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

Submitted via https://www.regulations.gov

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

Dear Dockets Manager:

America's Blood Centers (ABC) is the national organization bringing together community-based, independent blood centers. Our member organizations operate more than 600 blood collection sites providing close to 60 percent of the U.S., and a quarter of the Canadian, blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. All ABC U.S. members are licensed and regulated by the U.S. Food and Drug Administration (FDA).

FDA is proposing to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this amendment, FDA is proposing a policy under which the agency intends to phase out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs.

ABC appreciates FDA's commitment to safeguarding public health by recognizing the importance of LDTs and the need to ensure the safety and effectiveness of LDTs. However, the proposed rule is far too broad and, as written, will have a negative impact on public health and the U.S. blood supply. In order to protect public health, the agency must categorically exempt from its proposed enforcement approach and/or continue its enforcement discretion over all tests developed and utilized by blood centers. The additional requirements placed on blood centers as outlined in the proposed rule will place an enormous burden on this small industry subset, delay and prohibit patient access to tests necessary to ensure blood compatibility, and have the potential for a serious negative impact on patient care.

I. LDTs developed by blood establishments are not associated with the type of safety concerns FDA is addressing with this rule.

Under the proposed rule, FDA intends to phase out the general enforcement approach for LDTs because this approach does not best serve public health. Additionally, FDA notes it has highlighted the risks associated with IVDs offered as LDTs for decades, with concerns growing in recent years. The agency highlights scientific literature and FDA's own experience where the agency has observed laboratories that

fail to perform appropriate or adequate validation studies or have data demonstrating their test does not work as intended but offer the test anyway. FDA further notes it has received multiple complaints, adverse event reports, and other allegations identifying problems with IVDs offered as LDTs and describes the complaints and reports.

These risks and concerns outlined by FDA do not apply to blood centers. Blood centers have significant safeguards in place when developing and utilizing LDTs. Their laboratories work within the Clinical Laboratory Improvement Amendments (CLIA) regulations to create the reagents and procedures. Additionally, blood center laboratories ensure the quality and validity of tests through the existing regulatory framework and safeguards, including (1) federal, state, or local licensure of the facility; (2) CLIA certification; (3) compliance with extensive FDA regulatory requirements; (4) state requirements; and (5) accreditation. LDT procedures in blood centers are already highly regulated. They are usually performed in urgent, life-saving situations and are always performed for patients being treated in a healthcare setting. Given the oversight and inspection already in place for blood centers, adding an additional layer of regulation is unnecessary.

Blood centers' LDTs are extremely safe and effective under the current framework and do not have a history of safety issues. Blood centers and hospitals are required to report adverse events to FDA. The safety record of these tests is well-documented in this reporting system, and a mechanism exists to resolve any safety issues that are potentially identified. FDA has proposed not to include certain tests under its new regulatory scheme, including tests that are intended as blood donor screening or human cells, tissues, and cellular tissue-based products (HCT/Ps) donor screening tests required for infectious disease testing or for determination of blood group and Rh factors, since these tests must be licensed, approved, or cleared by FDA. Additionally, FDA intends to continue to enforce applicable requirements for Human Leukocyte Antigen (HLA) tests used for blood transfusions, since these tests are highly standardized across institutions. However, these are just a few of the tests used by blood centers to ensure the safety of the blood supply and blood compatibility.

II. Many LDTs developed in a blood center's lab are 1976-Type LDTs and/or are developed with a high level of standardization across institutions.

FDA is proposing to continue to apply the current general enforcement discretion approach to "1976-Type LDTs." These tests have the following characteristics common among LDTs offered in 1976: use of manual techniques (without automation) performed by laboratory personnel with specialized expertise; use of components legally marketed for clinical use; and design, manufacture, and use within a single CLIA-certified laboratory that meets the requirements under CLIA for high complexity testing. As FDA notes, these characteristics provide the greatest risk mitigation. As an example, FDA cites immunohistochemistry tests that involve no automated preparation or interpretation.

