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: Comments Regarding the FDA Proposed Rule Titled "Medical Devices; Laboratory Developed Tests." [Docket No. FDA-2023-N-2177]

Dear Commissioner Califf,

On behalf of Children's Hospital of Wisconsin (Children's), we appreciate the opportunity to provide comment on the Food and Drug Administration (FDA) proposed rule "Medical Devices; Laboratory Developed Tests." [Docket No. FDA-2023-N-2177]**.** 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 the work you are doing to forward this mission. As experts in the field of pediatric health care, Children's urges the FDA to revise this rule to address the unique health care needs of children.

Children's operates the state's only non-profit independent children's hospital providing complex care to the sickest and most vulnerable children. Children's main campus hospital in Milwaukee has 298 licensed beds, including a 72-bed Pediatric Intensive Care Unit, a 70-bed Neonatal Intensive Care Unit and a 24-bed Hematology/Oncology/Transplant Unit. Children's operates a Level I Emergency Department/Trauma Center and provides a comprehensive range of pediatric health care services, including pediatric medical and surgical care, cardiology, oncology, neonatology, neurology and intensive care.

To provide the range of pediatric and adolescent health care services described above, in partnership with the Medical College of Wisconsin (MCW), Children's operates approximately 150 pediatric sub-specialty programs, including, but not limited to, cardiac care, genetics, neurology, plastic surgery, sickle cell and spina bifida. Children's provides services at two inpatient locations and eight outpatient ambulatory pediatric specialty clinics located across the state. In 2022, Children's hospital-based facilities supported over 700,000 specialty care visits, 20,000 hospital visits, and 75,000 visits to our EDTC. In addition, through the Children's Medical Group, our health system employs more than 100 primary care pediatricians who provide care at our 21 primary care clinics located in southeast Wisconsin. In 2022, these clinics supported over 360,000 primary care visits.

Children are not just little adults. Children's, and other children's hospitals, rely on *specialty-trained* providers and specialized medications, diagnostics, therapeutics and equipment to provide safe, high quality, pediatric care. At Children's, LDTs are critical 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. Children's

hospitals either develop tests from scratch that are needed by their patients or perform the extensive validation work required to demonstrate that an FDA-approved test for adults can safely and reliably be used for children. As is the case with pediatric drug and device development, the relatively small population size and unique aspects of studying children are barriers to commercialization of tests for pediatric diseases. Furthermore, FDA-approved tests are often not approved for use in children and seldom include pediatric reference ranges.

We are very concerned about the impact of the proposed rule on access to testing to meet the specialized clinical needs of infants, children and those impacted by pediatric diseases, including rare diseases. The significant administrative barriers and costs associated with complying with the proposed rule will strain the capacity of pediatric laboratories and providers to meet the needs of kids today and, over the long-term, hinder innovation in clinical care for children.

To that end, 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:

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

Our detailed comments are below.

Overview of Children's Hospital of Wisconsin Clinical Laboratory

Children's Clinical Laboratories provide approximately one million tests each year to support the clinical care delivered in the inpatient, outpatient and primary care settings. In addition to holding expertise in general pediatric anatomic and clinical pathology, our board certified pediatric pathologists have nationally- and internationally- recognized expertise in a number of fields, including diagnosis of pediatric solid tumors, perinatal and placental pathology, pediatric vascular anomalies, pediatric cardiac and gastrointestinal pathology, pediatric cytopathology, nerve and muscle pathology, pharmacogenetic testing, biochemical genetic testing and molecular diagnosis of infectious and inherited disease.

This clinical team, along with over 100 medical laboratory technicians, medical technologists, and other staff, provides standard laboratory testing for routine diagnostic needs as well as a full range of subspecialized pediatric testing, including the following:

- Children's Clinical Chemistry Lab performs comprehensive biochemical testing for metabolic disorders as well as routine chemical analyses.

