



December 4, 2023

**RE: FDA Proposed Rule Medical Devices; Laboratory Developed Tests (88 FR 68006)**

**Dr. Jeffrey E. Shuren, MD, JD**  
**Director, Center for Devices and Radiological Health (CDRH)**  
**U.S. Food and Drug Administration (FDA)**  
**10903 New Hampshire Ave, Silver Spring, MD 20903**

Dear Dr. Shuren,

On behalf of the more than 30 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) is pleased to comment on FDA's proposed rule "Medical Devices; Laboratory Developed Tests" (88 FR 68006).

NORD is a unique federation of non-profit and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective diagnostics and therapies.

**Rare disease patients need and deserve accurate and reliable diagnostics and timely access.** In many cases, an incorrect diagnostic test result can actually be even more devastating for the rare disease patient and family than no diagnostic test at all. Many rare disease patients already face a long and protracted 'diagnostic odyssey.' According to our own survey data, more than 1 in 4 rare disease patients spend seven years or more until they receive a correct diagnosis, up from 15% thirty years ago.<sup>1</sup> In addition, more than 1 in 3 rare disease patients receive at least one misdiagnosis during their diagnostic journey.<sup>2</sup> Limited medical specialization is likely a driving factor, together with other factors such as: complex disease manifestations across multiple organ systems that span multiple medical specialties and share key similarities with other, often more common, diseases; wait times to see specialists; and the need for additional diagnostic testing to rule out or confirm a diagnosis.<sup>3</sup>

At the same time, expeditious access to diagnostic testing is of the essence for rare disease patients who often face progressive and degenerative diseases.<sup>4</sup> For instance, according to our own data, receiving newborn screening significantly increases the odds of rare disease patients being diagnosed in a timely

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<sup>1</sup> Barriers to rare disease diagnosis, care and treatment in the US. National Organization for Rare Disorders. (2020, November 19). [https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report\\_FNL-2.pdf](https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

<sup>2</sup> Id.

<sup>3</sup> Id.

<sup>4</sup> Id.

(i.e., within 6 months) manner.<sup>5</sup> Similarly, when individuals affected by rare diseases receive genetic testing, they are more likely to be diagnosed timely (i.e., within 6 months) than patients without, albeit the difference was not statistically significant in our limited-size data set.<sup>6</sup>

Diagnostic delays can have devastating effects as an accurate diagnosis is the first step in appropriately managing a rare disease to ensure the best possible clinical outcome for patients. While rare disease patients wait for an accurate diagnosis, illnesses progress, often leading to more complex manifestations and greater disease severity. This is on top of the mental health toll patients and caregivers experience while devoting extensive resources, time, and energy to the diagnostic journey.<sup>7</sup> Data also show that diagnostic delays disproportionately affect patients from historically underserved communities, exacerbating long-standing health inequities.<sup>8</sup>

Perhaps most importantly, an increasing number of innovative rare disease therapies have narrow treatment windows, so that any delay in diagnosis can – and does – exclude rare disease patients from participating in and potentially benefitting from clinical trials, or from receiving FDA-approved therapies. Given the limited or non-existing alternative treatment options for many rare diseases, such delays can be particularly devastating for patients and families. Finally, timely access to companion diagnostics,<sup>9</sup> which provide vital information about the safe and effective use of a corresponding drug or biologic, often determine if and when a rare disease patients can access life-altering therapies.

**Many rare disease patients and the physicians that care for them currently rely on LDTs.**

Although representative data to quantify these trends remain scarce, many diagnostic tests central to the medical care of rare disease patients are *in-vitro* diagnostics (IVDs) offered as lab-developed tests (LDTs).<sup>10</sup> As many as 80% of all rare diseases have a genetic component, and many genetic tests in clinical use today are LDTs.<sup>11</sup> Similarly, the vast majority of newborn screening tests administered by publicly funded and run newborn screening programs across the country are LDTs, as well as many companion diagnostics central to the safe and effective use of many rare disease therapies, particularly in the oncology space.<sup>12</sup>

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<sup>5</sup> Barriers to rare disease diagnosis, care and treatment in the US. National Organization for Rare Disorders. (2020, November 19). [https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report\\_FNL-2.pdf](https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

<sup>6</sup> Id.

<sup>7</sup> Id.

<sup>8</sup> Id.

<sup>9</sup> Center for Devices and Radiological Health. (2023). *Companion diagnostics*. U.S. Food and Drug Administration. <https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics#:~:text=A%20companion%20diagnostic%20is%20a,corresponding%20drug%20or%20biologica1%20product.>

<sup>10</sup> Richardson, L., Dobias, M., Akkas, F., Younoszai, Z., & McAndrew, E. (n.d.). *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*. The Pew Charitable Trusts. <https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf>

<sup>11</sup> Id.

<sup>12</sup> Id.

