Thomas A. Owens, MD
Office of the Executive Vice President &
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December 4, 2023

Robert Califf, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave.
Silver Spring, MD 20993

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

Submitted electronically via (www.regulations.gov)

On behalf of Duke University Health System (DUHS), we are writing to provide comments on the Food and Drug Administration's proposed rule to regulate Laboratory Developed Tests (LDTs).

DUHS is comprised of three hospitals – Duke University Hospital on our Duke University Medical Center campus, Duke Regional Hospital, and Duke Raleigh Hospital – and has an extensive, geographically dispersed network of outpatient facilities that include primary care offices, urgent care centers, multi-specialty clinics and outpatient surgery centers. The Duke Health Integrated Practice is the academic, multi-specialty physician practice of our Health System, and Duke Primary Care, focuses on our mission of caring for our community by providing services primarily to our North Carolina patients.

Our Duke Health Clinical Laboratories are a fully integrated core clinical service at Duke Health and are responsible for meeting the testing needs of our Duke patients. Our laboratory's expertise is broad and includes but is not limited to chemistry, hematology, microbiology, anatomic pathology, cytogenetics, molecular oncology, medical and biochemical genetics and transplantation medicine. Our testing systems range from high throughput, highly automated FDA approved systems, to highly manual tests that we have developed at Duke over the years out of necessity due to a lack of viable commercial FDA approved options and an absolute need for this testing to care for our Duke patients. DUHS has benefited from the expertise of its directors, who are nationally recognized experts in the sciences behind clinical laboratory medicine and in the realm of laboratory accreditation, proficiency testing and quality programs. In our laboratories, we put our Duke patients at the center of everything we do, and the safety of our patients and the quality of their care is our primary concern. Accordingly, like the FDA, our team of laboratorians and our health system understands the critical need to ensure the clinical validity and accuracy of LDTs used for diagnostic and treatment decisions. That said, we must collectively ensure that any regulation of LDTs does not interfere with this vital area of medical practice, negatively impact patient access, or create a burdensome, costly, redundant or laborious process that could make it more difficult to care for patients or stifle innovation at Duke or like academic medical centers across the country.

We recommend that the FDA consider how best to accomplish the goals of the proposed regulations without the deleterious effects that have been predicted by physicians and institutions that regularly perform these tests and the preponderance of professional societies that represent these providers of

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laboratory-based patient care. We also strongly urge the FDA to fully consider and understand the prevalence of LDTs in the routine practice of medicine, particularly within the academic medical center laboratory, and the tremendously positive impact on existing LDTs on the lives of our patients.

Our subsequent more specific comments will focus on the following areas:

1. Characteristics of academic medical centers (AMCs) and a recommendation for continued enforcement discretion for LDTs offered through AMC Laboratories.
2. Suggestions for continued enforcement discretion outside of the AMC Laboratory
3. The FDA's current regulatory structure and authority

1. Characteristics of academic medical centers (AMCs) and a recommendation for continued enforcement discretion for LDTs offered through AMC Laboratories.

DUHS appreciates the FDA's interest in formally defining an AMC laboratory and potentially taking this classification into consideration when creating rules for the regulation of LDTs. We believe that the following characteristics should be used to define an AMC laboratory when considering enforcement discretion. These are largely in alignment with those being proposed by the FDA.

- An AMC laboratory is part of an Academic Medical Center as defined as a nonprofit 501(c)(3) or public entity with an LCME accredited medical school, teaching hospital, residency training program and a mission which includes education of medical professionals and advancing our understanding of disease.
- An AMC laboratory is also a nonprofit or public entity, which primarily cares for the patients who are treated by providers at their affiliated AMC hospital(s) and clinics.
- An AMC laboratory does not operate as a reference laboratory and only a minority of tests are ordered by providers who are not part of the AMC's clinical practice or on patients who will not be seen by a provider who is part of the AMC.

An AMC laboratory is distinct from a commercial or reference laboratory in that the parent AMC is responsible for the entire scope of care of the majority of patients that it tests. This provides an additional level of safety to each patient for any testing performed, including LDTs. Test results are not used in isolation, the testing is not performed without knowledge of the patient's history and disease process to date, and the clinical and research scientists developing the LDTs are part of a team, which includes the physicians ordering the tests and seeing the patients. We believe that this creates an environment of safety with multiple real time checks and balances to ensure that each test result 'makes sense' and allows for rapid identification of errors. We think that this same rationale (an environment of safety) is the reason for the FDA's proposal to continue enforcement discretion for LDTs in the area of transplantation medicine, one of the highest risk areas of our practice with dire consequence of organ incompatibility, which is only prevented through LDTs.

We urge the FDA to continue to exercise enforcement discretion for testing offered through AMC laboratories. If this is not done, we strongly urge that AMC laboratories be subject to regulations that take into account the context of care of the patients being served and regulatory rules already in place through CMS and CLIA to eliminate unnecessary redundancy in regulatory oversight. We recognize that

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this environment of safety is not unique to Academic nonprofit medical centers. Health systems that are responsible for the complete clinical course of care, including laboratory testing, for the majority of their patients could also be considered for continued enforcement discretion. We also recognize that our definition of an AMC laboratory likely excludes some laboratories that are certainly academic and offer LDTs of exceptional quality without the aid of FDA oversight.