Many serological tests developed in a blood center's immunohematology reference laboratory (IRL) are 1976-type LDTs, and as such, FDA should continue to apply its current general enforcement discretion to these tests. These tests use manual techniques and are performed by highly trained laboratory personnel under the oversight of a blood center medical director and use licensed reagents.

Additionally, the tests are validated and rigorously quality-controlled, are well-established, and follow standard, published references for immunohematology. These test kits are not sold to any entity and are only utilized by the blood center. The volume of production for these tests does not make them commercially viable for mass marketing. Therefore, these important tests would be unavailable for use if not performed under the current enforcement discretion. If a new test is developed, it is developed under the principles that have been used for decades and based on established procedures and mechanisms to ensure safety.

For example, antibody titers performed to determine whether a blood product may be labeled as 'low titer' employs a very standardized procedure and uses licensed reagents. The test is performed by highly specialized and trained individuals and the method has not changed much since 1976. This type of testing is not marketed and is utilized by the blood center for labeling and blood safety purposes. The results are not used to diagnose a disease/condition.

However, there are times when licensed reagents are unavailable. The AABB "Technical Manual"[1] and Judd's Methods in Immunohematology[2] are standard references for immunohematology. They contain numerous procedures utilized in specific situations for clinicians caring for patients with various diseases or aiding in providing compatible blood for transfusion. For most of the procedures contained in these references, FDA approved kits and/or reagents are not available. These procedures go beyond the simple crossmatch, direct antiglobulin test, and common antibody identification, for which approved reagents are available, and help address some of the more infrequent immunohematology problems that hospitals and blood banks encounter. Examples include:

- Approved reagents for many enzyme treatment procedures for red blood cells are not available. They are made in the individual laboratory (e.g., bromelain 2%, useful in investigating some Rh antibodies, and alpha chymotrypsin, useful in investigating MNS antibodies).
- *Arachis hypogea* lectin for resolving polyagglutination in pretransfusion samples.
- Multiple elution techniques useful in concentrating and isolating red blood cell antibodies of interest. There are 16 different elution methods, and each has its use depending on the immunohematology problem to be resolved.
- Dithiothreitol (DTT) 0.2M for investigating anti-CD 38 (daratumumab) interference or distinguishing IgG from IgM class antibodies.
- Making reagent red cells by treating them with 2-aminoethylisothiouronium bromide (AET). Useful when working with antibodies to the KEL, KN, DO, LU, YT, LW^a, and JMH blood group systems.
- Platelet absorption of HLA antibodies. Removes anti-HLA interference sometimes encountered in identifying compatible blood for transfusion.

Other examples of necessary tests that would fall under FDA's new enforcement approach include:

ABO discrepancy resolution

If ABO discrepancy is caused by a cold reacting antibody at immediate spin, one strategy to resolve the discrepancy is by using antigen-negative cells for reverse typing. Those cells are not legally marketed components, which would make it fall outside of the discretion for 1976-type LDTs. ABO genotyping is complex, and there is no licensed platform. Being able to resolve ABO discrepancies is essential for issuing type-specific blood. Otherwise, it creates demands for group O red blood cells and group AB plasma when they are not needed and can cause shortages of the "universal" blood components, negatively impacting patient care. In addition, ensuring the concern is an ABO discrepancy and not caused by underlying conditions that are not related to an ABO discrepancy is essential for appropriate matching and patient care.

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[1] "Technical Manual," 21st Edition, edited by Claudia Cohn, MD, PhD; Meghan Delaney, DO, MPH; Susan T. Johnson, MSTM, MT(ASCP)SBBCM; Louis M. Katz, MD; Joseph (Yossi) Schwartz, MD, MPH, published by the Association for the Advancement of Blood and Biotherapies (AABB).

[2] "Judd's Methods in Immunohematology, 4th Edition," By W. John Judd, FIBMS, MIBiol; Susan T. Johnson, MSTM, MT(ASCP)SBB^{CM}; and Jill Storry, PhD, FIBMS, published by AABB, a compilation of "widely used references for serologic methods to address dilemmas in areas such as detection, identification, and investigation of antibodies; perinatal testing of mother and neonate; resolution of problems encountered with ABO typing; and in-house preparation of reagents."

