November 15, 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: Comments Regarding the FDA Proposed Rule Titled "Medical Device Laboratory Developed Tests." [Docket No. FDA-2023-N-2177)

Dear Commissioner Califf,

On behalf of the leading Children's Hospital in the nation, Cincinnati Children's Hospital Medical Center, we appreciate the opportunity to provide comment on the Food and Drug Administration (FDA) proposed rule "Medical Device Laboratory Developed Tests." [Docket No. FDA-2023-N-2177)**.** We share the goals of the FDA in protecting public health by assuring the safety and effectiveness of laboratory developed tests (LDTs) and thank you for the work you are doing to forward this mission. As one of the expert centers in the field of pediatric clinical diagnostic testing, we urge the FDA to revise this rule to address the unique health care needs of children and prevent healthcare inequities to ensure that all children, our nation's most vulnerable citizens, continue to have access to life-saving diagnostics and timely 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. Pediatric health care requires specialized medications, diagnostics, 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, and they are not always applicable to disorders that present uniquely in young children or manifest differently . 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. LDTs developed and used in pediatric healthcare settings account for all stages of childhood development, from newborn through adolescence and young adulthood. The types of testing represented by LDT's in pediatric healthcare settings account for these different stages of development, from newborns, infants, young children, older children, adolescents and young adults [1] and include numerous genetic and heritable diseases, pediatric

[1] The FDA recognizes four subpopulations within the pediatric population: neonates, infants, children, and adolescents. *See, e.g.,* Pediatric Medical Devices | FDA (defining neonates as from birth through the first 28 days of

cancers and tumors, and acquired conditions that are not well-represented in adult healthcare practice. Many pediatric diseases are considered rare diseases.[2]

We recommend that the FDA revise this rule to continue its current general enforcement discretion approach for all hospital and health system LDTs. At a minimum, it is essential that FDA ensure that all children continue to have access to life-saving diagnostics and timely care**.** To enable us to meet the specialized needs of the children we care for, enforcement discretion should continue for tests that are for:

1. Diseases/diagnoses that are related to infancy or childhood
2. Tests that must be altered or modified for pediatric off-label use
3. Pediatric rare and orphan diseases
4. Tests that cannot be performed by adult focused laboratories
5. Tests that are performed in hospitals for immediate patient care

Our detailed comments are below.

Overview of Children's Hospitals' Clinical Labs

Our hospital's clinical laboratory fills the gaps in pediatric diagnostic testing by either developing tests from scratch that are needed by our 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 by manufacturers for such use. Furthermore, these tests seldom include pediatric reference ranges, because of the difficulty inherent in obtaining samples from children that represent both normal and disease states. Instead, test instructions will specify an age under which the

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life; infants as 29 days to less than 2 years old; children as 2 years to less than 12 years old; and adolescents aged 12 through 21 up to but not including the 22nd birthday). When we refer to children or a pediatric population in this letter, we mean individuals from birth up to their 22nd birthday. However, we also note that FDA's recognition of these subpopulations further reflects the complications associated with developing treatments and diagnostics for a pediatric population. For example, tests that are effective in adolescents cannot necessarily be used on neonates without modification.

[2] The Orphan Drug Act of 1983 defines a "rare disease or condition" as "any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." 21 U.S.C. s360bb. Between 7,000 and 10,000 rare diseases are estimated to affect about 30 million, or 1 in 10, Americans. Rare Diseases at FDA | FDA; Our Impact on Rare Diseases | National Center for Advancing Translational Sciences (nih.gov). "About half of those with a rare disease are children." GAO-22-104235, Accessible Version, Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial (October 2021). Only about 500 rare diseases, or between 5-7% of rare diseases, have approved treatments. Rare Diseases | National Institutes of Health (NIH). The challenges of developing approved treatments for rare diseases will be replicated in the development of diagnostic tests for rare diseases if FDA abandons its nearly 50-year enforcement discretion policy.

test should not be offered. This age specification may differ between platforms, so depending on the equipment chosen by a particular hospital, their validation requirements may vary for children of different ages. This is also the case in pediatric drug and device development.

Therefore, our laboratory offers 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). LDT's account for up to 13% of our performed test types in our laboratory. These tests include standard laboratory testing that is safely performed in most hospital-based laboratories for routine diagnostic needs. In addition, our hospital laboratory performs assays to diagnose rare genetic abnormalities (like newborn screening and confirmatory tests), tests that monitor pediatric therapeutic drug levels, toxicology screening, monitoring interventions for heritable diseases of metabolism and other genetic disorders, diagnosis and management of immune system dysfunction, and the diagnosis and treatment of pediatric cancers and vascular malformations, including stem cell transplantation and gene/biotherapies.