The key reason for the preponderance of LDTs among rare disease diagnostics are clear: rare diseases are by definition rare, and many patient populations affected by the over 7,000 known rare diseases are geographically dispersed, resulting in a very low test-volume at a given diagnostic laboratory. This exceedingly low test-volume often makes filing an application for FDA pre-market approval (pma) or a submission for 510(k) clearance economically and logistically infeasible.<sup>13</sup> In fact, according to a recent survey of diagnostic lab managers, low volume is the leading reason why diagnostic labs develop LDTs.<sup>14</sup>

The fact that new rare diseases continue to be described every day is another key reason for the widespread use of LDTs in the rare disease space. In fact, novel tests - including many companion diagnostics - that simply have not yet received FDA approval or clearance, and quickly evolving science that requires modifications to diagnostic tests at speeds that exceed current FDA review times, are two other leading reasons why diagnostic labs develop LDTs.<sup>15</sup>

Importantly, while some LDTs are completely new tests, others are modified versions of FDA-approved or cleared tests, including tests that change the specimen type or replace elements of FDA-reviewed test kits with components made or acquired separately.<sup>16</sup> Such modifications can be critical to ensure rare disease patient needs are appropriately met, for instance to continue access to testing during public health emergencies and other critical supply chain disruptions; to allow safer and less invasive testing for rare disease patients with special health concerns; or to allow for diagnostic sample collection closer to home – after all, many rare disease patients travel far distances, often across state lines, to access medical care despite the unique mobility challenges and special health concerns associated with many rare diseases.<sup>17</sup>

**NORD is deeply concerned FDA’s proposed rule may inadvertently have devastating impacts on rare disease research and care, particularly given the lack of detail in the proposal and the overly ambitious implementation timelines.** As outlined above, LDTs are currently an integral part of virtually every aspect of rare disease research and care. Uncertainty about the future availability of and access to diagnostic tests for rare disease patients, including through LDTs, can have chilling effects on a sector that is already taxed by data scarcity, heterogenous disease manifestations, and unfavorable economics. Specifically, while NORD wholeheartedly agrees that any diagnostic test used in clinical care must perform reliably and be appropriately validated to be of value to rare disease patients, overly burdensome regulatory

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<sup>13</sup> Immune Deficiency Foundation. (2022). *Why laboratory-developed tests’ fate matters for Rare disease patients*. <https://primaryimmune.org/resources/news-articles/why-laboratory-developed-tests-fate-matters-rare-disease-patients>

<sup>14</sup> Richardson, L., Dobias, M., Akkas, F., Younoszai, Z., & McAndrew, E. (n.d.). *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*. The Pew Charitable Trusts. <https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf>

<sup>15</sup> *Id.*

<sup>16</sup> *Id.*

<sup>17</sup> *Barriers to rare disease diagnosis, care and treatment in the US*. National Organization for Rare Disorders. (2020, November 19). [https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report\\_FNL-2.pdf](https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

requirements ultimately also put rare disease patients at risk. What is even worse, lack of clarity about when and how – or if – rare disease diagnostics will be accessible to rare disease patients and providers risks interrupting future test development; such uncertainty can also disrupt the continued availability of current tests and thus upend patient care; and it risks delaying or destroying rare disease drug development programs that rely on companion diagnostics.

The stakes are high for the roughly 1 in 10 Americans living with a rare disease, and data on the use and performance of LDTs in rare diseases and beyond are very scarce. This makes careful, deliberate implementation of any sweeping changes to the LDT sector particularly important. It also reinforces the need for ample input from ALL parts of the impacted communities. While NORD appreciates the current opportunity to comment, it is hardly sufficient to provide the meaningful data and nuanced insights FDA needs to guide such sweeping reforms. In fact, in the proposed rule itself, FDA poses key questions to the public; while we strongly agree that these questions are vital to the implementation of this rule, a proposed rule is hardly the time or venue for FDA to elicit this kind of foundational information in a meaningful and rigorous manner.

**We urge FDA to 1) reconsider the timelines in the proposed rule and make adjustments to allow for a longer, more realistic implementation; 2) design rigorous processes that meaningfully engage all key stakeholders to answer the key questions outlined in the proposed rule - as well as gather other data that are key to finding and implementing feasible and practical solutions; and 3) provide greater clarity and regulatory predictability.**

Specifically, we urge FDA to appropriately consider and further clarify the following points:

1. **Not all diagnostic tests are created equal or carry the same risks for patients.** NORD appreciates FDA’s request for comments in the proposed rule specifically about whether LDTs performed at academic medical centers (AMCs) should be exempted from regulations, and if so for what rationale (and how to appropriately define AMCs). While NORD agrees that when, where, and how an LDT is performed impacts the associated risk to patients, we believe using an AMC as a proxy for the complex underlying root causes that determine the risk to patients would be overly simplistic, and that some LDTs performed outside of AMCs will likely have similar, or more favorable, safety profiles than some tests associated with some AMCs. We urge FDA to engage in a meaningful multi-stakeholder process to characterize the root causes that determine the risk to patients associated with an LDT – and how to appropriately manage the risk without overly burdensome regulatory requirements.