- Children's Microbiology Lab utilizes state-of-the-art MALDI-TOF identification of organisms and molecular detection of pathogens in collaboration with the Children's Molecular Diagnostics Lab, which also performs pharmacogenetic analysis as well as unique assays for coagulopathy and congenital hearing loss.
- Children's Hematology Lab includes routine blood counts and testing incorporating automated screening through Cellavision technology, bone marrow analysis including flow cytometry for leukemias and lymphomas and coagulation assays such as rapid thromboelastography (TEG).
- Children's Histology Lab performs a variety of routine, special, immunohistochemical, immunofluorescent, and *in situ* hybridization staining for surgical pathology, cytopathology and autopsy cases.

LDTs account for approximately 9% of our laboratory performed test types. These LDTs or modified FDA tests are developed and validated following quality requirements specified by the Clinical Laboratory Improvement Amendments Act (CLIA) of 1988. Furthermore, our laboratory is accredited under CLIA via the College of American Pathologists to ensure our practices are compliant with federal regulations and patient safety standards. LDTs are a critical component of lifesaving treatment plans designed for children and they fill a gap of health care that is not provided by commercial *in vitro* diagnostic companies.

Children's is very concerned about our ability to comply with the proposed rule's regulatory framework for medical devices, which, while well-intentioned, is not practically compatible with hospital laboratory operations. We currently do not have the staff or administrative resources that would be needed given the significant, disproportionate number of necessary submissions or controls that would be required by children's hospitals. It is important to recognize that Medicaid is the single largest insurer for children in the United States and serves as the backbone of children's health care. At Children's, over 50% of the patients we care for are covered by Medicaid. Yet, Medicaid reimbursement rates are generally well below Medicare and commercial insurance rates. In Wisconsin, Medicaid reimbursement only covers approximately 65% of the cost to provide care.[1]

In contrast to the commercial diagnostic sector, we do not have the financial resources, capacity or scale that would be required to comply with this proposed rule. Placing these extensive administrative barriers between the development of 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. We are very concerned that the proposed rule will delay and reduce the development of new, pediatric-specific LDTs.

Types of Pediatric-Related LDTs That Need Continued Enforcement Discretion

Diseases/diagnoses that are related to infancy or childhood

As mentioned previously, for many pediatric-related diseases and diagnoses there are no FDA-approved tests. Additionally, the technological basis for many of the LDTs pediatric laboratories

[1] Wisconsin Hospital Association, *2022 Community Benefits Report, (2022) https://www.wha.org/2022-Community-Benefits.pdf*

employ, as well as the clinical need to make immediate life or death decisions based on the results, constitute similar rationales to other tests for which FDA has proposed to continue enforcement discretion (i.e. HLA for organ transplantation).

For example, leukemia is the most common cancer in children. LDTs play a crucial role in the diagnosis and treatment of childhood leukemia. First, flow cytometry, the primary test used to diagnose childhood leukemia, is an LDT. Like the HLA tests for which enforcement discretion will continue, this LDT may be individualized within different children's hospital laboratories using reagents of different product types, including analyte-specific reagents and research use only (RUO) antibodies. At Children's, we have developed our own specific antibody panels and protocols which are targeted to detect pediatric leukemias; even though the adult hospital lab across the street uses the same model of instrument and manufacturer of reagents, they use different combinations of antibodies in different protocols to diagnose adult leukemias. For many children with leukemia, a curative treatment is bone marrow or stem cell transplantation. Here, again, the care of these children relies on an LDT. The genetic test used to monitor the health of the bone marrow transplant after it happens, short-tandem repeat (STR) analysis, is an LDT, which shares significant technologic overlap with some HLA testing. For children, there are no FDA-approved alternatives available for these time-sensitive tests that guide time-critical clinical decision making by treating pediatric specialists.

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. Many 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, there are many tests that are not approved for pediatric patients under a certain age. Thromboelastography (TEG) testing, used to assess the ability of whole blood to clot, is not approved by the FDA for use in patients under the age of 18 years, yet is essential to determining bleeding risk in surgical patients of all ages. TEG is critical in managing children during lengthy surgeries for congenital heart disease, organ transplantation and trauma, and guides safe and efficient administration of blood and blood products. Also, many platforms are not even FDA-approved for analysis of a routine complete blood count on patients under the age of 2 years. In addition, cell-free DNA testing for transplant organ rejection (such as heart or kidney transplant) is not validated for use in younger children (under 15 or 18 years depending on the platform).

