August 15, 2024

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10001 New Hampshire Ave
Silver Spring, MD 20903

Peter Marks, M.D., PhD.
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Comments on Draft Guidance, Platform Technology Designation Program for Drug Development (Docket FDA-2024-D-1829)

Dear Dr. Cavazzoni and Dr. Marks,

On behalf of the more than 30 million Americans living with one of the over 10,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance "Platform Technology Designation Program for Drug Development Guidance for Industry."

NORD is a unique federation of non-profits 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 41 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 therapies.

An estimated 95% of the more than 10,000 known rare diseases do not yet have an FDA-approved treatment, making continued progress in rare disease research and drug development critically important. Serial innovation and technologies, including gene therapy vectors, antisense oligonucleotides (ASOs), innovative manufacturing technologies, and other tools that can be leveraged for the investigation and development of medical products to address multiple rare disease indications is an increasingly important dimension of orphan drug development.[1] For this reason, the platform technology designation is a promising regulatory tool of significant potential value to the rare disease community.

Our comments primarily focus on areas where we believe greater granularity will help provide much-needed clarity, certainty, and transparency to ensure this critical new pathway will be appropriately leveraged in rare disease drug development. In addition, we point out areas where we believe more robust and comprehensive engagement of patients and other key rare disease stakeholders will be vital for the program's success.

[1] NORD letter, 1/29/24 at https://rarediseases.org/wp-content/uploads/2024/01/NORD_Memo__SB274_HB570.pdf

1. Provide additional clarity about the Agency's eligibility criteria for the Platform Technology Designation Program

NORD understands the challenges associated with defining eligibility criteria for a new designation program in a very rapidly evolving field and appreciates FDA's efforts to define eligibility in the guidance. However, we are concerned that considerable uncertainty remains, particularly for rare diseases that have scarce data and for this reason have historically necessitated greater regulatory flexibility. For instance, what exactly the Agency considers 'well-understood and reproducible technology,' 'significant efficiencies,' or 'developed and reviewed in a more streamlined manner' may be variable or subject to interpretation, in particular for nascent areas of rare disease drug development with widely varying scientific properties and limited regulatory precedent.[2] Moreover, our understanding of the key scientific properties of these emerging technologies continues to evolve, including for instance, the impact of specific structural elements on safety, efficacy, tissue tropism, etc.

The illustrative examples of potential platform technologies in the draft guidance are exceedingly useful in this respect. We encourage the Agency to periodically update that list, and to include additional examples of relevance to rare diseases, including ASOs and other RNA-based technologies that are currently missing from the list. As the program is implemented and requests for designation are received, it would be valuable for FDA to sustain an ongoing dialogue with sponsors, investigators and patients on qualifying platform technologies to assess and reassess potentially qualifying technologies.

In addition, while we understand the challenges involved, we urge the Agency to reconsider whether there is a path to leverage designated technologies for future applications and application by third parties. To that end, we encourage FDA and the Department of Health and Human Services to investigate ways to apply the regulatory validation that comes from designation to nonproprietary and noncommercial research uses, and potentially enabling non-licensed use of designated technologies for at least some rare diseases.

2. Create greater clarity, transparency, and predictability regarding the benefits associated with a granted designation

As outlined above, for many rare disease drug development programs that leverage innovative new platform technologies, scientific evidence continues to evolve quickly, including in areas that may impact the designation program. The associated uncertainty can hamper the value of the designation.
To help address this residual uncertainty, the draft guidance would benefit from clarifying that a granted platform technology designation creates a presumption that "leveraging platform technology information" in a subsequent application is valid unless there are strong countervailing, invalidating findings made by the Agency. Otherwise, much of the potential advantage of securing platform technology designation may be significantly reduced or delayed.