NORD would be delighted to work closely with FDA on this issue. Our more than 330 member organizations,<sup>18</sup> who are all disease-specific patient advocacy organizations in the rare disease

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<sup>18</sup> About NORD membership network: NORD. National Organization for Rare Disorders. (2023, January 27). <https://rarediseases.org/membership/>

space, as well as our network of 40 NORD Rare Disease Centers of Excellence,<sup>19</sup> which represent the leading AMCs researching and treating rare diseases across the U.S., and our more than 100 Corporate Council members,<sup>20</sup> who represent leading biopharmaceutical companies in the rare space, provide us with a unique depth and breadth of perspectives on this complex issue and we would welcome the opportunity to support FDA.

A deliberate and risk-based approach is particularly important given the extensive number and diversity of LDTs currently on the market that are likely to overwhelm FDA's review capabilities even if the next Medical Device User Fee Act (MDUFA VI) agreement substantially increases FDA's funding. History has shown time and again how cumbersome it can be for FDA to hire highly trained and experienced reviewers, and the exponential increases in staffing required to implement the current proposal are unrealistic to expect in a way commensurate with the ambitious timeline.

To begin developing a risk-based frameworks, some of the key factors to consider include:

- The extent to which an LDT is performed as part of the practice of medicine by an experienced, accredited, and specialized healthcare professional. As outlined above, the vast majority of diagnostic tests for rare diseases are ordered by highly specialized and accredited medical experts as part of their practice of medicine. These test results are typically considered as one part of the totality of clinical evidence by medical experts that for many reasons often tend to be much more directly involved in and familiar with the test performance characteristics than may be typical for an average diagnostic test ordered by any medical professional. At the other extreme, direct-to-consumer testing places the onus of correctly interpreting and appropriately acting upon the test result upon the end-user, with limited to no opportunities to detect and question unexpected or unlikely test results.
- The reasons why and exactly how an LDT is used in the provision of clinical care. Newborn screening tests, for instance, are used as primary tests on very large populations who usually do not show any current clinical symptoms associated with the diseases for which the tests screen the patients, with the goal of identifying patients for much more in-depth follow-up diagnostic testing. These tests do not directly impact clinical decision-making, as any positive test result will be followed up with a complete medical workup and extensive follow-up diagnostic testing under the oversight of a specialized and accredited healthcare professional. In contrast, during the diagnostic odyssey of rare disease patients, many diagnostic test panels are run to rule out rather than to confirm a diagnosis and in fact, many rare diseases can today still only be diagnosed by ruling out all differential diagnoses. Such uses have potential epidemiological ramifications including possible impacts on the expected

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<sup>19</sup> Centers of Excellence Archive. National Organization for Rare Disorders. (n.d.). <https://rarediseases.org/center-of-excellence/>

<sup>20</sup> Corporate Council members. National Organization for Rare Disorders. (2023, February 27). <https://rarediseases.org/corporate-council/corporate-council-members/>

prevalence and thus predictive value of the tests and may be different from more ‘traditional’ tests for common diseases in important ways, emphasizing nuanced risk profiles.

- The extent to which external validation and third-party accreditation may mitigate risks to patients. A variety of public and private certification and accreditation programs (e.g., existing programs through the Department of Veterans Affairs or New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP))<sup>21</sup> can provide reasonable assurances that LDTs meet minimum performance characteristics and perform with acceptable analytical and clinical validity. NYSDOH CLEP, for instance, among other things currently issues annual permits to 1,000 clinical laboratories and 900 patient service centers and blood banks, and registers approximately 5,000 limited-service laboratories throughout the state of New York to ensure the proper performance of diagnostic tests performed at these entities.<sup>22</sup> FDA’s existing 510(k) Third Party Review program provides another valuable model demonstrating the power and promise of external validation and accreditation.<sup>23</sup>
  - The type of LDT. This includes, among many other things, the extent to which remanufacturing of cleared or approved tests may be expected to meaningfully impact the performance characteristics of the test, or the amount of skill, specialized training and experience required to perform the test.
  - Other factors related to the diagnostic test, the relevant diseases, and the patient population(s) as well as potentially other factors that may adversely affect risk to the patient.
2. **FDA should further clarify that certain LDTs will be exempted from some or all regulatory requirements – and provide more guidance for how to navigate that process.** NORD strongly urges FDA to provide as much guidance and reassurance as possible to clarify exemptions or special pathways and reduced data requirements for:
- LDTs used in public health surveillance including newborn screening;
  - 1976-type diagnostic tests, many of which are still relied on by many rare disease practitioners;
  - Diagnostic tests for rare diseases that qualify for the Humanitarian Use Device (HUD) exemption;
  - LDTs that have gone through external validation and third-party accreditation by entities accepted and listed by FDA for third-party accreditation;
  - LDTs that otherwise pose a low risk to consumers as identified through the multi-stakeholder process outlined above.

