



December 1, 2023

Robert M. Califf
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Proposed Rule: Medical Devices; Laboratory Developed Tests (Docket No. FDA-2023-N-2177)

Dear Commissioner Califf,

The Association for the Advancement of Blood & Biotherapies (AABB) appreciates the opportunity to provide comments in response to the Food and Drug Administration's proposed rule entitled "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177).

AABB is an international, not-for-profit association representing institutions and individuals involved in transfusion medicine and biotherapies. The association is committed to "improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide." AABB works toward this vision by developing and delivering standards, accreditation, and educational programs that optimize patient and donor care and safety. AABB individual membership includes physicians, nurses, scientists, researchers, administrators, medical laboratory scientists and technologists, and other health care providers.

Executive Summary

AABB appreciates FDA's commitment to protecting public health and concern regarding certain laboratory developed tests (LDTs). We commend FDA for acknowledging the lifesaving, unique nature of tests required to ensure safe, compatible blood transfusions as well as tests that ensure the safety of biotherapies, such as human cells, tissues, and cellular and tissue-based products (HCT/Ps). AABB appreciates that FDA proposes to exclude or exempt from enforcement discretion certain tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories. However, we are concerned that FDA's proposed policy falls short of protecting patients' access to the range of tests required to ensure safe blood transfusions and biotherapies, which could negatively impact patient care.

FDA's proposed regulation is quite vague and does not provide the regulated community with sufficient information to evaluate the potential impact of the proposed rule. Due to the number of unanswered questions throughout the preamble and FDA's recognition that it will need to publish several guidances to clarify its enforcement approach, it is impossible for laboratories to fully assess whether the regulations will apply to their tests, and if they do, how they will apply.

Based on the information currently available and the limited timeframe for reviewing the proposed rule, AABB believes that the proposed rule would create unnecessary regulatory burdens for some of the urgent, lifesaving LDTs performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories. AABB requests that FDA specifically exclude from its proposed regulation of LDTs or extend enforcement discretion to all tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories for the following reasons:

- Existing regulatory and accreditation requirements protect the quality and safety of tests performed by these facilities.
- The lifesaving tests performed in these laboratories have not contributed to the safety concerns that led to the proposed rule, often rely on established testing procedures, and reflect medical practices that are critical to patient care.
- The proposed rule threatens patients' access to critical, lifesaving medical services and has the potential to result in negative health outcomes.
- The burdens and costs associated with the proposed rule will discourage laboratories from developing and performing tests, which will negatively impact patients.

Prior to moving forward with the rulemaking process, AABB encourages the Center for Devices and Radiologic Health (CDRH) to work with the Center for Biologics Evaluation and Research (CBER), federal advisory committees, provider groups, accreditation organizations, and other public and private stakeholders to ensure that its approach is evidence-based, risk-based, and does not inadvertently interfere with patients' access to the full course of lifesaving treatments.

1. FDA should exclude or continue enforcement discretion for all LDTs conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories because the existing regulatory and accreditation requirements protect the quality and safety of tests provided by these facilities.

Blood establishments, transfusion services, and accredited cell and gene therapy laboratories may conduct LDTs in laboratories including blood banks and transfusion services, immunohematology reference laboratories (IRLs), molecular testing laboratories, human leukocyte antigen (HLA) laboratories, flow cytometry laboratories, donor testing laboratories, perioperative services, and cellular therapy laboratories. AABB urges FDA to recognize that the existing regulatory framework ensures that blood establishments, transfusion services, and accredited cell and gene therapy laboratories provide high quality, safe, effective care.

- These laboratories are all part of federal, state, or locally licensed facilities and satisfy relevant licensure requirements.

- These laboratories are certified under the Clinical Laboratory Improvement Amendments (CLIA) program, which “regulates labs testing human specimens and ensure that they provide accurate, reliable, and timely patient test results.”¹
- Extensive FDA regulatory requirements apply to these laboratories, such as registration requirements; licensure requirements for donor screening and infectious disease tests as well as blood grouping and phenotyping reagents; premarket approvals and 510(k) clearance for certain products; new drug application (NDA) products; and reporting requirements related to adverse reactions (HCT/P establishments) and fatalities (blood establishments and HCT/P establishments).
- Some of the laboratories are subject to heightened regulations under State regulatory frameworks, such as the New York State Department of Health Clinical Laboratory Evaluation.