It is important to note that existing regulatory measures ensure quality of this testing, which is usually developed in partnership with clinical providers (pediatricians, surgeons, and other care providers), to meet well-defined clinical needs. Our laboratory is tightly regulated and further accredited under CLIA and the College of American Pathologists, to ensure our practices are compliant with federal regulations and patient safety standards. Our 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 in healthcare that is not provided by commercial IVD companies.

Types of Pediatric-Related LDTs That Need Enforcement Discretion

1) Diseases/diagnoses that are related to infancy or childhood

For many pediatric-related diseases, diagnoses, and treatment, like leukemia and neuroblastoma, there are no FDA-approved tests. Additionally, many of these laboratory technologies the tests employ, as well as the clinical need to make immediate life or death decisions based on the results, are similar rationales to other tests for which FDA has proposed to continue enforcement discretion (i.e., HLA for organ transplantation). Children with leukemia and neuroblastoma depend on these tests for their cancer diagnosis, treatment, and disease monitoring.

2) Tests that must be altered or modified for pediatric off-label use

There are numerous specific examples of FDA approved tests that do not work for children. These include tests with instructions for use that exclude pediatric age ranges, like Thromboelastography (TEG) testing, used to assess the ability of whole blood to clot. 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, like PCR testing for *C. trachomatis* and *N. gonorrhoeae* using the commonly available Cepheid platform. 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.

3) Rare and orphan pediatric diseases

Severe forms of inherited diseases are present in infancy and childhood, like inborn errors of metabolism and inborn errors of immunity. These are often caused by a mutation, or change, in an important gene that supports biological processes that are critical for life. When cellular metabolism pathways are deranged, dangerous byproducts or metabolites may build up that are toxic to the body, and can result in brain damage, coma, and death. When immune system cells or functions are missing or dysfunctional, patients suffer from life-threatening infections and complications of immune dysregulation such as severe autoimmunity and inflammation. Patients with the most severe forms of inborn errors of immunity, such as severe combined immune deficiency (SCID) typically die before the age of 1-2 years without appropriate diagnosis and subsequent treatment. Furthermore, there are other types of genetic diseases that are rare among children. Developing assays to diagnose and monitor these patients are often out of scope for manufacturers because of the low volume of testing and consequent low monetary returns. Many pediatric hospital laboratories, like our own, develop their own diagnostic tests that prioritize the types of genetic diseases that are seen in children. Children with these diseases require prompt diagnosis and ongoing treatment for their whole lives. Without the diagnosis and and monitoring of patients using LDTs, patients with metabolic disorders can develop seizures, brain damage, coma, and death, and patients with inborn errors of immunity can suffer catastrophic outcomes.

4) Tests that cannot be performed by adult focused laboratories

There are numerous situations in which an FDA approved test's instructions for use do not include the parameters needed to use the test in the pediatric population. Furthermore, adult focused laboratories may not have the pediatric specific instrumentation (i.e., tubing, syringes, etc.) that can be used in infants and small children. In addition, clinical laboratories that perform testing for pediatric patients face challenges unique to the sample collection, sample volumes and test reference (normal) ranges that account for the full range of human growth and development. LDTs allow us to make needed technical changes to serve pediatric patients, like expanding reportable range, changing reference intervals, or changing interference tolerance.

5) Tests for immediate patient care

Onsite testing facilitates rapid return of results to prevent delays in patient care for children. Common clinical examples of the need for immediate results include drug levels for drugs that have a narrow therapeutic window, like the pediatric cancer specific chemotherapy Methotrexate drug, and may include off label use of medications that do not have FDA approval for specific uses, among others. Other examples include biomarkers and screening tests for

Hemophagocytic Lymphohistiocytosis and vascular malformations, immediately life-threatening conditions.

Regulatory and Financial Implications of FDA Proposal for Children's Hospitals

We believe the regulatory burden of this rule will be greater on laboratories that perform testing for pediatric patients because there are a higher proportion of tests for children that are LDTs. The additional administrative burden and associated costs of complying with this rule has serious implications for our ability to provide timely diagnostics for the nation's children.

