



## Society for Pediatric Pathology

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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,

As physician members and leaders of the Society for Pediatric Pathology (SPP), 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]. The Mission of the Society for Pediatric Pathology is to promote the practice, education, and expertise of its members as well as to engage and educate other agencies that impact the practice of pediatric pathology.

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 clinical diagnostic testing, we urge the FDA to reconsider this rule as it pertains to 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’s hospitals account for fewer than 2% of hospitals in the United States, but they 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. They are patient-centered, research-focused institutions and leading centers for discovery and innovation in pediatric healthcare. Children’s hospitals are regional centers for children’s health, providing highly specialized pediatric care across large geographic areas. They are nonprofit institutions with a charitable mission and duty to serve the clinical needs of children, conduct research to advance pediatric medicine, and train future generations of pediatric health care providers.

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, diagnostic tools, 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. 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



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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, and include numerous genetic and heritable diseases, pediatric cancers, and acquired conditions that are not well-represented in adult healthcare practice. Many pediatric diseases are considered rare diseases.

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 done by adult focused laboratories
5. Tests that are run in hospitals for immediate patient care

Our detailed comments are below.

### **Overview of Children's Hospitals' Clinical Labs**

Children's hospitals clinical laboratories fill 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 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, FDA-approved test instructions will commonly specify an age under which the 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.

In addition, the relatively smaller population size and unique aspects of studying children are barriers to commercialization of tests for pediatric diseases. The market financial gains are too small for larger manufacturers to justify their development, and the FDA approval process requires studies that are difficult to feasibly complete in pediatric populations because of small patient numbers representing



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individual disease states and difficulty obtaining normal control subjects for validation purposes. The net result is that commercial companies producing in vitro diagnostic products (IVDs) typically choose not to produce tests for many pediatric diseases.

As a result, each of our laboratories offers up to 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). Depending on the laboratory, LDT's may account for up to 5-15% of our performed test types. These tests include standard laboratory testing that is safely performed in most hospital-based laboratories for routine diagnostic needs. In addition, pediatric hospitals perform 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, 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 laboratories are tightly regulated and further accredited under CLIA and accredited by our states, the College of American Pathologists, or the Joint Commission, in accordance with the CLIA regulations, 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 of 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**

Pediatric-type cancers and other conditions that present in early childhood, like inborn errors of metabolism or severe immune deficiencies are often diagnosed and managed using LDT's. For example, leukemias are diagnosed and prognosis is analyzed by performing flow cytometry and molecular testing on bone marrow samples as standard of care (both LDT's). Certain chemotherapeutic drugs are monitored using LDT's, to avoid overtreatment and drug toxicity or undertreatment and inefficacy. Furthermore, result turnaround may necessitate local rapid testing to be able to meaningfully adjust therapy to avoid side effects in under or overtreatment. Also, these patients usually require monitoring for a long period of term, if not for life, and so the same LDTs used for diagnosis may need to be used repeatedly and regularly to track disease recurrence, remission or progression. Many FDA-approved genetic testing panels don't target the genetic alterations that are implicated in pediatric diseases, which may be very different from the genes that drive adult cancers, so LDTs are developed to include pediatric disease in scope. This genetic testing panel design is further complicated by the fact that we learn about new gene-disease associations every day, and this testing relies on being able to change frequently to add new gene targets. This ability to change nimbly would be hindered by requiring FDA



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approval, especially since these are rare disease for which it is difficult to obtain a large validation sample.

### 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, as manufactured. These include tests with instructions for use that exclude pediatric age ranges. Tests like 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. 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. For instance, in cases of perinatal transmission, testing for chlamydia and gonorrhea using the commonly available Cepheid platform is not FDA approved for use in swabs of eye, rectum, or throat mucosal membranes, but LDTs permit this non-invasive testing of newborns who may have acquired these infections during delivery. Still other FDA approved tests may be used to measure the effectiveness of a pediatric drug that is used "off label", such as testing for antibiotic efficacy against certain infectious agents that are not part of the routine test, yet an appropriate antibiotic agent needs to be chosen.

### 3) Rare and orphan pediatric diseases

Severe forms of inherited diseases present in infancy and childhood. These are often caused by an alteration in an important gene that supports biological processes that are critical for life. When cellular 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. Furthermore, there are types of genetic diseases that are rare among children. Developing assays to diagnose them are often out of scope for manufacturers because of the low volume of testing and consequent low monetary returns. Many pediatric hospital laboratories develop their own genetic testing panels that prioritize the types of genetic abnormalities that are seen in the children they care for, since many present in childhood, and for pediatric cancers that may be attributed to germline genetic abnormalities.