Other tests using in-house donor cells

The issue of using cells of specific antigen makeup that are not commercially sourced also affects other immunohematology tests, including adsorption studies and antibody identification of rare or new specificities. Not being able to ascertain the antibody's specificity would affect the blood transfusion's safety. In these cases, the tests would not be commercially available because a variant of an antigen is either newly discovered or is too rare, and the urgency is too great to pursue full FDA approval when needed.

Tests using anti-sera created from donor plasma

McLeod phenotype determination, other rare phenotyping needs when commercial reagents are unavailable, and plasma inhibition tests require anti-sera/plasma from donors or patients. Having access to and being able to continue performing these tests is important because correct antibody identification is essential for safe blood transfusion. In these cases, the tests would not be commercially available because a variant of an antigen is newly discovered or is too rare, and the urgency is too great to pursue full FDA approval when needed.

Flow cytometric analysis

Flow cytometry is used in cell therapy to determine final product characteristics, cell viability, and product stability of leukapheresis collections.

Molecular Testing

Over the last 10 years, some larger blood centers have developed their own molecular testing platforms. Two companies are licensed (for a limited number of antigens), but some of the larger blood centers have developed their own molecular testing platforms that have been validated. These platforms allow for more flexibility to test for newly discovered antigens or variants or to specifically tailor to the patient population served by the blood center. Samples are tested concurrently with controls. These laboratories are also under evaluation through inspection and proficiency testing through accrediting agencies. Lab personnel performing these tests are highly trained and specialized. Like serological testing, these tests are validated and have undergone rigorous testing before being used on patients. Additionally, these tests are highly standardized within the lab itself. If molecular testing in blood centers falls under the new regulatory requirements, innovation will be seriously hampered, and patient care will be negatively impacted. For example, adding this additional layer of regulation would compromise innovation and implementation of new assays as blood center laboratories move to the use of next-generation sequencing. Additionally, molecular testing to predict antigens on red cells and platelets would be severely impacted. As new variants are constantly being discovered, there will be cases that can only be resolved by LDTs before or if FDA-licensed platforms become available in a timeframe that would allow for safe patient care.

There are numerous LDT Red Cell Genotyping (RCG) platforms used by blood centers across the country. These RCG platforms are able to provide more targets for rare blood groups. As the molecular basis of more blood groups is discovered, these LDT tests can incorporate these new discoveries in their platforms at a much quicker rate than those already licensed. An example of this is the Vel antigen. This antigen is certainly clinically significant and very rare. In order to find compatible blood for a patient with anti-Vel, 4,000 donors need to be screened to find a match. A few years ago, the molecular basis of Vel was discovered, allowing the use of a LDT to be added to these tests. Because of this, mass screening of donors can occur to find these rare donors for patients in need of lifesaving matched blood. There are many other antigens that are part of these LDTs. Without the ability to mass screen donors for these rare blood types, blood centers would not be nearly as successful as they are today in finding the right blood for these patients with difficult transfusion requirements.

In addition to LDT molecular and serological techniques utilized by blood centers to determine the safety of red cell-containing products, it is also critical to ensure specialty platelet products are available to those patients in need. Therefore, LDTs to test for patient-specific HLA and Human Platelet Antigens (HPA) and the associated antibodies relevant to a safe transfusion of platelet products is critical to ensure these complex transfusion needs of patients are met in a timely manner.

III. Blood centers' LDTs are comparable to Human Leukocyte Antigen (HLA) tests. FDA should apply general enforcement discretion to all HLA tests and blood center's LDTs.

FDA is proposing to continue to apply the general enforcement discretion to HLA tests that are designed, manufactured, and used in a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and "virtual" HLA crossmatch tests. FDA's rationale for exempting these tests from the new requirements is:

> "HLA LDTs for transplantation used in histocompatibility laboratories that meet the regulatory requirements under CLIA to perform high complexity testing, when used in connection with organ, stem cell, and tissue transplantation for certain purposes as described in this paragraph, are unique in that they are generally developed, and the testing is generally performed, in urgent, life-saving situations for the patient. Physicians must often make prompt decisions about transplantation based on medical judgment regarding their patient's condition and degree of mismatch between the donor and patient should an organ, stem cells, or tissue become available. Further, these tests are often individualized within each medical facility, for example, they include reagents that reflect local HLA polymorphisms and patient demographics."

