Clinical Immunology Society

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TO: Robert Califf, MD
Commissioner
US FDA

c/o: Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Submitted electronically to http://www.regulations.gov

Dec. 4, 2023

Re: Comments Regarding the FDA Proposed Rule Titled "Medical Device Laboratory Developed Tests." [Docket No. FDA-2023-N-2177]

Dear Commissioner Califf:

The Clinical Immunology Society (CIS) would like to respond to the FDA's proposed rules regarding LDTs. The CIS has strong and legitimate concerns to the proposed rules by the FDA to incorporate laboratory derived tests (LDTs) as medical devices under FDA oversight due to its negative impact on delivery of early and effective care for patients with rare immune disorders.

The Clinical Immunology Society, founded in 1986 and headquartered in Milwaukee, WI, has built an expanding network of immunologists, based primarily in North America yet with a global impact. With a current roster of 872 members (78% of whom work and operate within the United States), the CIS is the leading organization in North America for physicians and scientists who provide care for patients with complex immune disorders, including genetic disorders of the immune system (aka. the inborn errors of immunity-IEIs). The proposed changes will have far-reaching and an overwhelming negative impact on the delivery of care for these patients. The CIS uniquely represents many, if not all, academic medical centers (AMCs), which have highly specialized diagnostic immunology laboratories that focus exclusively on the care of patients with rare and/or complex immunological diseases. These laboratories are the only labs in the country that provide the cutting-edge, knowledge-based testing required to diagnose patients with rare immunological diseases. These laboratories do not make a profit on diagnostic testing, and they exist because they fulfill a critical need in this area of medicine, which cannot be provided by any other entity, commercial or private. The sheer financial and regulatory burden imposed by the proposed rule will lead to the closure of these labs which will have an adverse impact on the delivery of care to these patients, which cannot be easily reversed.

We have summarized our concerns below.

1) Inborn errors of immunity are rare diseases, but there are over 500 genetic defects now associated with defective immunity. Functional gene specific testing using LDTs at academic centers is critical to evaluate genetic variants (e.g. variants of uncertain significance), to ensure that the correct therapy is pursued (e.g. bone marrow transplantation vs. thymic implantation vs. gene therapy), to monitor response to these treatments (e.g. bone marrow chimerism and immune reconstitution), and to correctly curate gene-disease relationships and classify pathogenic genetic variants (e.g. gene and variant curation expert panels through ClinGen). Because of the rarity of these diseases, only one or a few labs do such testing, and the tests are done in limited numbers. With the proposed rule changes and excessive financial burden

it imposes, none of these labs will be able to provide this service, resulting in irrevocable harm to our patients.