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 is required to be performed on all babies born in all 50 states, and these are usually LDTs. If not treated soon after birth (usually by dietary supplementation or restriction), these babies can develop seizures, brain damage, coma and death. Whenever a NBS test is positive, the infant 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.<sup>1</sup> Children with these diseases require ongoing

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<sup>1</sup> Such as: Amino Acid Analysis, Organic Acid Analysis, and Acylcarnitine analysis, etc. Some examples of diseases that require patients to receive regular, ongoing lab monitoring are Maple Syrup Urine Disease, Phenylketonuria, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency or trifunctional protein deficiency (metabolic disorders involving abnormal fatty acid oxidation).



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monitoring for the rest of their lives to ensure their specialized diet is keeping their system in check. Another example are primary or inherited immunodeficiencies, which result in non-functional immune systems, making children much more susceptible to infections than unaffected individuals. These diagnoses are usually made with flow cytometry LDTs to study the properties of their immune cells and confirm observed abnormalities with genetic testing. Additionally, even where adults and children present with the same cancer, the genetic driver for the cancer in children is different. Pediatricians cannot rely on the same tests used in adults for children. LDTs allow us to develop genetic tests specific to pediatric populations and modify testing rapidly to include additional genes that are newly implicated in childhood disease and adopt more efficient and sensitive testing platforms and methodologies.

#### **4) Tests that cannot be done 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, working with smaller volumes from smaller bodies. For example, hemolysis (destruction of red blood cells) often occurs in samples taken from tiny veins, so pediatric testing may need to be optimized for more frequent hemolysis. By doing so, we are able to continue testing on a sample that would be discarded and re-drawn in an adult patient. One example is the evaluation of ferritin in young children with suspected hemophagocytic lymphohistiocytosis. Measuring ferritin in this patient population is critical. FDA approved ferritin tests do not allow reporting when the hemolysis index is  $>100$  units. However, for the treating pediatrician, a specific measurement of ferritin for a patient with HLH is critical, even when the hemolysis index is very high. Pediatric clinical laboratories may perform additional validations to allow the laboratory to not reject the sample, and to report meaningful clinical information. LDTs validated tests in our laboratories allow continued testing of ferritin levels outside the FDA approved reporting level in critically ill children where the result is very important to clinical management. LDTs allow us to make needed technical changes to serve pediatric patients, like expanding the reportable range of results, changing reference intervals, or changing interference tolerance.

Adult focused laboratories do not have to use pediatric reference ranges for clinical decision making. In contrast, children's hospitals treat patients from infancy through young adulthood and routinely develop different reference ranges to reflect those different stages of 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 and across different technologies (testosterone level in an adult male is different than a 2-year-old boy).

#### **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 of efficacy. Certain pediatric solid tumors are treated with the chemotherapy Methotrexate drug, at high dosing levels. This dosing regimen is not used for the treatment of adult



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cancers, only for pediatric cancers. The effective use of Methotrexate requires a rapid return of result: 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 an LDT to permit rapid test turnaround time.

Immunosuppressive drugs like infliximab are used to manage pediatric autoimmune diseases, and the standard of care when starting these drugs is to make sure the dosing level is therapeutic. While a test may be offered by external laboratories (also as an LDT), the time to receive the result is 3 – 4 days, forcing the patient to stay admitted to the hospital for careful observation, driving up the cost of health care. Having an in house LDT allows rapid turnaround time to result allowing the patient to be discharged the same day of testing, keeping the cost of healthcare down and ensuring that if the patient needs dose changes to prevent toxicity or maintain therapeutic levels, those clinical decisions can be made in a clinically viable timeline.

### **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.

As a result of the heavy reliance on Medicaid (up to 75% of income in some children's hospitals), 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 care. The proposed rule, when applied to pediatrics, will delay and reduce the development of new pediatric specific LDTs by our laboratories, and more importantly, there are not back-up labs that can perform the testing in our stead.

### **Conclusion:**

In summary, the proposed new FDA rule would be incredibly detrimental to pediatric hospital laboratory testing for many reasons and would result in an inequitable regulatory burden on these laboratories. Not only is innovation endangered by the rule, but pediatric laboratories would be crippled in their ability to perform unique and timely testing for children and the rare diseases they encounter. We urge



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the FDA to consider the effects the proposed rule would have on our pediatric laboratories and consider exempting them from the proposed rule.

Thank you for considering our perspective in this important proposal development.

Signed,

A handwritten signature in blue ink, appearing to be "Linda M. Ernst". The signature is fluid and cursive, with a long horizontal stroke at the end.

Linda M. Ernst, M.D., M.H.S., President  
On behalf of the members and leadership of the Society for Pediatric Pathology