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December 4, 2023

Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: FDA–2023–N–2177 for Medical Devices; Laboratory Developed Tests.

Dear Commissioner Califf:

On behalf of the EveryLife Foundation for Rare Diseases, we are pleased to provide comments relevant to the proposed rule on the regulation of Laboratory Developed Tests (LDTs). While we acknowledge the agency's intent to regulate LDTs, the EveryLife Foundation expresses deep concern with the potential negative impact the current version of the proposed rule will have on access to current tests and innovation of new tests, particularly for the rare disease community. The historically overlooked rare disease community already faces numerous challenges in garnering interest for the development of diagnostics and therapeutics. The recommendations included within this comment are made to ensure that the final rule does not add to the already significant challenges that exist in finding a diagnosis within the rare disease community.

EveryLife's policy priorities are informed by the needs of our community and our shared mission of advancing the equitable development of, and access to, lifesaving diagnoses, treatments, and cures. To inform our policy work, we convene the Community Congress, a forum for collaboration across stakeholders, representing over 200 individual rare disease patient advocacy organizations in addition to over 90 other healthcare and biotechnology organizations.

Over 30 million Americans live with one or more rare diseases, most of whom experience a prolonged diagnostic odyssey. According to the National Economic Burden of Rare Disease Study, obtaining a confirmed rare disease diagnosis takes an average of 6.3 years, 16.9 specialist visits, and 2.4 out-of-state trips[1]. These visits contribute significantly to the estimated $966 billion annual impact of rare diseases on the healthcare system, families, and society. Notably, avoidable costs attributable to delayed diagnosis were estimated between $86,000 and $517,000 per patient for the seven conditions assessed.[2,3]

[1] https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf
[2] Ibid
[3] https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

We know that patients and caregivers both benefit from receiving timely diagnosis. Timely diagnosis ensures optimal disease management, timely treatment initiation, and helps to alleviate the anxiety of the diagnostic odyssey. However, the nature of rare diseases makes the development of diagnostic options difficult for the rare disease community. The proposed rule recognizes that LDTs "…were typically intended for use in diagnosing rare diseases…"; notably, many of the challenges for developing rare disease diagnostics still exist. In a recent Pew Charitable Trusts study, which FDA cited in support of the proposed rule, when laboratory managers were asked why an FDA-approved IVD did not exist for a testing indication, the top answer was "test is too low-volume to warrant filing for IVD." Additionally, "filing for IVD would be too expensive" was also cited as a top five reason[4].

Ensuring that the rare disease community can trust the diagnostic tests they are utilizing is an important part of decreasing the length of the diagnostic odyssey. Simply put, no patient benefits if they lack confidence in a diagnostic test, and we recognize the need to instill confidence in patients. However, a balance must be struck to ensure that the new regulations do not inhibit innovation that results in certain communities either losing current tests or never receiving a diagnostic test for their condition. The number of variants in ClinVar, the National Institutes of Health (NIH) public database on the relationships between human genetic variations and phenotypes, increases an average of 60 percent each year, with a total of more than 3.5 million submissions in the database.[5,6] The current proposed rule will stifle the innovation that translates the growth in understanding of genetic variants into new diagnostic tools.

The current proposed rule will have a negative impact on the rare disease diagnostic odyssey, creating hurdles for development that will limit the diagnostic options for the community. We offer the following comments highlighting potential impacts of the proposed rule on the rare disease community and further action FDA can take to support high quality, reliable rare disease diagnostic tests.

Protect Rare Disease Innovation

Innovation within the rare disease space has long been a challenge. Small disease populations, growth in the number of identified rare diseases, lack of incentives for test development and limited clinical experts have led to challenges with diagnosing rare diseases. In a 2018 FDA/NCATS study designed to better understand the unmet needs for medical devices for rare diseases, 91 percent of participating clinicians believed that a new or improved device was needed for rare diseases[7]. In addition, when asked what the top obstacles to the development of new devices were, 74 percent of respondents stated lack of profitability for industry and 67 percent cited the cost of development[8].

It is imperative that the FDA ensures that the final rule does not inhibit laboratories that want to develop new diagnostic tests – or continue to offer diagnostic tests - for rare diseases due to the costs associated with going through the IVD regulatory process. The FDA acknowledges that large laboratories "…are less likely than the small laboratories to exit the market or reduce operations as a result of

[4] https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market
[5] https://academic.oup.com/nar/article/48/D1/D835/5645007
[6] https://www.ncbi.nlm.nih.gov/clinvar/submitters/
[7] https://www.fda.gov/media/111309/download
[8] Ibid

compliance costs." Under the proposed regulatory framework, the largest cost associated with the proposed rule would occur during the premarket review process. **Therefore, we propose offering a user fee exemption for test developers for all tests to diagnose rare diseases which are defined as any condition affecting less than 200,000 individuals in the United States.** This would mirror the user fee exemption granted to drug and biologic applications with orphan designation, reducing the cost of the FDA review process and the potential negative impact on rare disease diagnostic innovation.

