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December 4, 2023

Robert M. Califf
Commissioner
Food and Drug Administration (FDA)
Docket No. FDA-2023-N-2177
Submitted Electronically via <https://www.regulations.gov>
Re: Medical Devices: Laboratory Developed Tests

Dear Commissioner Califf:

University of California Health (“UCH”) is pleased to submit the following comments regarding the Food and Drug Administration (FDA) proposed rule on Medical Devices and Laboratory Developed Tests (LDTs). UCH shares the FDA’S goals of protecting public health by assuring the safety and effectiveness of LDTs and is grateful for its efforts in advancing this mission.

UCH includes six academic health centers located at the Davis, Irvine, Los Angeles, Riverside, San Diego, and San Francisco campuses and 20 health professional schools. Together, UCH programs are the nation’s largest health sciences and medical education training programs, the leading providers of certain specialty services and medical procedures, world leaders in clinical discoveries, and the second largest provider of Medicaid inpatient services in California.

UCH shares the FDA’S desire to ensure that LDTs provide accurate, timely diagnostic information so that providers, with patients and their families, can best determine a course of treatment. That is precisely the goal, the mandate, and the experience of the academic medical centers (AMCs) that have successfully developed LDTs for years to guide decisions about treatment plans. UCH is concerned that, as proposed, the FDA’S new enforcement policy would have an immediate and detrimental effect on the ability of AMCs to provide specialized and patient-centric medical care.

As further described below, these are UCH’S primary concerns:

1. The FDA has not established that a new broad, disruptive oversight mechanism is warranted with respect to LDTs created at AMCs, which differ substantially from other types of LDTs as a result of the highly-regulated

- environment in which they are created and their use in patients for whom commercially available tests are insufficient. The FDA's mandate to protect the public health points instead to a targeted enforcement policy to address the concerning reports that nearly all come from in vitro diagnostic products (IVDs) that are manufactured outside of AMCs.
2. The volume of tests that would need to be submitted to and reviewed by the FDA would create a regulatory bottleneck that would prevent the agency from addressing identified problems with direct-to-consumer and other LDTs developed purely for commercial purposes, decreasing the FDA's ability to respond to the public health threat the agency has identified.
 3. As a result of the proposed change in approach to LDTs, AMCs would be forced to make decisions for which tests FDA applications would be assembled and submitted, versus those which would be no longer used or not developed, to the detriment of the patients that could benefit from them.
 4. Rather than spur innovation through competition as asserted, the enforcement policy would instead result in tests that are never developed or can no longer be used. This threat to patient care is neither addressed in the proposal nor considered in the cost benefit analysis for the proposal.
 5. Patients with rare diseases/illnesses and pediatric patients will be hurt in particular, since most of the critical testing for these populations is performed using LDTs at AMCs. Rare illnesses include unusual infectious diseases that mainly affect immunocompromised patients (typically transplant patients). In most cases, these testing volumes are so low that commercial labs do not have a financial incentive to develop, validate and offer these tests commercially, which is why they are offered as LDTs by the AMCs that treat these populations. Given commercial labs do not have a financial incentive to develop and validate these tests, they will not have incentives to complete the lengthy and costly FDA approval process.

Accordingly, UCH urges the FDA to maintain its enforcement discretion for tests that are developed in these highly regulated, specialized environments to allow the agency to focus on those tests being marketed directly to patients without the safeguards and oversight already fundamental for LDTs at AMCs. Prior to embarking on a comprehensive enforcement policy, the FDA should: 1) prioritize collecting data about the LDTs that would be impacted and identifying those tests that present the highest risk to the public as a result of the environment in which they are developed and used, 2) pilot this new regulatory approach on the highest risk tests, and 3) use the resulting data on cost, time for review, and percent of applications rejected to determine the best approach for future enforcement activities.

UCH's specific comments are provided below.

AMC laboratories operate under unique circumstances.

Importantly, operating under the existing rules and process of CLIA High-Complexity Lab certification, the development of LDTs in pathology laboratories is a critical tool for advancing the science of medicine and training the next generation of pathologists. Pathologists work closely with physicians in a number of other specialties and scientific disciplines to develop diagnostic tools that are useful and advance patient care across a variety of illnesses. Losing the flexibility to operate LDTs in this setting will slow

both scientific progress and training. Enforcement discretion for AMCs will ensure that the development of new, innovative LDTs in an academic setting and the training of a future generation of pathologists will not be significantly constrained in the way it would be if pathology departments were limited to providing only the tests that will be financially viable enough to warrant the long and expensive FDA approval process.

Types of AMC LDTs That Need Enforcement Discretion

Academic medical centers, their clinicians and patients rely upon LDTs, which provide an otherwise unmet need to patients with serious and rare conditions. Below are examples of testing that occur at UCH laboratories that would be considered LDTs under the FDA proposal and would present a negative impact on patient outcomes without an AMC laboratory exemption in the proposed rule. This list does not represent the entirety of tests run at UCH laboratories that would be impacted, but is meant to illustrate some of the direct clinical harms that could result from a rule that does not allow continued enforcement discretion for AMC LDTs.

