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Advancing Health in America

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December 1, 2023

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Docket No. FDA-2023-N-2177: Medical Devices: Laboratory Developed Tests Proposed Rule (Vol. 88, No. 190), October 3, 2023.

Dear Commissioner Califf:

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, and our clinician partners — including more than 270,000 affiliated physicians, 2 million nurses and other caregivers — and the 43,000 health care leaders who belong to our professional membership groups, the American Hospital Association (AHA) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) Laboratory Developed Tests (LDTs) proposed rule.

Many hospitals and health care systems develop and use LDTs, particularly larger hospitals, including academic medical centers. LDTs are diagnostic tests that are not commercially distributed to other laboratories but, instead, are developed, validated and performed in-house by individual laboratories. They range from routine tests such as blood counts to more complex molecular and genetic tests for cancer, heart disease, and rare and infectious diseases. LDTs are critical in providing timely patient access to accurate and high-quality testing for many conditions for which no commercial tests exist or where an existing test does not meet current clinical needs. They also provide physicians with important clinical information to diagnose and treat patients and are essential to the practice of all areas of medicine. Indeed, these tests are typically developed at the request of, and in close collaboration with, clinical caregivers.

The AHA commends the FDA for its work on LDTs and in vitro diagnostics products (IVDs) offered as LDTs, along with the agency's commitment to protecting the public's health. We agree that there is a need for additional oversight of the development and use of some LDTs and IVDs offered as LDTs. **However, we strongly believe that the FDA should not apply its device regulations to hospital and health system LDTs. These tests are not devices; rather, they are diagnostic tools developed and used**

in the context of patient care. As such, regulating them using the device regulatory framework would have an unquestionably negative impact on patients' access to essential testing. It would also disrupt medical innovation in a field demonstrating tremendous benefits to patients and providers. Instead, AHA urges the FDA to continue to apply its enforcement discretion to hospital and health system LDTs and defer regulation of these laboratory tests mainly to the Centers for Medicare & Medicaid Services (CMS) strict Clinical Laboratory Improvement Amendments (CLIA) oversight, the College of American Pathologists (CAP) accreditation and state law, as it currently does.

Enforcement discretion is particularly important for low- and moderate-risk LDTs, including for modifications to FDA-approved IVDs, and for laboratories subject to established laboratory evaluations programs, such as that developed by New York state. Moreover, in recent years, Congress has worked with laboratory stakeholders, including hospitals and health systems, to develop legislative approaches that build on existing, rigorous regulatory oversight for hospital-based testing. The FDA may wish to consider some additional flexibilities taken from these efforts for incorporation into their final rule.

Despite the agency's decision not to extend the comment period as we and many other stakeholders requested, we have consulted with our hospital and health system members to assess the proposed rule's potential impact on the critically important work hospitals do to ensure safe, effective and accessible diagnostic testing for their patients. **In short, continued enforcement discretion is necessary because the proposed rule is far too broad, does not contain sufficient detail, and, as written, has the potential to significantly increase hospital burden and costs, stifle innovation, and ultimately decrease hospitals' ability to provide the most effective and appropriate care to patients.**

For example, if implemented as proposed, many hospitals would be unable to bear the significant costs associated with complying with the FDA's unfamiliar device regulatory framework and exorbitant user fees. Efforts to comply would cause confusion and delays that would prevent hospital and health system laboratories from continuing to develop cutting-edge LDTs in response to immediate clinical-care needs. This could dramatically slow down advances in laboratory medicine, leading to patients' loss of access to many critical tests.