In addition, within the proposed rule, the FDA acknowledges the potential harms the new oversight standards will have on small entities, stating that "…the proposed rule will have a significant economic impact on a substantial number of small entities." We appreciate the FDA acknowledgement of the expected negative impact of the proposed rule on innovation that occurs at small business entities. Many small laboratories have never submitted premarket approval or a 510(k) submission and do not have the staff or expertise to begin those submissions. The FDA must ensure that the lack of expertise on the submission does not prohibit the development of needed new diagnostic tools. **We recommend that FDA utilize a ten-year extended phaseout for all small laboratories as defined by the Small Business Administration.**

Ninety-five percent of rare diseases do not have an approved treatment. Innovations in science and regulatory policy have accelerated the development of therapies for rare diseases, but the vast majority of the 10,000 rare diseases still lack viable therapeutic development programs due to the numerous complexities in designing and conducting clinical trials in very small disease populations. Limited natural history data and limited understanding of disease progression puts further emphasis on the need for early diagnosis to ensure clinical trials are fully enrolled. **We encourage the FDA to clarify that it will continue its enforcement discretion for the use of LDTs used to support drug clinical trials in addition to the investigational device exemption outlined in the current proposed rule.**

Support Newborn Screening

Newborn screening, widely acknowledged as one of the most successful public health programs in the country, plays a crucial role in identifying heritable conditions immediately upon birth. The unique ability to provide timely, pre-symptomatic diagnosis ensures that newborns can begin life-saving treatment as early as possible. Each year, approximately four million newborns are screened in the U.S. and about 12,000 infants are identified to have a condition and benefit from these life-saving diagnoses[9]. A timely diagnosis provides a cost benefit for patients and the health care system more broadly. As supported in the "Cost of Delayed Diagnosis" study, the avoidable costs associated with providing a timely diagnosis at birth as opposed to a delayed diagnosis were calculated for three newborn screening conditions. The studied conditions, X-ALD, Pompe Disease, and SCID showed savings of $301,647, $168,718, and $517,638 in avoidable costs respectively when a timely diagnosis at birth was provided[10]. Newborn screening benefits both the individual family as well as the overall healthcare system, which is why it is often referred to as one of the most successful public health programs in the country.

LDTs are widely used within newborn screening. For example, Severe Combined Immunodeficiency (SCID) was added to the federally recommended uniform screening panel (RUSP) in 2010 and is now

[9] https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2.htm

[10] https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf

screened for in all 50 states[11,12]. Its inclusion has proven extremely successful, raising the five-year survival rate for kids diagnosed with SCID to 92.5 percent - an increase of 73 percent[13]. Ninety percent of state laboratories screening for SCID use an LDT to do so[14]. The first FDA screening test for SCID was approved and available in 2015, five years after the condition was added to the RUSP[15]. The FDA approved test is expensive for laboratories, costing approximately $6.50 per specimen, making it six times more expensive than a lab's LDT, particularly considering that labs do not generate profits from these tests[16]. Due to regulatory enforcement discretion, labs had the flexibility to innovate their own LDT; without this discretion, they might have been compelled to wait for FDA-approved tests, costing numerous lives in those five years. In describing the benefits and costs of the proposed regulation, FDA should consider the benefits that LDTs have provided in newborn screening, and the costs that would be incurred if some of these tests were discontinued because of increased FDA regulation.

While not subject to FDA regulation, laboratories are still subject to multiple levels of oversight. Newborn screening programs are all CLIA accredited and often receive additional accreditation from College of American Pathologists (CAP) and follow Clinical & Laboratory Standards Institute (CLSI) guidelines. State newborn screening programs also work with the CDC's Newborn Screening Laboratory Quality Assurance Program (NSQAP), under the National Center for Environmental Health. NSQAP supplies dried blood spot reference materials, conducts proficiency testing, and validates new screening tests to ensure that the results laboratories generate are accurate. In addition, the programs work with communities to improve on current standards. In 2023, the CDC published a paper that developed a new, validated screening method for classical homocystinuria that utilized a new biomarker that improved on the false positive rate of the previous method[17]. Ultimately, these screening tests do not go unchecked and undergo validation, a process overseen by the federal agency dedicated to advancing public health, the CDC.