The rationale and reasons stated by FDA for exempting HLA LDTs for transplantation apply to all LDTs in blood centers and to all HLA tests. These tests are generally developed, and the testing is generally performed in urgent, life-saving situations for the patient, where a physician must make a prompt decision about the transfusion based on medical judgment regarding their patient's condition and the degree of mismatch between the donor and patient when performing a blood transfusion. FDA should continue to apply general enforcement discretion to all HLA tests and blood centers' LDTs.

IV. Impact on Patient Access

Unless blood centers' LDTs are fully excluded from FDA's enforcement approach applied to IVDs, there will be significant patient harm due to delays in care and the lack of patient access to medically necessary tests due to the new regulatory burdens. As noted above, these tests are generally developed, and the testing is generally performed in urgent, life-saving situations for the patient, where a physician must make a prompt decision about the transfusion based on medical judgment regarding their patient's condition and the degree of mismatch between the donor and patient when performing a blood transfusion. If these tests are unavailable, physicians must still make a prompt decision about the transfusion, and they will have less information available to them to determine the safest course of action. Suppose blood centers are required to follow the proposed regulatory framework for LTDs. In that case, many of these tests will not be available, and/or patient access to the tests will be seriously delayed, potentially causing significant patient harm.

Additionally, these new regulatory burdens would exacerbate the impact of the existing laboratory workforce shortage without improving safety. Blood centers would need to hire additional specialized staff and provide training to staff on a new, complicated FDA regulatory scheme. This would come at a time when pathology and laboratory medicine are experiencing extreme workforce challenges. For

example, the overall vacancy rate for blood bank immunohematology laboratory departments was 17.8% in 2022, with staff vacancy rates at 18.9%.[3] Additionally, blood centers may be subject to user fees, creating additional financial burdens on these already financially stressed centers.[4]

FDA must also ensure it has the workforce necessary to enforce the new requirements. LDTs are highly technical lab tests, and this will be a new area of FDA enforcement requiring highly trained individuals. Unless FDA has the resources available to enforce the new requirements, and provide timely reviews, patients will be additionally impacted by further delayed development of tests. When these tests are necessary, they are often needed very quickly or immediately. Patients will be unable to timely access the tests required to ensure the safest blood products are administered.

LDTs are critical in the search for compatible blood and blood products for patients with complex antibody issues. The reagents (primarily antisera and RBCs) used in these LDTs are often derived from rare donors and patients identified by the blood establishment. They are applied to clinical problems too rare to support the development and approval of licensed materials. The methods are well-documented in reference texts and peer-reviewed journals and have been used for decades. The work is most frequently performed by the highly trained and specialized reference laboratory personnel at the blood center providing the blood products for transfusion rather than the hospital's transfusion service. This is due to the expertise needed to perform and interpret the procedures, the availability of rare reagents for which no licensed alternatives exist, and the close relationship between blood centers and transfusion services working together to identify suitable products for the patients.

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In order to protect public health, FDA must categorically exempt from its proposed enforcement approach and/or continue its enforcement discretion over all tests developed and utilized by blood centers. The additional requirements placed on blood centers as outlined in the proposed rule will place an enormous burden on this small industry subset, delay and prohibit patient access to tests necessary to ensure blood compatibility, and have the potential for a serious negative impact on patient care.

ABC appreciates the opportunity to comment on the proposed rule. If you have any questions or require additional information, please contact Justine Coffey, Director of Regulatory Affairs and Public Policy (jcoffey@americasblood.org).

Thank you again for your collaborative work to ensure a safe, adequate, and available blood supply.

Sincerely yours,

Kate Fry, MBA, CAE
Chief Executive Officer

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[3]" 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; p. 7.

[4] U.S. Department of Health and Human Services, *Adequacy of the National Blood Supply*, Report to Congress 2020, Figure 2, p. 5, Median Operating Margin by Year.