In addition, the quality and safety of care provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories is supported and continuously validated by accreditation programs. For example, AABB-accredited laboratories adhere to longstanding and internationally recognized standards that evaluate the facility’s quality management system and provide tools to monitor performance, capture deviations, and analyze suboptimal outcomes. The standards relate to organizational requirements; resources; equipment; supplier and customer issues; agreements; process control; documents and records; deviations, nonconformances, and adverse events; internal and external assessments; process improvement; and safety and facilities.²

AABB appreciates that FDA recognizes the rigorous regulatory requirements that govern donor screening tests required for infectious disease testing, the detection of blood group and Rh factor, and Human Leukocyte Antigen (HLA) tests used for blood transfusions. However, as highlighted in the case studies included in sections 2 and 3 below, we do not believe that the proposed rule excludes or extends enforcement discretion to all urgent, lifesaving tests provided for these purposes. Rather, some tests would be exempt from the new regulatory paradigm, other tests would remain subject to enforcement discretion, and other tests would be regulated as LDTs.

We recommend that FDA recognize that the existing regulatory and accreditation requirements are sufficient safeguards for protecting the quality and safety of tests performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories, and exclude or extend enforcement discretion to all tests performed by these facilities. If FDA continues to believe that other quality assurances are needed for LDTs conducted by these

¹ Centers for Medicare & Medicaid Services, MLN Fact Sheet, CLIA Program & Medicare Lab Services (May 2023), available at <https://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnproducts/downloads/cliabrochure.pdf>.

² See AABB Standards, Blood Banks and Transfusion Services, 33rd Edition; AABB Standards, Cellular Therapy Services, 11th Edition; AABB Standards, Immunohematology Reference Laboratories, 12th Edition; AABB Standards, Molecular Testing for Red Cell, Platelet, and Neutrophil Antigens, 6th Edition; AABB Standards for Perioperative Autologous Blood Collection and Administration, 10th Edition; AABB Standards for Out-of-Hospital Administration Services, 1st Edition; AABB Standards for a Patient Blood Management Program, 4th Edition, available at <https://www.aabb.org/standards-accreditation/standards>.

laboratories, AABB encourages FDA to accept evidence of accreditation, including AABB accreditation, as a sufficient safety measure. If FDA determines that additional oversight is necessary, AABB recommends that CDRH work with accreditation organizations and CBER to minimize burdens and leverage existing requirements and inspections to the maximum extent possible.

2. FDA should exclude or extend enforcement discretion to the lifesaving tests performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories since they have not contributed to the safety concerns that led to the proposed rule, often use established testing procedures, and engage in medical practices that are critical to patient care.

The tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories have not contributed to the safety concerns that led to the proposed rule. These laboratories perform urgent, lifesaving laboratory procedures and tests for patients being treated in healthcare settings. The tests are not marketed or sold to consumers. Additionally, the testing procedures are often established, may be reflected in FDA guidances, and are an integral part of medical practice.

Many LDTs performed by blood establishments, transfusion services, and cell and gene therapy laboratories involve testing procedures that have been rigorously validated and performed for years. They may provide patients with access to accurate and high-quality laboratory tests for conditions for which no commercial test exists or where an existing test does not meet clinical needs. A laboratory may customize a test to meet the individual needs of a patient or may use reagents that are not licensed, approved, or cleared by FDA. Additionally, the tests may be manual, automated, or hybrid (i.e., semi-automated), so they may not be considered “1976-Type LDTs.”