The proposed rule severely inhibits the ability to innovate new newborn screening tests for a public health program that has a long history of developing safe, accurate tests. We propose the following recommendation that individually or collectively would ensure the continued success of newborn screening:

1. **Extend the phaseout period to 10 years for the agency's enforcement discretion for newborn screening programs which will give FDA additional time to thoroughly review the quality measures that inform the potential continuation of enforcement discretion in relation to newborn screening and premarket approvals.**

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[11] https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/summary-nominated-conditions.pdf
[12] https://www.newsteps.org/resources/data-visualizations/newborn-screening-status-all-disorders
[13] https://www.ucsf.edu/news/2023/06/425636/newborn-screening-biggest-factor-bubble-baby-disease-survival-last-40-years#:~:text=SCID%20newborn%20screening%20enables%20earlier,%2Dyear%20survival%20to%2092.5%25.
[14] https://www.frontiersin.org/articles/10.3389/fimmu.2020.577853/full
[15] https://www.newsteps.org/sites/default/files/idf_arizonascidfactsheet.pdf
[16] Ibid
[17] https://academic.oup.com/clinchem/article/69/5/470/7068836?login=false

2. **Develop comprehensive guidance that provides clarity and direction for newborn screening programs, ensuring compliance with the new proposed rule without hindering their operational flexibility and stifling innovation.**
3. **Creation of a preliminary regulatory pathway for newborn screening tests for use in pilot studies and public health laboratories to ensure continued access to screening until there is an FDA-approved test for the condition.**

The proposed rule intends to ensure that diagnostic tools are working properly and to accomplish that objective the FDA should work to avoid unnecessary disruptions when successful public health programs are functioning at a high level.

Protect Access to Current Newborn Screening Tests
Due to the lack of a grandfathering provision, the proposed rule risks the ability for newborn screening programs to continue to offer the screening tests currently in use. While there is no published data on how many LDTs are used in each state, it is well-known that state programs rely heavily on LDTs to conduct many of the screens within newborn screening panels. These programs may have to halt the screening for certain diseases due to the lack of extra resources to submit for FDA-approval, creating an environment in which conditions on newborn screening panels for many years will no longer be included in the screening process. **We recommend that the final rule allows for all current newborn screening LDTs to be grandfathered into the new enforcement policy to ensure the continued success of newborn screening.**

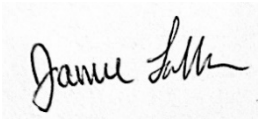
Genetic Testing
An estimated 70-80 percent of rare diseases are genetic in origin, making genetic testing a key component in shortening the diagnostic odyssey[18,19]. There has been an increase in a variety of genetic testing technologies paired with a decrease in the amount of time and cost it takes to run a test, including whole genome sequencing (WGS), whole exome sequencing (WES), and targeted gene panels. We have seen a rise in use of genetic testing, with Medicare seeing a 230 percent increase in genetic tests they paid for between 2016 and 2019[20].

While impactful, there is still plenty of growth available for the use of genetic testing within rare diseases. In the previously cited 2018 FDA/NCATS study, the report found that 77 percent of clinicians cite a need for entirely new diagnostic and/or therapeutic devices, with 64 percent are dissatisfied with existing diagnostic and/or therapeutic devices[21]. Genetic testing will continue to play a large role within the diagnostic space and the proposed rule does little to discuss how it will treat this specific IVD. However, unique challenges exist for the regulatory oversight of genetic testing with the always increasing understanding of the connection between genetic variants and disease phenotypes. **We recommend that the FDA include within the proposed rule a plan to release future guidance during Phase 1 on how they will treat the oversight of genetic tests as IVDs.**

[18] https://www.nature.com/articles/s41431-019-0508-0
[19] https://pubmed.ncbi.nlm.nih.gov/31023718/
[20] https://oig.hhs.gov/oas/reports/region9/92003027.pdf
[21] https://www.fda.gov/media/111309/download

Thank you for the opportunity to provide comments on the proposed oversight of LDTs at the FDA. Please contact Dylan Simon, Director of Policy at dsimon@everylifefoundation.org if we can provide any additional information to inform your process.

Sincerely,



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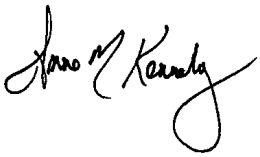

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