ADDITIONAL DETAIL IS NEEDED

The FDA provides minimal detail on the proposed regulatory changes in this rule. The agency merely makes explicit that IVDs, including those "manufactured" by laboratories, would be considered devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act), and therefore would be subject to the full scope of the FD&C medical device regulations after a proposed four-year phase out of the FDA's

enforcement discretion.[1] The rule does not include any relevant or specific information about how the FDA's medical device regulations would apply to LDTs. Indeed, the FDA itself has acknowledged it would need to publish a series of guidance documents to clarify its enforcement approach after the final rule is issued. **Thus, it is currently impossible for hospital and health system laboratories to fully assess how each part of the device regulations would apply to their LDTs. This uncertainty is problematic; it further underscores the need for continued enforcement discretion, most particularly in certain areas, such as for low- and moderate risk tests.**

Our specific comments and recommendations follow.

BROAD SCOPE OF THE RULE

Differentiating Hospital and Health System Clinical Laboratories from IVD Manufacturers. Hospital and health system-based clinical laboratories have several distinctive characteristics that distinguish them from other types of commercial laboratories and IVD manufacturers that develop and market IVDs and IVDs offered as LDTs. These factors are a large part of the reason why the FDA for many years applied enforcement discretion to the development and use of LDTs in hospitals and health systems.

Specifically, hospital and health system laboratories that develop LDTs:

- Are typically integral components of teaching hospitals and/or academic institutions which provide direct patient medical care.
- Have a primary role in providing testing and interpretation for the benefit of the patients and clinicians in affiliated hospitals or health systems as a part of larger clinical treatment decision-making processes for patients of these institutions.
- Have been certified to conduct high-complexity tests by the CMS through the CLIA program.
- Are subject to comprehensive oversight and regulation by other federal, state and private regulatory bodies, such as: CMS' enforcement of the Medicare Conditions of Participation (COP); state agencies' licensing and oversight of the function of these facilities; and respected laboratory accreditation organizations, such as CAP and The Joint Commission's (TJC) provisions of

[1] By adding to § 809.3 Definitions "(a) * * * These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory."

stringent laboratory and other oversight. In fact, CAP addresses LDTs in five separate checklists as part of its accreditation process.[2]

Moreover, unlike commercial companies that develop IVDs and IVDs offered as LDTs, hospital and health system LDTs are typically developed at the request of, and in close collaboration with, clinical caregivers for use within the context of comprehensive patient care within a hospital or health system. That is, the testing is conducted for hospital inpatients and outpatients and provides physicians with important clinical information to diagnose and treat patients in all areas of medicine.

Given that hospitals and health systems integrate laboratory test development and use into the continuum of patient care, the many other safeguards for patients to which such laboratories are already subject, and the FDA's existing ability to investigate and remove any IVD or LDT from the market regardless of the entity that develops it, **the AHA strongly recommends that the FDA not prioritize for oversight these clinical laboratories and their LDTs. Rather, we recommend that the FDA continue to use its general enforcement discretion for hospital- and health system-developed LDTs and that they be exempt from the proposed regulatory changes.**

We further recommend that, for health systems with multiple locations, this enforcement discretion be applied at the health system level so that LDTs developed by one health system laboratory would be permitted to be used for the care of patients located in another health system location without having to forfeit their enforcement discretion. This is particularly critical for certain specialties where care is regionalized, such as pediatric specialty care, where the patient would only have access to such testing if the LDT developed by one health system clinical laboratory can be performed at another system location. This is especially true for children on Medicaid with medically complex conditions, like cancer or other rare diseases. This approach enables children to receive follow-up and continuing care from local providers, allowing them to stay in their homes, communities and schools, reducing stress and burden on their families and overall well-being.