1) Cytogenetics

Testing in cytogenetics covers genetic diseases and cancer diagnoses and would negatively impact patient care by delaying care related to cancer diagnostics, prenatal diagnostics, genetic disorders identified in the neonatal/postnatal period including but not limited to rare microdeletion syndromes, disorders of sexual development, pregnancy loss, and reproductive risk assessment. Some samples collected for cytogenetic testing (amniotic fluids, lymph nodes) have short stability windows for testing and delays caused by routing/transport to alternate labs would have a negative impact on the ability to provide results. There are no FDA-approved testing methods available for these assays; there would be no alternatives to purchase, nor outside labs where testing could be routed. Some testing covers rare diseases with low volume testing, where there is little incentive for larger manufacturers or laboratories to submit to the FDA for approval. This will be a huge undertaking, as all probes associated with fluorescence in situ hybridization (FISH) testing are IVDs and are not FDA-approved.

2) Clinical Genomics

Testing in clinical genomics covers genetic diseases, prenatal disorders and cancer diagnosis. There are often no FDA-approved alternatives for many of the diseases and conditions for which we have LDTs, negatively affecting patients needing the cardiomyopathy and hematologic malignancy panels. Samples in this area, particularly associated with clonality, have sensitive stability requirements. Transport to outside labs could have negative effects on results. NGS has become a staple for cancer diagnosis and treatment; the service lines for these conditions depend on turnaround time for test results. Reference laboratories no longer achieve turnaround times compatible with supporting timely clinical decision-making for patients and supporting cost-effective workflows. For example, the Neogenomics NeoType Myeloid Panel reports turnaround times of 14 days whereas in-house sequencing provides significantly lower turnaround times of 2 to 7 days. Next-generation sequencing LDTs offered by AMCs provide an unquantifiable benefit to patients. To upend this will create unanticipated disruptions in healthcare.

3) Toxicology/Microbiology

The proposed FDA regulation has the potential to significantly harm UCH's ability to provide toxicology tests to our patients. This would include drugs of abuse confirmation testing by or liquid chromatography (LC) tandem mass spectrometry (MS) (LC/MS). For example, University of California, San Diego (UCSD) performs an annual volume of over 20,000 LDTs solely on toxicology. The proposed rule would put a number of toxicology LDTs at risk, including (but not limited to) the confirmation of amphetamines, cocaine metabolite, opiates, PCP, THCOOH, and benzodiazepines. Without LC/MS, providers will not be able to determine if a patient is taking morphine or heroin, which has important implications for patient care. The proposed rule would also halt the current practice of measuring antifungal drug concentrations for therapeutic drug monitoring purposes. This would adversely affect treatment of infectious diseases, often in immunocompromised patients (typically organ transplant patients) such as candidiasis, aspergillosis, and cryptococcosis. Moreover, many of the tests in our microbiology labs are LDTs due to the clinical needs of our immunocompromised patients who are prone to infections caused by unusual or emerging pathogens that are often challenging to identify. For example, UCLA developed and validated next-generation sequencing (NGS)-based bacterial and fungal species identification tests to identify clinical isolates that are not able to be identified by conventional methods or the FDA-approved MALDI-TOF platforms.¹ Not having these LDTs will make these patients with rare infectious diseases lose access to the only available tests that can precisely identify the exact cause of their infections, potentially causing severe harm, including death.

4) Pediatrics

There are numerous examples of FDA approved tests that do not work for children. These include tests with instructions for use that exclude pediatric age ranges. Other FDA-approved tests are available for testing of blood, plasma and serum, but testing on other types of body fluids or specimens that are needed to care for children's specific needs are not approved. Still other FDA approved tests may be used to measure the effectiveness of a pediatric drug that is used "off label." These tests must remain available for assuring the diagnosis and treatment management are confirmed to prevent misdiagnosis.

One specific example is herpes simplex virus (HSV) testing for neonates who are clinically suspected to have congenital HSV infection, a disease which often is deadly and requires rapid diagnosis and treatment. There are NO FDA-approved tests currently for HSV in neonates. Our UCH labs use a LDT, which is a modified FDA approved PCR test, for this patient population.

