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December 4, 2023

Commissioner Robert Califf, MD
c/o Division of Dockets Management (HFA-305) Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Medical Devices; Laboratory Developed Tests. [Docket No. FDA-2023-N-2177]

Dear Commissioner Califf,

On behalf of the more than 200 children's hospitals nationwide, we appreciate the opportunity to comment on the FDA's proposed rule, *"Medical Devices; Laboratory Developed Tests." Requirements Related to the Mental Health Parity and Addiction Equity Act (MHPAEA*). We share the goals of the FDA in protecting the public health by assuring the safety and effectiveness of laboratory developed tests (LDTs) and thank you for your work to forward this mission. This rule has a unique impact on children and we urge you to revise it to address their needs.

The nation's children's hospitals are dedicated to advancing child health through innovations in the quality, cost and delivery of care—regardless of payer—and serve as a vital safety net for uninsured, underinsured and publicly insured children. Children's hospitals account for fewer than 2% of hospitals in the United States, but care for almost one-half of children admitted to hospitals and provide tertiary and subspecialty care for most children with serious illnesses and complex chronic conditions. We are patient-centered, research-focused institutions and leading centers for discovery and innovation in pediatric healthcare. We are also regional centers for children's health, providing highly specialized pediatric care across large geographic areas.

Pediatric health care requires specialized medications, diagnostics, tests, therapeutics, and equipment that the nation's children's hospitals provide. Importantly, diagnostic tools and treatments that are developed for adult populations do not immediately or easily translate to pediatrics. Therefore, LDTs fill a critical gap in the practice of pediatric medicine as they allow for accurate, timely, accessible, and high-quality testing for many pediatric conditions for which no commercial test exists or where an existing test does not meet current clinical needs. They are critical to our ability to provide timely, cost-effective, and high-quality diagnostics and care for all children and particularly for children in need of treatment for rare and difficult-to-diagnose pediatric disorders.

It is essential that FDA ensure that all children continue to have access to life-saving diagnostics and timely care. Therefore, we recommend that the FDA continue its current general enforcement discretion approach for all hospital and health system LDTs. At a minimum, enforcement discretion should continue for the following pediatric-related LDTs, which will enable children's hospitals to meet the specialized needs of the children.

- Tests for diseases/diagnoses that are related to infancy or childhood.
- Tests that must be altered or modified for pediatric off-label use.
- Tests for pediatric rare and orphan diseases.
- Tests that cannot be done by adult-focused laboratories.
- Tests that are run in hospitals for immediate patient care.

Children are not just little adults. They are constantly growing and developing, and their health care needs and the delivery system to meet those needs are different from those of adults. LDTs developed and used in pediatric healthcare settings

account for all stages of childhood development, from newborn through adolescence and young adulthood and include numerous genetic and heritable diseases, pediatric cancers, and acquired conditions that are not well-represented in adult healthcare practice.

Our detailed comments are below.

Background on Pediatric Clinical Tests

Children's hospitals clinical laboratories fill the gaps in pediatric diagnostic testing by either developing tests from scratch that are needed by their patients or performing the extensive validation work needed to demonstrate that an FDA-approved test for adults can safely and reliably be used for children. FDA- approved tests for pediatric diseases frequently do not exist for several reasons. First, numerous FDA- approved tests could potentially be used for children but are not validated for such use. Furthermore, these tests seldom include pediatric reference (normal) ranges. Instead, test instructions will specify an age under which the test should not be offered.

In addition, the relatively smaller population size and unique aspects of studying children are barriers to commercialization of tests for pediatric diseases. Similar to the development of new pharmaceuticals, which are usually developed for adults, children are often left behind in the development of commercial testing, given the small market and highly specialized nature of pediatric diseases.

Therefore, children's hospital laboratories offer several hundred in-house LDTs or modified FDA tests, all developed and validated following requirements specified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA). These laboratories are tightly regulated and further accredited under CLIA and by their states, the College of American Pathologists or the Joint Commission – in accordance with the CLIA regulations -- to ensure their practices are compliant with federal regulations and patient safety standards.

Children's hospitals' in-house tests offer precise and accurate results; they are a critical component of lifesaving treatment plans designed for children and they fill a critical gap of health care that is not provided by commercial companies. These tests include standard laboratory testing for routine diagnostic needs, as well as assays to diagnose rare genetic abnormalities (like newborn screening and confirmatory tests); tests that monitor pediatric therapeutic drug levels and interventions for heritable diseases of metabolism and other genetic disorders; toxicology screening; and tests related to the diagnosis, treatment and management of immune system dysfunction and pediatric cancers, including stem cell transplantation and gene/biotherapies.