It is important to note that Medicaid is the single largest health insurer for children in the United States and serves as the backbone of children's health care. However, Medicaid reimbursement rates are generally well below Medicare and commercial insurance rates. As a result of the heavy reliance on Medicaid, the budgets of children's hospital laboratories are tight. The additional financial resources and staff needed to pursue the large numbers of FDA submissions that will be required under this proposed rule will hinder innovation and further strain our capacity to meet the needs of the children in our care today and over the long-term. We predict that most of the LDTs we perform will be graded as Class 2 and 3 devices due to their clinical importance, raising the regulatory requirements to their highest and most resource intensive level. Placing these extensive administrative barriers between the development of a clinical testing and care for patients will lead to delays in timely treatment and management of conditions and will jeopardize our ability to integrate the latest scientific discoveries into clinical testing and care for our pediatric patients. The proposed rule, when applied to pediatrics, will delay and reduce the development of new pediatric specific LDTs by our laboratories.

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 believe that this is essential. Grandfathering would help pediatric laboratories continue current essential, time sensitive testing that is made most effective by being performed rapidly in-house by using highly effective LDTs. Not grandfathering will lead to a large negative impact on healthcare for children and their families in need of healthcare.

For instance, there are FDA approved tests that have known analytical weaknesses compared to the "gold standard" LDT test for the same analytic for children. For example, the most used FDA-approved immunoassay screening tests do not accurately measure different vitamin D derivatives, and infant formula can interfere with the assay, yet accurate testing is required for definitive diagnosis of vitamin D deficiency. Liquid chromatography, tandem mass spectrometry testing is the "gold standard" for diagnosis of vitamin D deficiency in infants and children and is a pediatric focused LDT.

Furthermore, the requirements to prepare for FDA submission will lead hospital laboratories to consider abandoning existing effective pediatric-related tests since hospital laboratories do not have available human or financial resources to accomplish FDA approval. This will impact children and those with rare and uncommon and often life-threatening diseases a great deal. The for-profit sector will not step in to make tests for small markets.

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

We are concerned that children of color, who are more likely to be impacted by chronic diseases and violence necessitating medical care, will have their access to healthcare limited because the rule will lower the ability of laboratories to perform LDT tests for children[3]. For example, Black children in America are significantly more likely to have elevated blood lead levels compared to White children[4]. The only tests available today that can accurately measure blood lead levels according to CDC requirements[5] are performed using mass spectrometry or atomic spectroscopy, which are LDTs. Access to accurate testing is key to identifying children that require treatment and prevention measures to prevent ongoing brain damage. Pediatric patients of color are impacted at higher rates with sexually transmitted infections, such as HIV, *C. trachomatis* and *N. gonorrhoeae* and syphilis[6,7,8]. This is the same for COVID-19 infection[9]. While FDA approved tests for these infectious diseases exist, many of the tests must be modified to be used in pediatric patients. Medicaid beneficiaries are more likely to be from minority and disadvantaged populations who face challenges receiving the same care that those on private insurance may receive[10]. We are very concerned that implementation of regulations making it harder to use LDTs in children will lower access and increase the cost of laboratory diagnostics. This could further exacerbate healthcare disparities of minority children, especially those from low socioeconomic households, including those who are Medicaid beneficiaries.

[3] Cohen JS, Donnelly K, Patel SJ, Badolato GM, Boyle MD, McCarter R, Goyal MK. Firearms Injuries Involving Young Children in the United States During the COVID-19 Pandemic. Pediatrics. 2021 Jul;148(1):e2020042697.PMID: 33850026.

[4] Yeter D, Banks EC, Aschner M. Disparity in Risk Factor Severity for Early Childhood Blood Lead among Predominantly African-American Black Children: The 1999 to 2010 US NHANES. Int J Environ Res Public Health. 2020 Feb 28;17(5):1552. PMID: 32121216

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

[6] Townes A, Kota KK, Dailey AF, Henny KD. Racial/ethnic disparities in estimated undiagnosed HIV infection among adolescents and adults in the United States, 2017-2021. AIDS. 2023 Oct 1;37(12):1912-1914. doi: 10.1097/QAD.0000000000003665. Epub 2023 Jul 26. PMID: 37646592.

[7]https://www.cdc.gov/nchhstp/healthdisparities/africanamericans.html#:~:text=From%202014%20to%202018%2C%20the,100%2C000%20live%20births%2C%20respectively).

[8]https://www.cdc.gov/nchhstp/healthdisparities/africanamericans.html#:~:text=From%202014%20to%202018%2C%20the,100%2C000%20live%20births%2C%20respectively

[9] Simpson JN, Goyal MK, Cohen JS, Badolato GM, McGuire M, Ralph A, Boyle MD, Hamburger EK, Gorman KC, Cora-Bramble D, Delaney M. Results of Testing Children for Severe Acute Respiratory Syndrome Coronavirus-2 Through a Community-based Testing Site. J Pediatr. 2021 Apr;231:157-161.e1. PMCID: PMC7831849.