Some established laboratory practices and procedures that could inadvertently be captured by the proposed rule are reflected in authoritative resources used by laboratory professionals, such as the *AABB Technical Manual*. Examples include, but are not limited to:

- Method 3-18 Treating Red Cells Using DTT or AET
- Method 3-19 Neutralizing Anti-Sd^a with Urine
- Method 3-20 Adsorption procedure
- Method 4-2 Glycine-HCl/EDTA Elution Procedure
- Method 4-9 Adsorbing Warm-Reactive Autoantibodies Using Allogeneic Red Cells
- Method 4-11 Performing the Donath-Landsteiner Test
- Method 4-12 Detecting Drug Antibodies by Testing Drug-Treated cells
- Method 5-2 Testing for Fetomaternal Hemorrhage – Modified Kleihauer-Betke test³

³ See e.g., Cohn, C., Delaney, M., Johnson, S. et. al. *AABB Technical Manual*, 21st Edition: Methods and Appendices. (2023), available at <https://www.aabb.org/aabb-store/resources/technical-manual-methods>.

Other tests that could be captured by the proposed rule are recognized in FDA Guidance. FDA recognizes in its *Labeling of Red Blood Cell Units with Historical Antigen Typing Results, Guidance for Industry* that blood establishments use unlicensed reagents or unapproved molecular tests when providing care, and provides instructions for their use.⁴ Since the language in the preamble to the proposed rule suggests that tests encompassed by the proposed exclusion for tests that prevent incompatible blood transfusions must be licensed, approved, or cleared by FDA, the tests covered in the FDA guidance may not be captured. These tests may be manual, automated, or hybrid, so they may not be considered “1976-Type LDTs.”

Tests performed by blood establishments, transfusion services, and cell and gene laboratories reflect medical practices and inform time-sensitive medical care. Pathologists, other physician subspecialties, such as blood banking/transfusion medicine physicians, and physician extenders provide care through laboratory medicine.⁵ For example, pathologists “practice medicine by establishing diagnoses, monitoring disease progression and treatment, determining disease risk and cause of death, and overseeing blood and cellular transfusions. This may include directing laboratories or developing new testing methods using patient tissues, blood cells and body fluid specimens.”⁶ For instance, physicians and laboratory professionals:

- Use their medical judgement to make timely decisions about blood compatibility for patients with rare blood types, such as patients with sickle cell disease or thalassemia. They practice medicine by directing or performing laboratory tests that identify antigen-matched blood and reduce a patient’s risk of experiencing adverse events, such as hemolytic transfusion reactions, life-threatening anemia, pain crisis, acute chest syndrome, and/or acute renal failure. The tests are often individualized within each medical facility and are not approved, licensed, or cleared by FDA since they use reagents derived from donors and patients with rare blood types.
- Regularly use LDTs when furnishing care to pediatric patients since routine tests are often not approved for the pediatric patient population or need to be modified to be used for children.
- May conduct metagenomic next-generation sequencing for the broad-based detection of rare or unexpected pathogens and may use the results from the tests to inform patient care.⁷

Additionally, laboratory medicine is at the forefront of advancing personalized medicine and driving medical innovation. LDTs are critical for personalized medicine because they leverage an individual’s genetic information to guide decisions regarding preventing, diagnosing, and

⁴ Center for Biologics Evaluation and Research. Labeling of Red Blood Cell Units with Historical Antigen Typing Results: Guidance for Industry. December 2018.

⁵ See ACGME Program Requirements, FAQs, and Applications for Pathology Specialties, available at <https://www.acgme.org/specialties/pathology/program-requirements-and-faqs-and-applications/>.

⁶ I.e. ACGME Program Requirements for Graduate Medical Education in Anatomic Pathology and Clinical Pathology, available at https://www.acgme.org/globalassets/pfassets/programrequirements/300_pathology_2023.pdf (effective July 1, 2022, update effective July 1, 2023);

⁷ Gould CV, Free RJ, Bhatnagar J. et. al., Transmission of yellow fever vaccine virus through blood transfusion and organ transplantation in the USA in 2021: report of an investigation. *The Lancet Microbe*, Vol. 4, No. 9, e711-721 (Aug. 3, 2023).

treating disease. Furthermore, researchers invest significant effort in developing new biotherapies and several LDTs are used to evaluate novel products.

Please see section 3 below for other examples of LDTs provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories that are safe, integral parts of lifesaving care provided to patients.

AABB urges FDA to avoid finalizing a proposed rule that conflicts with authoritative resources and existing FDA guidance, and that interferes with patients' access to established medical practices and services that inform the practice of medicine. Rather, we encourage FDA to exclude or continue enforcement discretion for all tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories.