2) There are fewer than 20 laboratories, which offer advanced immunologic testing, and these are all associated with AMCs and directed by board-certified physicians or laboratory medicine-trained scientists. Performance of this testing in an AMC may be considered an extension of medical practice and outside of FDA's authority to regulate IVDs (in vitro devices). As part of AMCs, they are part of the non-profit enterprise in these institutions. Highly specialized functional and multiparametric phenotyping is performed by a limited number of labs for patients with rare diseases. For example, ADA1, ADA2, XIAP and DNA repair functional testing are currently run in single reference laboratories necessitated by the rarity of the diseases and expertise within that particular AMC for those diseases. There are many such examples. Many of these tests have an annual test volume of 50-500 per year. Therefore, these tests will not be profitable to commercial laboratories, particularly if additional fees have to be paid to the FDA. Also, many commercial laboratories do not have the extensive technical, clinical or scientific expertise or access to the relevant patient populations to undertake the analytical and clinical validation of such esoteric tests. Many commercial laboratories perform relatively basic immunological testing, which has been in existence for decades (e.g. T cell proliferation to mitogens and antigens, lymphocyte subset analysis). In fact, these commercial laboratories send more specialized testing to AMC reference laboratories. In addition, the AMC labs are run by academicians with extensive knowledge of Clinical Immunology, and these experts make themselves available to discuss these results with the referring providers, discuss next steps or testing, and aid in the workup and diagnosis of these patients. This would not happen when testing is sent to commercial laboratories, where the relevant scientific and clinical expertise is not present. This “out-of-the-box” thinking, which is not present in commercial laboratories, is essential in the diagnosis of rare diseases.
3) The premise behind the proposed rule is that FDA oversight of LDTs would improve the quality of laboratory tests. There is no objective evidence to support this claim, and references to prenatal testing false positives or Theranos does not logically support the argument to aggregate all LDTs under this rubric. The diagnostic immunology laboratories at AMCs are either under CAP and/or CLIA oversight, and all testing is developed and validated under stringent analytical conditions, including quality control, personnel competency assessment and proficiency testing. Assay verification with patient samples known to have a disease is also performed to the extent possible given that the rarity of these diseases. This is only possible due to collaboration between experts who can obtain these samples, something no regulatory agency would be able to replicate. These labs spend considerable time and resources to ensure these tests are performed to appropriate standards for clinical care. We also have evidence that certain FDA-approved tests are not of the high analytical quality as is deemed by the label, because commercial manufacturers developing tests look for the simplest approach for performance and analysis, which is not necessarily always accurate for immunological studies, which by its very nature is inherently complex.
4) Proposed solutions.
    a. *Exemption of academic medical centers (AMCs):* Specialized diagnostic immunology laboratories reside within AMCs. Therefore, CIS welcomes the possibility of an exemption for AMCs from the proposed rules to enable such laboratories and hospitals to continuously innovate and deliver high-quality patient care. However, there remains an overriding concern that the geographical restrictions imposed on AMCs will defeat any potential benefit of an exemption. Due to the esoteric testing provided by these laboratories and the patient populations they serve (i.e. rare diseases or rare complications of chronic or more common diseases), geographical restrictions will prevent these laboratories from operating as reference laboratories, thereby restricting access to the best-quality care for patients around the country leading to healthcare inequity. Therefore, any exemption provided to AMCs must include the ability of these laboratories to serve patients and physicians across the country and globally.
    b. *Grandfathering:* The CIS does not think grandfathering current testing is a viable answer to these issues. Within the last two decades, there has been discovery of over 350 genetic disorders of the immune system, which has been driven by advances in genetic testing, but has also necessitated advances in immunological testing, both phenotyping and functional studies. Care of rare disease patients requires a systems biology approach, and cherry-picking what will be exempted and what will be regulated poses an intolerable burden for AMCs and harm to the patient population being served by these tests.

c. *Financial Threshold*: While the possibility of having a financial threshold to protect small and highly specialized laboratories is a welcome proposition, there remains the thorny question of what financial threshold would be viable. Developing and validating these highly complex, low-volume tests is already a significant financial burden, which is incurred by academic medical centers in the interest of patient care. A revenue cut-off of <$150,000 is not practical as it ensures that these specialized laboratories will no longer have an operating margin. It is unclear if this cutoff is revenue per test or total revenue of the lab. With the FDA fees varying from $21,000 to $480,000 per test per year, any revenue cut-off needs to take into account these fees, which would require a revenue cut-off much higher than what is currently proposed.

While we could provide several additional pages of evidence and logic to support our claims, we recognize that these discussions should be had in a collegial dialogue with the FDA. Therefore, we urge the FDA for a moratorium on the proposed rules, while the framework of LDTs in AMCs can be discussed with appropriate time for consideration of the significant ramifications these rules will have on patient care throughout the country, in small and large hospitals. The decision to implement these rules in haste without appropriate discussions with key stakeholders will cause irrevocable harm to patients, hospitals and laboratories. We recognize that this is not the intention of the FDA, but we maintain that this subject requires considerable additional discussion to ensure that any proposed changes are suitable for patient care and advancement of healthcare in the US.

We appreciate the consideration of the FDA in reviewing this letter and we remain available for any additional discussions on this topic.

Sincerely,

Elie Haddad, MD, PhD
President, Clinical Immunology Society (CIS)

Dr. James Verbsky
Chair, CIS Diagnostic Laboratory Immunology Committee