2. Suggestions for continued enforcement discretion outside of the AMC Laboratory

Every day, Duke Patients benefit from safe and scientifically sound LDTs offered by our DUHS Clinical Laboratories. Many of these LDTs have been in place for years. Our LDTs range from simple modifications of FDA approved assays to use alternative sample types, to mass spectrometry based drug testing that was implemented to combat the opioid epidemic, to flow cytometry based-testing without which we could not diagnose leukemia or lymphoma. ***We have had to develop all of these LDTs because of a lack of FDA approved testing options at the time. FDA approved options remain unavailable to this day for the great majority of our LDTs.***

Our LDT validations have been reviewed by the CAP as part of our every other year routine inspections. Our molecular LDT validations have been reviewed independently by Palmetto, acting as an agent of the Center for Medicare services, as part of their MolDx program. We have successfully participated in externally monitored proficiency testing programs as mandated by CLIA. The quality and safety of this testing has been proven through an ongoing quality management program as mandated under CLIA. Without this testing we would not be able to care for many of the patients who come to Duke. The same is likely true for every other academic medical center. Therefore, DUHS recommends continued FDA enforcement discretion in several categories: LDTs deployed prior to the rule's enactment ("grandfathering"), Human Leukocyte Antigen (HLA) testing and Manual tests.

DUHS is in support of the proposal that allows LDTs offered prior to the date of this proposed rule and whose indications for use or performance have not changed to remain under the agency's enforcement discretion policy. The majority of LDTs currently in use would be considered low to moderate risk and rely on testing platforms produced by independent manufacturers which are commonly FDA approved for specific analytes and sample types. All of our existing LDTs have been monitored as part of a CLIA and CAP mandated quality management program, which includes external audits and proficiency testing. In short, we believe that existing LDTs at Duke and like AMCs do not pose a safety risk to patients. In fact, we believe the opposite, that the care of our Duke patients is greatly enhanced by their existence and that our potential inability to continue offering these tests because of the burden of cost and time that would result from another regulatory review would be devastating to patient care.

DUHS is in support of the proposal that enforcement discretion remain for some specific tests, including HLA, forensics, manual and public health surveillance tests. However, we would caution the FDA not to limit the category of manual tests to only those that do not utilize automation. Immunohistochemistry and flow cytometry are examples of a widely utilized technique that has advanced over the years from the less consistent manual process to one utilizing commercially available automation. In addition to a thorough validation, Pathologists utilizing these tests must also assess intra-

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assay positive and negative controls to confirm the accuracy of the test performance prior to the *manual* interpretation of any patient result. The interpretation of the result still relies on the visual assessment by the pathologist. This should still meet the intent of a manual test and remain under the FDA's enforcement discretion.

DUHS recommends that the FDA should keep adverse event reporting for clinical laboratories under their enforcement discretion. These types of events should be quite rare and for the vast majority of labs, likely never occur. As such, clinical laboratories have never had the need to report or educate themselves on the process. Therefore, until such a time the need is understood, education and guidance is provided, and the process is clear, we recommend not requiring adverse event reporting of existing LDTs.

3. The FDA's current regulatory structure and authority

DUHS understands the FDA's position regarding its regulatory authority over LDTs, however, we have serious concerns regarding the use of the FDA's existing medical device regulations as the foundation for LDT oversight and the negative impact that will have on clinical laboratories across the country and ultimately on patient care.

Risk classification. The current three-tiered risk classification system is based on medical devices and medical subspecialties and does not translate appropriately to laboratory-based tests or assays. Many well-established and validated LDTs would likely be categorized as being high risk when in reality their risk is mitigated by the fact that they are part of a multi-faceted medical assessment and are rarely used in isolation for clinical decision-making. As such, **DUHS recommends a re-assessment of the proposed risk classification system to better account for the actual risk to the patient and that until such time, the FDA consider delaying the implementation of the proposed roll out**.

Rare Disease and Investigational Device Exemptions. Currently the Humanitarian Device Exemption (HDE) Program creates a regulatory pathway for products intended for diseases or conditions that affect small (rare) populations (≤ 8000 individuals/year) as a Humanitarian Use Device (HUD). This process requires an HUD designation and HDE application that is akin to premarket approval (PMA). This is an overburdensome process which would predominantly affect AMC laboratories which often provide these types of laboratory services as part of their academic or service missions.

Similarly, the FDA is proposing to apply the investigational device exemption (IDE) process to any LDT being evaluated in a lab when determining its safety and effectiveness. While exemptions exist for devices that do not pose physical harm or impact treatment decisions, clinical laboratory tests do play an important role in clinical and treatment decisions and therefore it is uncertain if they would be considered exempt. Furthermore, the fact that FDA terminology often differs from that used in the CLIA regulatory process, we anticipate much confusion around when an IDE will be needed. **Accordingly, DUHS recommends continued enforcement discretion for LDTs related to rare diseases and for the need of utilizing the IDE process**.

In summary, Duke Health appreciates this opportunity to provide comments to the FDA's proposed rule regarding LDTs. We have concerns regarding the negative impact to patients and health care systems

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with such regulation. We stand ready as a resource to FDA, offering clinical perspectives and provider/patient experience data as appropriate to inform the agency's critical long-term decision-making on policies impacting patient care and medical innovation.

Please let us know if you have any questions or if any of the comments provided require further clarification.

Sincerely,

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