3. The proposed rule threatens patients' access to safe blood transfusions and biotherapies and has the potential to result in negative health outcomes.

The proposed rule has the potential to negatively impact health equity and reduce patients' access to the full course of lifesaving treatments for patients with conditions such as sickle cell disease, cancer, and rare diseases. Below, we have provided a few examples of case studies to demonstrate how pathologists and other medical professionals use LDTs when treating different patient populations that require blood transfusions and biotherapies. The case studies illustrate the types of lifesaving LDTs provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories, but are not intended to be a comprehensive representation of the types of LDTs performed by these facilities or the patient populations that rely on these tests.

AABB is concerned that laboratories may no longer offer these tests and others if they are subject to new burdens and costs associated with being regulated as devices. Additionally, the proposed rule could impact laboratories' willingness to share new methods and rare reagents with each other, which would negatively impact patient care. Many patients requiring blood transfusions or biotherapies have challenges accessing subspecialized care, and the Biden Administration and the Department of Health and Human Services have prioritized addressing barriers through commendable efforts such as the Cancer Moonshot Initiative and the HHS Equity Action Plan. We believe that the proposed rule has the potential to adversely impact these efforts by creating obstacles to accessing safe, compatible blood transfusions and timely biotherapies.

Case Study 1: Course of treatment for a child receiving a stem cell transplant for sickle cell disease.

A 7-year-old male patient is admitted to a hospital to receive an allogeneic stem cell transplant to treat sickle cell disease. The patient will be treated by a variety of providers, including but not limited to those who specialize in hematology, immunology, bone marrow transplantation, and pathology.

While FDA proposed to continue applying the general enforcement discretion approach to HLA tests required in advance of transplants, including HLA allele typing, for HLA antibody

screening and monitoring, or for conducting real and “virtual” HLA crossmatch tests, additional LDTs are necessary throughout the patient’s course of treatment, including post-transplant. Examples of LDTs used throughout the patient’s course of care may include:

- Genotyping LDTs to confirm the patient’s type of sickle cell disease.
- Flow cytometry panels to characterize the patient’s blood after transplant and to enumerate the stem cell graft provided by the healthy donor.
- Colony forming units (CFU) assays, which evaluate the qualitative and quantitative features of stem cell grafts.
- Post-transplant patient and donor chimerism [i.e., short tandem repeat (STR) assays] to assess engraftment and evaluate the potential for relapse.
- Testing biomarkers critical to the transplant process.

Case Study 2: Course of treatment for an oncology patient receiving CAR T-cell therapy to treat his multiple myeloma.

A 57-year-old male patient received a commercial CAR T-cell therapy to treat his multiple myeloma. Following administration of the therapy, the patient will need to be monitored by his clinical care team for signs of toxicity or therapy failure. Examples of LDTs that may be used to support the patient’s care include:

- Flow cytometry panels to count the number of cells that have been engineered into CAR T-cells.
- Immunoassay LDTs to rapidly determine the presence and severity of cytokine release syndrome, an acute inflammatory syndrome associated with CAR T-cell therapy that can lead to organ failure and death, as well as to distinguish it from other clinical responses with similar symptoms.

Case Study 3: Course of treatment for a patient with leukemia receiving a stem cell transplant.

A 41-year-old female patient is admitted to a hospital to receive a bone marrow transplant to treat her leukemia. The bone marrow donor is a family member, however due to geographic and socioeconomic restrictions, the family member must donate their bone marrow at an institution separate from where the patient is being treated. Because of this the donated bone marrow must be cryopreserved prior to shipment to the patient. In this scenario, the patient will rely on a variety of LDTs to ensure optimal care, such as:

- Flow cytometry panels, which are used to diagnose leukemia and to enumerate the bone marrow donation at the collection site and again at the facility treating the patient.
- Flow cytometry panels to measure the effectiveness of pre-transplant conditioning regimens provided to the patient.
- Colony forming units (CFU) assays, which evaluate the qualitative and quantitative features of bone marrow after thawing and preparation for transplant.