Continued Enforcement Discretion for Pediatric-Related Tests

We urge the FDA to continue general enforcement discretion for all pediatric-related LDTs. Specifically, enforcement discretion should continue for: tests for diseases/diagnoses that are related to infancy or childhood; tests that must be altered or modified for pediatric off-label use; tests for pediatric rare and orphan diseases; tests that cannot be done by adult focused laboratory; and tests that are run in hospitals for immediate patient care. These tests are vital to our ability to meet the needs of children of all ages who rely on us for timely, high-quality and age-appropriate care.

- **Tests for diseases/diagnoses that are related to infancy or childhood.**
  For many pediatric-related diseases and diagnoses there are no FDA-approved tests. For example, LDTs play a crucial role in the diagnosis and treatment of childhood leukemia, the most common cancer in children. First, the test used to diagnose childhood leukemia, using flow cytometry, is an LDT that may be individualized within different children's hospital laboratories for the specific child. Second, the care of these children relies on an LDT. The curative treatment for children with leukemia is bone marrow or stem cell transplantation. and the genetic test used to monitor the health of the bone marrow transplant after it happens (short-tandem repeat analysis), is an LDT. For children, there are no FDA-approved alternatives available for these time-sensitive tests that enable immediate clinical decision making by their treating pediatricians.

- **Tests that must be altered or modified for pediatric off-label use.**
  As noted above, FDA-approved tests for pediatric diseases frequently do not exist. Furthermore, there are numerous situations in which the instructions for use for an FDA-approved test do not include the parameters needed to use the test in the pediatric population. Numerous FDA-approved tests could potentially be used for children but are not validated for children under a certain age or for their particular condition, or they do not include pediatric reference ranges.

  For example, 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. Other examples include Thromboelastographic testing, which is used to determine bleeding risk in surgical patients of all ages, but is not approved by the FDA for use in patients under the age of 18 years.

- **Tests for pediatric rare and orphan diseases.**
  Many pediatric hospital laboratories develop their own genetic testing panels that prioritize the types of genetic abnormalities that are seen in children and can lead to severe forms of inherited and rare diseases in children and many types of pediatric cancers. They do so because developing assays to diagnose these rare conditions is often out of scope for manufacturers because of the low volume of testing and consequent low monetary returns. Furthermore, even where adults and children present with the same cancer, the genetic driver for the cancer in children is different, which means that their pediatric subspecialist cannot rely on the same tests that are used in adults. LDTs allow children's hospital laboratories to develop genetic tests specific to pediatric populations, modify testing rapidly to include additional genes that are newly implicated in childhood disease, and adopt more efficient and sensitive testing platforms and methodologies.

  For example, many genetic diseases called "inborn errors of metabolism" are considered so high-risk for early death that they are included in the "newborn screening test" (NBS) that all states require be performed on all newborns. Those NBS tests are usually LDTs. Furthermore, whenever a. NBS test is positive, the child patient needs immediate medical consultation and testing to confirm the diagnosis. The confirmatory tests are all highly specialized tests that do not have FDA-approved versions for children and are LDTs. Children with these diseases require ongoing monitoring for the rest of their lives to ensure their specialized diet is keeping their system in check. LDTs are used to monitor affected patients throughout their life span to prevent seizures, brain damage, coma, and death.

- **Tests that cannot be done by adult-focused laboratories.**
  LDTs allow children's hospital laboratories to serve pediatric patients of all ages through the use of age-appropriate equipment and needed technical changes (e.g., changing the sample volumes, expanding the reportable range, changing reference intervals, etc.) to account for the full range of human growth and development. Adult-focused laboratories often do not have the pediatric-specific instrumentation (e.g., tubing, syringes, etc.) that must be used when testing newborns, infants, small children and even older children. In contrast, children's hospitals treat patients from infancy through young adulthood and have the right-sized equipment to conduct diagnostic tests as needed, regardless of the child's age or size. For example, extremely small sample sizes and equipment, including microtainer tubes are needed when testing low-birth-weight preterm newborns.

  Furthermore, adult-focused laboratories typically do not use pediatric reference ranges for clinical decision-making. Children's hospitals routinely develop different reference ranges to reflect the different stages of a child's development and to guide and inform age-appropriate clinical decision-making. For example, for common tests of hormone levels, pediatric clinical laboratories have to determine pediatric reference ranges across the age range (e.g., testosterone level in an adult male is different than a 2-year-old boy) using LDTs.

- **Tests for immediate patient care.**
  Having an in-house LDT allows rapid turnaround time to get test results, ensuring that timely clinical decisions can be made and care is not delayed. For example, pediatric solid tumors are treated with the chemotherapy drug, Methotrexate, at high dosing levels. This dosing regimen is only used for pediatric cancers, not adult cancers. The effective use of Methotrexate requires a rapid return of test results to ascertain whether dosing levels should be modified to prevent under or overtreatment, which can lead to kidney or other organ damage. LDTs are used in these clinical situations to permit rapid test turnaround time.