Pediatric rare and orphan diseases

Children's clinical laboratory, like other pediatric hospital laboratories, develops and validates our own genetic testing panels that prioritize the types of genetic abnormalities that are seen in severe forms of inherited and rare diseases of childhood and in many types of pediatric cancers. We 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 often different than in adults, which means that our pediatric subspecialists cannot rely on the same tests that are

used in adults. LDTs allow Children's 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. Other examples include our hearing loss and pharmacogenomic testing panels which are regularly updated to detect and analyze genetic changes when new clinical implications are recognized.

Additionally, 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 is required to be performed on all babies born in all 50 states. The NBS test samples are collected soon after a child is born, and NBS tests, usually performed in state laboratories, are themselves usually LDTs. Whenever a NBS screening test is positive, the child needs immediate medical consultation and testing to confirm the diagnosis. The confirmatory tests are all highly specialized pediatric LDTs for which no FDA-approved versions exist. Children with these diseases require ongoing monitoring for the rest of their lives to ensure their specialized diet is keeping their system in check. Without regular monitoring using these LDTs over the life span of affected patients, they can develop 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, at Children's we 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 often do not typically use or provide pediatric reference ranges for clinical decision-making. We routinely develop multiple 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., the expected testosterone level in an adult male is different than a 2-year-old boy) using LDTs.

Tests for immediate patient care

Every day our physicians and providers rely on onsite testing to facilitate rapid return of results and 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 and may include off label use of medications that do not have FDA approval for specific uses but are employed for specific pediatric indications, among others.

For example, some types of pediatric leukemia are treated with high levels of methotrexate, a form of chemotherapy. This dosing regimen is not typically used for the treatment of adult cancers but has

been highly efficacious in children. Safe and effective use of methotrexate requires frequent measurement of drug levels and a rapid return of results: if it takes three days to get a result, modification of dosing levels is not practical and can result in under or overtreatment, including organ damage (i.e. kidneys). This test is often performed as an LDT to permit rapid test turnaround time.

FDA Requests for Comments

The proposed rule includes a request for comment on whether "FDA should continue enforcement discretion of any specific requirements (such as premarket review) for tests manufactured by academic medical laboratories (AMC)" and suggests a proposed definition of an AMC that, among the various provisions, includes a requirement that the clinical care, treatment, specimen collection and testing all occur at the same physical location as the medical center laboratory performing the test protocol.

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 those impacted by pediatric diseases, including rare diseases.

At Children's, in affiliation with MCW, we offer a graduate medical residency training program and fellowship program related to *in vitro* clinical test development, application and interpretation which is integrated with patient care. Therefore, we believe that the proposed definition of an AMC would generally encompass our laboratory, as long as any proposed definition was inclusive of all our health system staff, regardless of whether they were employed by the hospital or our academic partner. However, we have strong concerns with the "same physical location" requirement as it does not realistically reflect the way pediatric specialty care is practiced and could impede timely diagnosis and care for children.

Children's serves kids in every county in the state of Wisconsin and, in order to best serve families, we have created regional clinics to extend the reach of our pediatric specialty services, such as cardiology, neurology and gastroenterology, so that families can receive high quality pediatric care closer to home. It is common practice for us to swab (sample collection) at a variety of Children's locations across the state and send them for testing to be done centrally in our laboratory located at main campus. These tests are often ordered by specialists (Children's Specialty Group) or physicians within our primary care practice (Children's Medical Group). The "same physical location" requirement seems to be targeted to allow diagnostic tests in the inpatient setting but does not take into account the utilization in the outpatient setting to support clinical pediatric care, including testing to diagnose rare or uncommon pediatric conditions. This provision would limit our ability to utilize the same testing across our system, based solely on where the patient chooses to receive care. This would impede access to timely, convenient pediatric care for many families across Wisconsin.

Conclusion

Thank you for the opportunity to comment on this proposed rule regarding LDTs and sharing our perspectives on the impact this will have on Children's Hospital of Wisconsin and the kids and families we serve. 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 health care needs of children.

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