- Post-transplant patient and donor chimerism to assess engraftment and evaluate the potential for relapse.
- Flow cytometry panels for evaluating the presence of any minimal residual disease following transplant.

Case Study 4: Course of treatment for a patient with sickle cell disease requiring multiple blood transfusions.

A 20-year-old female patient with sickle cell disease has received several red blood cell transfusions throughout her life and requires another blood transfusion. She has rare antigen phenotypes and due to being a recipient of chronic transfusions, she has multiple red blood cell alloantibodies. Thus, the patient is at increased risk of experiencing adverse reactions to blood transfusions, which can be life-threatening. Examples of LDTs that are instrumental to her care include:

- Molecular genotyping tests, which will be conducted on the patient and the donor to identify closely matched blood, which is important for optimal patient outcomes.
- Blood compatibility tests, including adsorptions and elutions, incorporate laboratory prepared reagents and well-characterized anti-sera derived from rare donors and patients. Laboratories use established quality control to verify reactivity of the non-licensed reagent or anti-sera.
- Expired reagent red blood cells may be used to confirm or rule-out a suspected antibody. Laboratories use quality to verify the reactivity of the expired reagent red cells.

We encourage FDA to avoid finalizing a proposed rule that has the potential to threaten patients' access to lifesaving laboratory procedures that support safe, compatible blood transfusions as well as safe cell and gene therapies.

4. The burdens and costs associated with the proposed rule will discourage laboratories from developing and performing tests, which will negatively impact patients.

The proposed rule does not adequately capture the human resources required and anticipated costs that will be incurred by blood establishments, transfusion services, and accredited cell and gene laboratories and services if they need to comply with the medical device regulatory requirements.

Due to the existing laboratory workforce shortage, blood establishments, transfusion services, and accredited cell and gene therapy laboratories cannot absorb the significant, new regulatory requirements laid out in the proposed rule. The American Society for Clinical Pathology recently published an article that highlights pervasive vacancies in medical laboratories in the United States. In addition to current workforce shortages, the pipeline of individuals entering the field will not meet the needs of the future. For example, blood banks have the highest staff vacancy

rate – 18.9% - as well as an 18.1% rate of employees expected to retire within the next five years.⁸

We anticipate that it would be difficult for blood establishments, transfusion services, and cell and gene therapy laboratories to identify new, qualified individuals who understand the complex, specialized work conducted by these laboratories and can support compliance with the FDA’s medical device regulatory requirements. Further, costs related to hiring and training new staff are not accounted for in the proposed rule. The workforce shortage will impact limit laboratories’ abilities to catalogue their LDTs, complete novel submissions for FDA, and learn and comply with medical device regulatory requirements.

In addition to human resources and the costs associated with completing and submitting required applications and information to FDA, blood establishments, transfusion services, and accredited cell and gene therapy laboratories would be subject to user fees for tests regulated as LDTs. User fees would be new expenses for these laboratories, which operate under extremely tight budgets.

If blood establishments, transfusion services, or accredited cell and gene therapy laboratories need to redirect existing resources or incur increased costs to address unnecessary regulatory burdens, it is possible that the increased costs would be passed on to the healthcare system and patients. The laboratories would likely need to reduce the number of tests they offer and may not be able to provide test results in a timely manner. This would result in patients not having access to medically necessary tests that prevent adverse events and inform lifesaving healthcare.

Conclusion

AABB appreciates FDA’s dedication to protecting public health. We are committed to working with the Agency to ensure that policies promote quality and safety, while also protecting patients’ access to lifesaving laboratory procedures that are critical for blood transfusions and biotherapies. If you have any questions or need additional information, please contact me at 301-215-6554 or lmstone@aabb.org.

Sincerely,

[*Signature on file*]

Leah Mendelsohn Stone, JD
Vice President, Public Policy and Advocacy
Association for the Advancement of Blood & Biotherapies

⁸ Edna Garcia, Iman Kundu, Melissa Kelly, Ryan Soles, The American Society for Clinical Pathology 2022 Vacancy Survey of medical laboratories in the United States, *American Journal of Clinical Pathology*, 2023; aqad149, <https://doi.org/10.1093/ajcp/aqad149>.