Similarly, we urge the Agency to provide a stronger commitment to the statutorily listed benefits of platform technology designation. One of the crucial benefits from the designation is the ability of sponsors to "[r]eceiv[e] timely advice from and having additional engagement with FDA during the

[2] Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024, May). Platform Technology Designation Program for Drug ... U.S. Food and Drug Administration. https://www.fda.gov/media/178938/download

development program, such as additional interactions and/or meetings."[3] Yet the guidance states that "[d]epending on resources, FDA might prioritize interactions or additional engagements regarding a designated platform technology for those products where the Agency has determined that there is the most significant public health benefit or impact."[4] We understand that the platform technology designations, like expedited review pathways, are not funded by user fees and are not linked to explicit performance goals for the number and timeliness of sponsor meetings. For this reason, the Agency may understandably be constrained in fulfilling the requisite sponsor "engagements" resulting from granted platform technology designations. However, the draft guidance creates unnecessary ambiguity and uncertainty for sponsors. We encourage FDA to specify a set number or minimum number of meetings resulting from a granted designation, or to otherwise secure reliable funding through the upcoming user fee negotiations to ensure consistent conduct by the Agency and predictability for participating sponsors.

3. Emphasize patient engagement and the inclusion of patient perspectives througout the guidance and ensure appropriate formal and informal engagement of the rare disease community

NORD understands and appreciates the guidance's intentional focus on increasing efficiencies for FDA review and medical product development. However, patients and caregivers play a number of vital, unique, and outsized roles in rare disease drug develoement. It is deeply concerning that the word 'patient' is not mentioned once in the 18-page draft guidance. Patient engagement and patient perspectives could and should inform key issues from whether efficency gains merit eligibility to considerations around the revocation of a designation and beyond; however, mechanisms for such structured engagement are not contemplated. Moreover, the guidance fails to appropriately engage other key stakeholdes in the rare disease space, including the Centers for Medicare and Medicaid Services and other public and private payors who have to reach coverage and reimbursement decisions for the impacted products, the National Institutes of Health and others who provide vital upstream funding, and the academic community that is driving the development of many of the nascent technologies as well as enhancements in our understanding of the relationship between physical structures and functions for these emerging technologies and hence potential designation eligibiity.

From a policy perspective, platform technology designations are promising incentives that have the potential to expedite, shape, and guide investments and the future of rare disease drug development. As outlined previously, implementaiton of this designation will involve many nuanced, gray areas with limited and/or rapidly evoving knowledge. Close interactions with the rare disease community are vital, in particular given the guidance's strong focus on efficency gains – for both sponsors and FDA- as a key part of the desingation program. NORD believes strongly that this guidance will not have its full and beneficial effect unless the Agency seeks robust, structured, and sustained stakeholder discussion and engagement. In addition to the areas already mentioned, these efforts should encourage the sharing of best practices and successful platform technology programs among sponsors, as well as targeted educational programs for rare disease patients, their providers, advocacy groups and public and private payors.

[3] Ibid.
[4] Ibid.

4. Consider ways to leverage some of the benefits associated with platform designation earlier in the drug development process, potentially before a predicate drug receives FDA approval or licensure

We understand the resource constraints under which FDA operates and why a platform technology designation can be only granted once a predicate drug product has been "approved or licensed" by FDA under the statute (section 506K(b)(1) and (2)).[5] With a predicate product in the market, the Agency encourages submission of designation requests "concurrent with or at any time after the submission of an IND application".[6] However, we urge FDA to also consider earlier engagement in pre-submission discussions with early-stage and emerging companies, and academic investigators, in particular, who lack a predicate approved product, but are in the process of clinically developing potentially-qualifying platform technologies for rare diseases.
Pre-designation engagement with such sponsors with promising platform technologies could be an efficient use of time and resources, particularly if such outreach is accomplished in partnership with stakeholders and in open, public fora, rather than individual sponsor meetings. To that end, we encourage FDA to also work in partnership with relevant agencies including the National Center for Advancing Translational Sciences (NCATS), the Advanced Research Projects Agency for Health (ARPA-H), and the Biomedical Advanced Research and Development Authority (BARDA), which has explicit statutory mandates regarding enabling platform technologies, to disseminate information about the designation, share nonproprietary findings about the outcomes of designations, and afford itself new opportunities to learn about emerging technologies of importance to rare disease drug development.