Regulatory and Financial Implications for Children's Hospitals and Children's Health

We are concerned that the additional administrative burden and associated costs of complying with this rule will have serious implications for children's hospitals' ability to provide timely diagnostics for the nation's children. It is important to note that, though children's hospitals account for only 2% of hospitals in the U.S., they account for about 45% of all hospital days for children on Medicaid. Medicaid is the single largest health insurer for children and serves as the backbone of children's health care.

Medicaid, on average, provides health insurance coverage for half of children's hospitals patients and for some children's hospitals patient mix, closer to three-quarters. This makes children's hospitals among the largest Medicaid recipients and Medicaid is a critical funding source for the care they provide to our nation's children. However, Medicaid currently reimburses children's hospitals an average of only 79% of the cost of providing care.[1]

As a result of the heavy reliance on Medicaid, the budgets of children's hospital laboratories are tight. Furthermore, most of the LDTs performed by children's hospitals will likely be graded as Class II and III devices under the rule due to their clinical importance. As a result, the regulatory requirements related to the approval process will be the most resource-intense.

The financial resources and staff needed to pursue the large numbers of FDA submissions that would be required under this proposed rule will be in addition to resources already used to meet the stringent regulatory and accreditation requirements under CLIA, the College of American Pathologists, the Joint Commission, state standards, etc. These extensive administrative requirements will not improve outcomes for our pediatric patients. Rather they will lead to delays in timely treatment and management of conditions affecting our pediatric patients, hinder innovation by jeopardizing children's hospital laboratories' ability to integrate the latest scientific discoveries into clinical testing, and strain the capacity of children's hospital laboratories to meet the needs of children today and over the long-term.

FDA Review Capacity

We are also concerned about FDA's capacity (staffing, expertise, etc.) to complete the necessary reviews of pediatric-related LDTs that will be required under this rule in a timely manner, given the anticipated volume of applications. We are especially concerned about the breadth of the agency's pediatric diagnostics expertise, which will need to be bolstered to meet the increased volume of applications for approval. We respectfully note that, over time, the FDA has had to contend with updates and modifications to the regulations that guide drug development for children to account for the unique aspects of studying children and creating health care devices that support their needs. Ongoing challenges have meant that the needs of our nation's children have not always been adequately met by the current regulatory structure, which the agency recognizes in its May 2023 "Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations."

[1] Annual Benchmark Report, FY 2000. Children's Hospital Association.

FDA Requests for Comments

The proposed rule includes several specific requests for comments. Our responses are below.

- *Is there a public health rationale for grandfathering in enforcement discretion from premarket review and QS requirements for currently marketed LDTs?*

  We urge FDA to grandfather in enforcement discretion for currently marketed pediatric-related LDTs to ensure that children continue to have access to the specialized clinical diagnostics and care that children's hospitals provide. In the absence of a grandfathering provision, it is likely that some, if not many, children's hospital laboratories will be unable to make the substantial administrative and financial investments that would be required under this rule to prepare submissions for FDA review for the range of LDTs currently in use. As a result, they will have to make extremely difficult decision to consider abandoning existing effective pediatric-related tests putting their child patients at risk.

  At the same time, we know that the for-profit sector will not step in to make tests for rare pediatric and orphan diseases as the market is too small. As a result, many needed tests for children, including those with rare, uncommon and often life-threatening, diseases will no longer be available with significant negative implications for their overall health and wellbeing.

- *Could there be unintended consequences as a result of this rule on particular patient populations (e.g., Medicare beneficiaries or rural populations)?*

  We urge FDA to consider the disparate impacts that the proposed rule may have across a diverse pediatric patient population. We are concerned with the disproportionate impact that the proposed rule will have on children, especially those enrolled in Medicaid, and their access to the vital testing, screening, diagnostics, and care that they require. As we have detailed above, Medicaid is the largest insurer of children in the United States and, on average, covers one-half of children's hospitals' patients. For some children's hospitals, closer to three-quarters or more of its patients are enrolled in Medicaid. Between one-third and one-half of Medicaid covered children have special health care needs[2] and other health conditions for which FDA-approved diagnostics are not available. These children depend on LDTs for the specialized pediatric health care they need.

  Moreover, we are concerned that this proposed regulation will exacerbate already existing health inequities faced by the populations that we serve. According to the CMS, children enrolled in Medicaid "are more racially and ethnically diverse than the broader U.S. population…with 61% of children being from racial and ethnic minority backgrounds."[3] Not only are children of minority backgrounds more likely to be enrolled in Medicaid, but they frequently face higher disease exposure risks. For example, according to the CDC, those at highest risk of lead exposure in the United States include non-Hispanic Black or African American children.[4] Access to accurate testing is key to identifying children that require treatment for lead exposure and prevention measures to prevent ongoing brain damage. The only tests available today that can accurately measure blood lead levels, according to CDC requirements, are performed using mass spectrometry or atomic spectroscopy, which are LDTs.