Instead, the AHA recommends that the FDA apply its regulatory oversight only to commercial manufacturers and for-profit laboratories developing, selling and distributing IVD test kits and IVDs offered as LDTs, all of which, unlike hospital and health system LDTs, are developed outside of the physician-patient context. The IVDs and IVDs offered as LDTs sold by such manufacturers do not have the mitigating factors described above and, as a result, often have a history of serious issues and deficiencies that may cause patient harm and danger to the public's health. An example is the widely reported issue with prenatal genetic tests

[2] The biannual CAP accreditation inspection process includes LDT validation requirements in five checklists. These include the "all common" checklist, which all labs must go through, and the checklists for molecular pathology, microbiology, anatomic pathology and cytogenetics.

developed by commercial IVD companies.[3] Other examples include IVDs offered as LDTs by commercial manufacturers for detecting autism[4], detecting genetic variants for breast cancer[5] and for predicting response to certain medications.[6]

Modifications to FDA-approved Tests. Under current FDA device regulations, certain types of changes or modifications to FDA-approved or -cleared devices require a premarket approval (PMA) supplement, a new 510(k) or other submission to the FDA. Under the proposed rule, such modifications to IVDs and LDTs, which are very common and necessary practices undertaken by hospitals and health system laboratories, would also become subject to these device regulations.

For hospital and health system purposes, modifications may improve the performance of approved diagnostic tests on certain patient populations, address problems or issues with the FDA-approved devices and allow the latest research and clinical knowledge to be rapidly incorporated. They are intended to improve testing accuracy and safety. For example, changes could be made to scoring systems or to add specimen types that are dictated by medical guidelines or regulations (e.g., National Comprehensive Cancer Network, American Society of Clinical Oncology or CAP). They could be made to modify sample locations or types, which is particularly important in pediatric specialty care. For example, in cases of perinatal transmission, testing for *C. trachomatis* and *N. gonorrhoeae* polymerase chain reaction using the commonly available Cepheid platform is not FDA-approved for use in swabs of eye, rectum or throat mucosal membranes, but modifications resulting in LDTs permit this non-invasive testing of newborns. Such modified LDTs are regulated by CLIA and must undergo validation prior to their use for patients.

To require a hospital or health system laboratory to prepare burdensome and costly submissions to the FDA, such as a PMA supplement or a new 510(k) for all these modifications is not practicable. It would be too onerous and would serve as a disincentive for laboratories that otherwise would make such changes to improve the capabilities of FDA-approved tests. This would harm patient access to the most advanced diagnostics. **As such, low- and moderate-risk modifications to commercially marketed IVDs certainly should be exempted from FDA regulatory oversight, as long as the laboratory is in compliance with the CLIA regulations and is subject to the mitigating factors described above.**

Leveraging Established Laboratory Evaluation Programs. The AHA appreciates that the FDA requested comments on whether the agency should leverage established laboratory evaluation programs when considering which tests to subject to its device

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[3] https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html
[4] https://www.spectrumnews.org/news/blood-test-autism-not-fast-experts-say/
[5] U.S. FDA, "Letter to deCODEme Complete Scan," https://www.fda.gov/media/79216/download
[6] U.S. FDA, "Letter to 23andMe Personal Genome Service," http://web.archive.org/web/20191214010336/https:/www.fda.gov/media/79205/download.

regulations. Indeed, many hospital and health system laboratories participate in validity and quality review programs, such as those directed by the New York State Department of Health's (NYS-DOH's) Wadsworth Center. **The value of such programs is clear and yet another reason that the FDA should continue to use its general enforcement discretion for hospital- and health system-developed LDTs, including for those approved by programs such as the Wadsworth Center's Clinical Laboratory Evaluation Program (CLEP).** In New York state, LDTs are already subject to review and approval by the Wadsworth Center and its CLEP, under which the state surveys New York laboratories in lieu of CMS, given the quality of the Wadsworth Center's standards and survey process. The Wadsworth Center's CLEP has been reviewing LDTs since 1991. It also reviews and approves not only LDTs developed by laboratories in New York state, but also those developed in laboratories across the country and the world.

In the proposed rule, the FDA asks about the specific characteristics of and activities within this program that would justify an enforcement discretion approach. The CLEP's first step of review is for a committee of subject matter experts to assign each LDT to a risk category that determines the subsequent technical review process. This process allows certain low-risk tests to be approved without technical review. It also allows Wadsworth to prioritize reviews for higher-risk tests and has enabled laboratories to begin offering lower-risk tests more quickly. The only LDTs that do not go through the committee are those submitted by laboratories that lack approval to offer that category of testing, because these tests are automatically designated high-risk.