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<sup>21</sup> *Federal Register / Vol. 88, No. 190 / Tuesday, October 3, 2023 / Proposed Rules* . Department of Health and Human Services. (2023). <https://www.govinfo.gov/content/pkg/FR-2023-11-30/pdf/2023-26209.pdf>

<sup>22</sup> About the program. New York State Department of Health, Wadsworth Center. (2022, December 20). <https://www.wadsworth.org/regulatory/clep/about-the-program>

<sup>23</sup> Center for Devices and Radiological Health. (2022). 510(K) third party review program. U.S. Food and Drug Administration. <https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/510k-third-party-review-program>

3. **Companion diagnostics play an increasingly important role in rare disease drug development, and delays in the approval or clearance of a companion diagnostic could lead to devastating delays in drug approval or biologic licensure.** NORD urges FDA to develop a pathway that will, permanently or at least temporarily, allow companion diagnostics, which are integral to the labelled use of a rare disease drug or biologic, to be marketed without FDA clearance or approval so as not to unduly disrupt access to the therapy. FDA's new voluntary pilot program for some oncology drugs used with some LDTs to identify cancer biomarkers provides a potentially valuable model.<sup>24</sup> Among other things, the pilot establishes minimum analytical performance characteristics for the companion diagnostic that, once properly established through validation studies, would allow extrapolation of the clinical validity to additional tests of the same type including LDTs. This could provide a much-needed pathway for companion LDTs with known performance characteristics, thus protecting vital patient access to diagnostic testing and the safe and effective use of vital rare disease therapies. Unfortunately, the pilot program is to date only available for a very limited number of companion diagnostics; only companion diagnostics for certain oncology drugs qualify, and among these only companion diagnostic that meet very narrowly defined criteria.<sup>25</sup> Moreover, as part of the pilot FDA will evaluate at most nine drug sponsors for possible acceptance into the program.<sup>26</sup> Given that FDA has to date cleared or approved more than 160 companion diagnostics, many of which are applicable to rare diseases, it will be vital to appropriately expand and fund the program – and to ensure FDA will be able to devote appropriate resources to the program to avoid lengthy delays due to staffing issues.
4. **The existing regulatory framework for devices was not made for LDTs and key regulatory questions remain unanswered.** This includes, among many other open questions, how to appropriately apply the risk classification for devices, which is in large part based on FDA's prior regulatory experience with the device, to LDTs. Other questions include how to define predicate devices for current LDTs, and how to logistically implement the 510 K clearance process for current LDTs given the restriction to one *de-novo* application. The potential applicability of change-control plans to IVD remanufacturing represents another open question, together with many other unanswered regulatory questions.

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<sup>24</sup> Office of the Commissioner. (2023, June 20). FDA launches pilot program to help reduce risks associated with using laboratory developed tests to identify cancer biomarkers. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-reduce-risks-associated-using-laboratory-developed-tests-identify>

<sup>25</sup> Center for Devices and Radiological Health (CDRH), Oncology Center of Excellence (OCE), & Center for Drug Evaluation and Research (CDER). (2023, June 20). Oncology drug products used with certain in vitro diagnostic tests ... U.S. Food and Drug Administration. <https://www.fda.gov/media/169616/download>

<sup>26</sup> Office of the Commissioner. (2023, June 20). FDA launches pilot program to help reduce risks associated with using laboratory developed tests to identify cancer biomarkers. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-reduce-risks-associated-using-laboratory-developed-tests-identify>

5. **Data on LDTs are scarce but will ultimately be central to success.** We urge FDA to begin building evidence on the availability, performance, and use of LDTs in rare diseases (and beyond) and to use these data to track potential impacts including unintended consequences on test availability, access, and patient outcomes.

In keeping with NORD's mission to promote the best interests of the rare disease community, we look forward to continuing to work with FDA, Congress, and other key public and private stakeholders to advance constructive, tangible policy solutions that will reduce the diagnostic odyssey and ensure rare disease patients will have time access to the robust and reliable diagnostic testing rare disease patients and the providers who care for them need to appropriately inform medical care. NORD again thanks FDA for the opportunity to provide public comments, and we look forward to continuing the discussion. For questions regarding NORD or the above comments, please contact Karin Hoelzer, DVM, PhD, Director, Policy and Regulatory Affairs at [khoelzer@rarediseases.org](mailto:khoelzer@rarediseases.org).

Sincerely,



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National Organization for Rare Disorders