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[2] Medicaid Access in Brief-Children and Youth with Special Health Care Needs (macpac.gov); Children with Special Health Care Needs: Coverage, Affordability, and HCBS Access | KFF

[3] https://www.cms.gov/blog/cms-releases-data-briefs-provide-key-medicaid-demographic-data-first-time#:~:text=Further%2C%20the%20programs'%20enrollees%20were,racial%20and%20ethnic%20minority%20backgr ounds [cms.gov].

[4] https://www.cdc.gov/mmwr/volumes/70/wr/mm7043a4.htm?s_cid=mm7043a4_w.

- *Should the FDA continue enforcement discretion for any specific requirements (such as premarket review) for tests manufactured by AMC laboratories?*
    - *Is there evidence and/or a public health rationale to support such a policy?*
    - *If FDA continues the enforcement discretion approach for tests manufactured by AMC laboratories, are there any additional considerations that should be taken into account, such as whether an FDA-cleared or approved test is available for the same intended use as the test manufactured by an AMC laboratory?*
    - *Is there is a general definition of an AMC laboratory that should be used under a continuation of enforcement discretion?*

Hospitals that care for children are often based at academic medical centers and share many of the same characteristics. While we appreciate FDA's consideration of an AMC exemption, we urge the agency to give special attention to those tests that are developed to meet the specific needs of infants, children, and all of those impacted by pediatric diseases, including rare diseases, regardless of where the tests are developed.

Therefore, we urge the FDA to continue general enforcement discretion approach for all pediatric-related LDTs. As we note above, enforcement discretion should continue for tests for diseases/diagnoses that are related to infancy or childhood; tests that must be altered or modified for pediatric off-label use; tests for pediatric rare and orphan diseases; tests that cannot be done by adult-focused laboratories; and tests that are run in hospitals for immediate patient care.

We also strongly caution against any policies or requirements that result in the centralization of FDA-approved tests to certain locations, or any requirements that care and tests be conducted at the same physical location. Given the regionalization of pediatric specialty care, it is not uncommon for children to travel long distances to receive specialty care at a children's hospitals a long distance from home because the services they need are not available close by. This is particularly true for children on Medicaid with medically complex conditions, like cancer or other rare diseases. These children will then receive follow-up and continuing care from local providers to allow them to stay in their homes, communities, and schools, reducing stress and burden on their families and overall well- being.

When a test is sent out to a centralized laboratory, decision-making is delayed and the length of stay for that child increases, leading to additional stress on the child and family, worse outcomes and higher costs. In addition, centralization to just a single or two labs in the country greatly endangers patient care, as there is no resiliency in the system if these labs suffer issues. Finally, tests performed on site are always preferred for faster results and therefore better patient care.

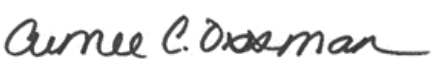
Furthermore, a "same physical location" requirement does not realistically reflect the way pediatric specialty care is practiced and could impede timely diagnoses and care for our sickest children. It is common practice for children's hospital providers to swab (sample collection) at a variety of children's hospital locations (including outpatient primary care and specialty centers) that are near a child's home and then send those samples for testing at a laboratory located at the children's hospital main campus. While a "same physical location" requirement might be appropriate for diagnostic tests in the inpatient setting, it will not support clinical pediatric care in the outpatient setting, including testing to diagnose rare or uncommon pediatric conditions.

For example, a pediatric specialized laboratory may offer confirmatory tests for newborn screening tests, which are all LDTs. These are highly specialized tests that are low volume, but needed in a very fast turnaround time to diagnose a newborn and ensure they are treated and fed without exacerbating their genetic/metabolic disorder. Oftentimes NICUs at other hospitals send tests for these specialized labs to their nearest pediatric lab. The pediatric tertiary academic centers perform clinical laboratory testing to support these fragile patients with diagnostic tests that are lifesaving, which would not be possible under a "same physical location" requirement.

Thank you for the opportunity to comment on this proposed rule. It is critical that the FDA revise this rule to address the unique health care needs of children and ensure that they continue to have access to life-saving diagnostics and timely care. We encourage you to focus your regulatory oversight on manufacturers and commercial laboratories that sell and distribute test kits, rather than on LDTs developed and used by children's hospitals that rely on those tests to meet the specialized health needs of children.

We look forward to continuing to work with you to meet the health care needs of the nation's children. If you have any questions about our comments, please contact Jan Kaplan at 202-753-5384 or jan.kaplan@childrenshospitals.org.

Sincerely,



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