The risk criteria include the laboratory's experience with the test method, the importance of the test in diagnosis/prognosis/treatment and the impact of an inaccurate test result on the patient. LDTs identified as low-risk or that fall under an exemption are not subject to technical review and are approved at the time of risk assignment. In contrast, high-risk LDTs are subject to technical review and the laboratory cannot offer the test until fully approved. Moderate-risk LDTs are subject to technical review, but they are conditionally approved and can be offered by the laboratory during the technical review process. Tests used only for clinical trials are not reviewed for analytical and clinical validity.

Last, but certainly not least, the Wadsworth Center's procedures for reviewing LDTs are considered to be of such high quality and so rigorous that the FDA itself has accredited the Wadsworth Center as a third-party reviewer on behalf of the agency for the premarket clearance process.

HIGH BURDEN AND COST

Applying the FDA's device regulations to LDTs, even with a four-year phase out of the current enforcement discretion, would pose nearly unsurmountable burdens and costs on both the FDA and hospital and health system laboratories. The unfortunate outcome likely would be the decline in the rate of clinical innovation, which would negatively

impact the U.S.' ability to keep our health care system at the forefront of discovery, provide quality care to patients, and respond quickly to emerging public health risks. **This is yet another reason we urge FDA to continue to use enforcement discretion, particularly for the areas we have highlighted, for LDTs developed by hospitals and health systems.**

Increased Burden on the FDA and Hospitals. Subjecting all hospital and health system LDTs to the FDA's device regulations would result in a tremendous surge in the number of applications submitted to the FDA. This is because under these regulations, nearly all LDTs would require a PMA, a 510(k), or other application to the FDA. One large health system noted that they have at least 1,600 existing LDTs; under the proposed rule, they would need to submit 1,600 applications for approval in the first year of the phase-in. Another large hospital has developed over 150 new LDTs in the areas of microbiology, chemistry, molecular pathology, transplant medicine and digital pathology over just the last two years, for each of which during the first year of the phase-out they would have to submit applications. These figures are from one single health system and one additional hospital out of AHA's nearly 5,000 member hospitals. Because a substantial number of these hospitals likely develop LDTs, such a change would quickly result in overwhelming burdens on the FDA, hospitals and health systems.

Even under the current scope of the FDA's oversight, the agency does not have a strong track record for timely processing of submissions for PMAs, 510Ks and emergency use authorizations (EUAs). For example, for Class 2 devices, the FDA is required to respond to complete 510(k) submissions with a notice indicating a complete application and acceptance for review within 60 days of receipt. However, according to a Qualio report[7], currently the average length of time for clearance under the traditional 510(k) pathway is almost three times as long — nearly six months. For Class 3 devices using the PMA pathway, the average approval time is over four times as long — over eight months. Several hospitals laboratory leaders with whom we consulted said that during the COVID-19 pandemic they submitted EUA applications to the FDA and are still awaiting a final response from the FDA — over two years later. The novelty of the FDA review process for hospitals and health systems means that the processing timeframe for these applications would likely be even longer.

Looking at the figures another way, according to a recent report from Emergo[8], in 2022 the FDA received approximately 18,800 submissions. Yet, under the proposed rule, additional submissions likely would be in the tens of thousands. We are concerned that the FDA is not prepared to process this volume of applications in a reasonable timeframe.

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[7] https://www.qualio.com/blog/fda-medical-device-approval-process
[8] https://www.emergobyul.com/news/us-fda-annual-report-nearly-6000-medical-device-authorizations-2022#:~:text=In%202022%2C%20FDA%20authorized%3A,3%2C229%20510(k)s

For hospitals and health systems that have hundreds, or even thousands of LDTs that would need to go through this process, this poses not only a delay for approving already existing LDTs but would also drastically slow down medical innovation for new LDTs and for modifications to currently marketed IVDs/LDTs.