[10] https://www.cms.gov/blog/cms-releases-data-briefs-provide-key-medicaid-demographic-data-first-time

- *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, it is of primary importance to us that special attention be given 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; pediatric rare diseases; as well as tests that cannot be done by another laboratory; tests that are run in our hospitals for immediate patient care; and tests that must be altered for off-label use.

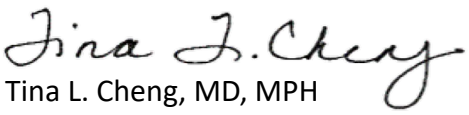
We also strongly caution against any policies or requirements that result in the centralization of FDA-approved tests to certain locations, or any requirements that care and tests be conducted at the same physical location. When a test is sent out to a centralized laboratory, decision-making is delayed and the length of stay for that child increases, leading to higher costs, additional stress on the child and family and poorer outcomes. 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. Tests performed on site are always preferred for faster results and therefore better patient care.

Conclusion

Thank you for the opportunity to comment on this proposed rule. We encourage the FDA to focus on the oversight of manufacturers and commercial laboratories that sell and distribute test kits. To ensure that children continue to have access to life-saving diagnostics and timely care, we urge the FDA to revise this rule to address the unique healthcare needs of children.

Children and their families deserve timely access to high quality age-appropriate health care. We must work together to find a way to improve pediatric healthcare in America, not make it harder to provide.

Sincerely,



Tina L. Cheng, MD, MPH
BK Rachford Professor & Chair of Pediatrics, University of Cincinnati
Director, Cincinnati Children's Research Foundation
Chief Medical Officer, Cincinnati Children's Hospital Medical Center

Attachment

Tables:

Examples of FDA approved tests that are modified for pediatric use:

Thromboelastography (TEG)
Complete blood count (CBC)
Cell-free DNA testing for transplant organ rejection
C. trachomatis and *N. gonorrhoeae* PCR
Streptococcus pneumoniae PCR
Antimicrobial cefazolin susceptibility (Vitek)
Confirmatory thyroglobulin testing using mass spectrometry
Liquid chromatography, tandem mass spectrometry (LC-MS) for vitamin D
Cytomegalovirus Quantitative PCR; can also be LDT
EBV Quantitative PCR; can also be LDT
BK virus Quantitative PCR; can also be LDT

Examples of LDTs created in laboratories that test for pediatric diseases including rare and orphan pediatric diseases:

Acylcarnitine
Androstenedione
Carbohydrate-deficient transferrin
Carnitine, Total/Free Quantitative
CSF AA Quant
Free T4 (confirmatory test)
Glycine, CSF
HVA/VMA

Galactitol
Galactokinase
Galactose-1-Phosphate
17-Hydroxyprogesterone
25-Hydroxy Vitamin D
MSUD from DBS
MSUD Profile (Branch Chain)
Orotic Acid
Oxidative phosphorylation, fibroblast
Phenylalanine, Plasma
Phenylalanine/Tyrosine from DBS
Plasma AA Quant
Plasma N-Glycans
Rapid Urine Organic Acids
Succinylacetone
Testosterone, Total
Tyrosine
Urine AA Quant
Vitamin A
Vitamin E
Engraftment with Cell Selection Post BMT
Engraftment without Cell Selection Post BMT
Factor II Prothrombin
Angiopoietin 2
Fragile X
TPMT Genotyping
Genetic Sequencing for Germ line or somatic mutations
Genetic Sequencing for numerous pediatric cancers
Oxidative Burst Assay (Chronic granulomatous disease, CGD)
Complex Immunodeficiency Phenotyping Panels and single cell marker variations
Leukocyte Adhesion Deficiency, Type 1
Phenotyping for TCRα/β depletion HSCT protocol
Flow cytometry for hematologic neoplasia
Adenovirus Quantitative PCR
Human Herpes Virus 6 PCR
Mass spectrometry or atomic spectroscopy for blood lead level
CD40 Ligand/CD40 Fusion Protein
Perforin/Granzyme B
Wiskott-Aldrich Syndrome Protein (WASP) Detection in Leukocytes
Autoimmune Lymphoproliferative Syndrome (ALPS) Panel

CD107a Mobilization
CD34 Stem Cell Immunophenotyping
CXCL9
Soluble IL-2Ralpha
Alemtuzumab (Campath) Level
X- Linked Lymphoproliferative Disease (XLP) (SAP & XIAP)
Platelet Quinacrine Uptake and Release
Platelet Glycoprotein Expression
Osmotic Gradient Ektacytometry
HistioTrak Minimal Residual Disease rapid TAT test
Urinary Bile Acid Profile by FAB-MS
Fractionated & Total Serum Bile Acids by LC-MS