5. Create transparency and trust by proactively reporting adoption of the designation program and agency progress

In addition to the statutorily mandated annual report to Congress, we urge FDA to maintain up to date public data on designation requests and those "issued, active and revoked" through the FDA Dashboard.[7] Additionally, we believe the Agency and public alike would benefit from qualitative, non-sponsor-specific conclusions about the rigor of requests received, lessons learned from their review, and any resulting advice to assist prospective sponsors.

6. Place greater emphasis on leveraging prior knowledge, findings, and proven best practices in the platform designation program

We applaud the Agency's clarifying statement that "[i]neligibility for designation does not preclude a sponsor from leveraging prior knowledge across applications."[8] We agree that the platform technology designation is one important, highly visible, but not exclusive method by which sponsors may "leverage prior knowledge from previously submitted applications" for new premarket submissions.[9] However, we also know that many sponsors who are new to rare disease drug development continue to struggle in this regard. Given the iterative nature of rare disease drug development, with many approved orphan drugs

[5] Ibid.
[6] Ibid.
[7] See (section 2503(c) of Consolidated Appropriations Act, 2023 P.L. 117–328) …https://www.govinfo.gov/app/details/PLAW-117publ328
[8] Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024, May). Platform Technology Designation Program for Drug ... U.S. Food and Drug Administration. https://www.fda.gov/media/178938/download
[9] Ibid.

having more than one approved rare disease use,[10] we urge FDA to expand upon and broadly disseminate more guidance, best practices, and case studies regarding such regulatory efficiencies to better educate sponsors, investigators, and patients on regulatory approaches that can be leveraged to this end. In addition, we urge FDA to create, curate and share an inventory methods and technologies that underlie multiple drug products and the extent to which they have achieved the statutory goals of section 506K of "significant efficiencies to the drug development or manufacturing process and to the review process."[11]

Finally, we encourage FDA to consider application of its lengthy experience with Drug Master Files (DMFs) to the platform technology designations to help secure "significant efficiencies to the review process" (section 506K(b)(3)).[12] We believe Master Files may be a useful procedural tool to simplify FDA's administration of the program, facilitate sponsor sharing of essential data in an efficient fashion, and potentially enable third party and external reliance on Master Files in the future. We note that the European Medicines Agency (EMA) is moving towards expanded reliance on Master Files for vaccines[13,14] and potentially drugs and other biological products.[15]

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around platform technology designations as well as other strategies to bring safe and effective rare disease drugs to market. For questions regarding NORD or the above comments, please contact Karin Hoelzer at khoelzer@rarediseases.org or Hayley Mason at hmason@rarediseases.org.

Sincerely,

Karin Hoelzer, DVM, PhD
Senior Director, Policy and Regulatory Affairs
National Organization for Rare Disorders

Hayley Mason, MPA
Policy Analyst
National Organiztion for Rare Disorders

[10] Miller et al (2024) found that of "491 novel orphan drugs… approved between 1990 and 2022 [,…]15 percent have been approved for multiple rare diseases, and 20 percent have been approved for both rare and common diseases." Miller KL, Lanthier M. Orphan Drug Label Expansions: Analysis Of Subsequent Rare And Common Indication Approvals. *Health Affairs*. 2024;43(1):18-26. doi:https://doi.org/10.1377/hlthaff.2023.00219

[11] Center for Drug Evaluation and Research (CDER), & Center for Biologics Evaluation and Research (CBER). (2024, May). Platform Technology Designation Program for Drug ... U.S. Food and Drug Administration. https://www.fda.gov/media/178938/download

[12] Center for Drug Evaluation and Research. (n.d.). Drug master files (dmfs). U.S. Food and Drug Administration. https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs

[13] EMA, Committee for Medicinal Products for Human Use (CHMP), EMA/CHMP/ BWP/211968/2023, June 22, 2023. Accessed July 26, 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-development-guideline-quality-aspects-mrna-vaccines_en.pdf

[14] Ibid.

[15] EFPIA-CEPI-Vaccines Europe, Position paper: Expanding Master Files for human medicinal products in the EU/EEA , March 21, 2023. . Accessed July 26, 2024. https://media.tghn.org/medialibrary/2023/04/EFPIA-CEPI-position_paper_PTMF_21Mar2023v2.pdf