Increased Costs to Hospitals. Hospitals and health systems continue to face significant financial challenges as sustained increases in the costs required to care for patients have been met with woefully inadequate increases in reimbursement. In fact, between 2019 and 2022, hospitals' expenses increased 17.5%, while Medicare reimbursement for inpatient care only increased 7.5%. This reality, in part, created an environment where in the first quarter of 2023 the highest number of bond defaults among hospitals occurred in over a decade. While hospitals have seen a meager stabilization of their operating margins in 2023 relative to historic lows in 2022, with median operating margins hovering around 1%, many hospitals continue to operate in the red. Moreover, workforce shortages coupled with upward wage pressures continue to create new and challenging workforce dynamics for hospitals and health systems. These changes are particularly problematic because labor on average accounts for about half of a hospital's budget. Collectively, these indicators signal uncertainty to hospital operations and financing in the future.

At a time when hospitals and health systems are facing persistent financial headwinds, we are very concerned about the impact of the FDA's proposal to impose its costly and largely redundant regulatory framework on hospitals, particularly in terms of compliance with the proposed rule. Such compliance would impose tremendous additional costs on hospitals and health systems, including the additional staff time and outside expertise needed to understand, complete and manage FDA applications for both existing and new LDTs, as well as the exorbitant FDA user-fee costs[9] that would be required for nearly every LDT.

Hospitals and health systems, unlike traditional device manufacturers, are largely inexperienced in working through the FDA's regulatory processes. As a result, they do not have internal FDA regulatory mechanisms in place to complete all the steps necessary to gain approval in a timely and accurate manner. Thus, they would have to retain experienced consultants and outside counsels to prepare, submit and manage their applications. These new costs would rapidly escalate for the hundreds or thousands of applications that hospitals and health systems would have to submit to the FDA in the first year of the phase-in alone.

The FDA's user fees would also rapidly escalate with the number of applications filed. For instance, in 2023, the FDA charges $6,493 to register a facility. In 2023, the FDA

[9] https://www.registrarcorp.com/blog/fda-announces-new-medical-device-user-fees-for-fy-2023/

charges $19,870 for one 510(k) application, $441,547 for one De Novo application[10] and $132,464 for one PMA. Although there are reduced rates for "small businesses," the fact that hospitals would need to submit many applications, both for their existing LDTs as well as new and modified LDTs, would rapidly escalate these costs. **For example, in the health system example we mentioned above, even if all of the health system's 1,600 applications were 510(k) applications, they would be required to pay a staggering $31,798,493 throughout the approval process.** Even if this health system was able to qualify as a "small business," the amount would still be almost $8 million — a substantial amount. Hospitals and health systems simply will not be able to absorb these costs. Indeed, several hospital leaders told us that these fees would lead to tough choices about which LDTs they could continue to offer and restrictions on how they can adapt their diagnostic testing to care for patients.

Imposing these additional costs and burdens is untenable and would ultimately lead to institutional decisions that would limit the types and number of LDTs offered by the institution, leading to a substantial reduction in patient access to innovative and targeted diagnostic tests.

1976-Type LDT. The FDA proposes to continue to apply its general enforcement discretion to 1976-Type-LDTs. The rule describes such tests as having characteristics such as: 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. **However, additional information is needed on which LDTs would fall into this category.** Hospitals have many tests that could be considered 1976-Type-LDTs; given the importance of this possible grandfathering, we recommend that the final rule include much greater detail, including more specific definition of terms such as "automation" and "specialized expertise," as well as and specific examples of such LDTs.

We appreciate your consideration of these issues. Please contact me if you have questions or feel free to have a member of your team contact Roslyne Schulman, AHA's director for policy, at rschulman@aha.org.

Sincerely,

/s/

Stacey Hughes
Executive Vice President

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[10] The De Novo request provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.