD 12/4/2023

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