5) Chemistry

There are many LDTs in genetics/genomics, cancer diagnostics, cytogenetics and hematology areas of clinical labs. For example, University of California, San Francisco (UCSF) performs over 300 LDTs solely on genetics/genomics, cancer diagnostics, cytogenetics and hematology areas of clinical lab, but these tests only represent a small fraction (less than 1%) of the **8 million total tests** annually performed by UCSF. The LDTs at UCSF's clinical chemistry lab are mostly used for therapeutic drug/hormone monitoring, performed by LC/MS. Busulfan monitoring is used often

¹ Salem-Bango, Z., Price, T.K., Chan, J.L., Chandrasekaran, S., Garner, O.B., Yang, S. (2023, January 29). Fungal Whole-Genome Sequencing for Species Identification: From Test Development to Clinical Utilization. <https://pubmed.ncbi.nlm.nih.gov/36836298>

by the Hematology Oncology services, and a lack of this test would severely impact UCSF's bone marrow transplant program. There are no FDA-approved immunoassays available to quantify busulfan. When patients are treated with this drug, therapeutic drug monitoring is required due to the narrow therapeutic index - there is a requirement for the drug concentrations to be high enough to be efficacious, but low enough so that they do not cause toxicity. Busulfan is used in patients who are undergoing a hematopoietic stem cell transplant for example, for leukemia, gene therapy and also for patients with severe combined immunodeficiency (SCID).

The proposed rule would disrupt patient care at AMCs and pose significant risks to patient safety. Previous versions of proposed regulation of LDTs were tiered according to risk, an approach that takes into consideration patient safety, but also enhances patient care and minimizes impact on the current standard of care, which necessarily relies on LDTs.

Additionally, the FDA's proposed rule has the potential to significantly harm the resilience of testing at AMC facilities. Currently, UCH laboratories are able to make substitutions when shortages occur in established reagents used for FDA-approved tests; these substitutions allow our laboratories to continue testing as a LDT until supplies stabilize. For example, demand can spike quickly for testing in infectious disease outbreaks and the ability to continue testing in the face of shortages can be a critical tool in the public health response.

The large volume of LDTs would make implementation of the proposed enforcement policy infeasible for both the FDA and AMCs, ultimately to the detriment of patients and to the FDA's stated goal of addressing identified urgent public health threats.

As proposed, the number of test applications that would need to be submitted in the four (4) years after the policy is finalized far exceeds the capabilities of the AMC community, both collectively and per institution. The volume of tests for which an application would be required would very quickly outstrip the resources, expertise and personnel at AMCs, few of which have designated staff for FDA regulatory submissions. Moreover, clinical labs nationally are experiencing staffing shortages that are not expected to abate in the near term. In a recent survey by the Association of Pathology Chairs, 100% of the 39 responding labs indicated they were experiencing staffing shortages. Staffing shortages range from 7-19% over all areas of the lab in a recent survey of vacancy rates by the American Society of Clinical Pathology (Garcia et al, Am. J. Clin. Path. 2023; 160 doi:10.1093/ajcp/aqad149), and several lab areas with the highest numbers of LDTs (such as Toxicology) have the highest vacancy rates (17%). The compliance mechanisms at these academic centers are extensive, focused on the work needed for the robust accreditation of labs through CLIA, hospital accreditation through the Joint Commission, many other regulatory and accreditation bodies, and the exacting standards the labs use to validate their own tests, using feedback and expertise from the academic health care providers. Even though the FDA has suggested that laboratories could continue to deploy LDTs while awaiting the FDA's review of the submission, the rate of submission required would quickly overwhelm most academic institutions, with the result that some of those tests would no longer be offered.

UCH shares the concerns expressed by many others that the FDA itself does not have the resources or capacity to be able to undertake a timely review of the vast numbers of applications. A conservative estimate of the number of tests that would be submitted in the first year alone would be many times the total number of medical device approvals that FDA typically completes in a year, with an increasing

number of complex applications in subsequent years. Without a substantial increase in staff and review capacity at the FDA, the successful and meaningful implementation of this policy would be thwarted, and the true expense and burden of the program would be difficult to assess.

The FDA should instead focus on rapidly deploying oversight of those tests for which enforcement discretion is no longer appropriate-- non-validated, direct-to-consumer commercial tests that have taken advantage of the FDA's enforcement discretion of LDTs and pose a significant threat to public health, which aligns with the concerns raised by the FDA in its background justification for the policy change:

- The test is provided directly to consumers for the purpose of them making health care decision without the benefit of interpretation by a healthcare provider.
- The test is developed for commercial purposes by an entity unaffiliated with an AMC.

Conclusion

UCH appreciates the opportunity to submit comments on the proposed rule. We urge the FDA to consider the disparate impacts that the proposed rule may have on the unique care that AMCs provide to a diverse patient population. The increase in the FDA oversight of LDTs will slow down innovation and access to testing. This will not only delay the advance of critical testing but also cause a negative impact on patient outcomes. Those who seek care at AMCs rely on their health care providers to have access to accurate and timely diagnostic tests to guide treatment decisions. We encourage the FDA to provide an exemption for AMC laboratories to ensure that UCH can continue providing access to cutting edge care and provide critical testing that is not always available elsewhere.

If you have any questions, please contact Tam M. Ma, JD, Associate Vice President for Health Policy and Regulatory Affairs at Tam.Ma@ucop.edu.

Sincerely,



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