Re: Food and Drug Administration, Draft Guidance, Platform Technology Designation Program for Drug Development

July 29, 2024

Attn: Food and Drug Administration

Re: FDA-2024-D-1829

Innovative Genomics Institute
University of California
Berkeley, CA 94704
www.innovativegenomics.org

N=1 Collaborative
https://www.n1collaborative.org

Please direct inquiries regarding this comment letter to:
Dr. Winston Yan (winston@n1collaborative.org) and
Dr. Manar Zaghlula (manar.zaghlula@berkeley.edu).

To the FDA Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research,

The Innovative Genomics Institute (IGI), a public, academic research institute formed in partnership between multiple University of California campuses, and the N=1 Collaborative, a nonprofit organization comprising clinician-scientists, researchers, patients, and companies committed to advancing the field of individualized medicines, below submit comments on the draft guidance on the *Platform Technology Designation Program for Drug Development*.

We thank Agency staff for developing a thoughtful draft guidance document and the opportunity to provide comment. We believe the suggestions below will strengthen the Platform Technology Designation Program and accelerate drug development for N-of-Few disorders. Our organizations welcome any questions and the opportunity to engage further on this crucial topic.

On behalf of the Innovative Genomics Institute and the N=1 Collaborative,

Fyodor D. Urnov, Ph.D.
Professor of Molecular Therapeutics, UC Berkeley
Director of Technology & Translation, Innovative Genomics Institute

Winston X. Yan, M.D., Ph.D.
Founding President, N=1 Collaborative

Manar Zaghlula, Ph.D.
Health Policy Manager, Innovative Genomics Institute

General Comments

We are grateful for the opportunity to comment on the Docket Number FDA-2024-D-1829, Platform Technology Designation Program for Drug Development: Guidance for Industry (Draft). **The commitment to improving efficiency of drug development by harnessing the modular nature of platform technology in drug development may have its biggest impact in rare disease, where such efficiencies have the unique ability to address thousands of rare diseases that collectively affect millions worldwide.** We appreciate FDA's commitment to accelerating rare disease treatments, and CBER's leadership on rapidly advancing cell and gene therapy (CGT) development.

The following comments are collated feedback from key constituents within the world of N-of-few drug developers. Specifically, the implementation of the Platform Technology Designation Program as written would still leave large gaps in enabling treatments for the "long tail" of rare disease. Critically, not enabling "academic" INDs for N-of-1/few conditions is a lost opportunity to evaluate the robustness of given platform technologies, as even dosing a small number of participants across disparate diseases will yield important data on the impact of platform modifications on safety and efficacy.

Genomic medicines, including antisense oligonucleotide-based therapies and CRISPR gene editing, have the potential to unlock the development of treatments for a substantial majority of rare genetic diseases and cancers that have been previously intractable. However, as the FDA and Congress have recognized, the *status quo* of one-by-one development and approval of drugs and biologics will not deliver on the promise of these transformative therapies. Establishing a robust program that leverages the platform nature of genomic medicines, in particular CRISPR-based modalities, will dramatically accelerate drug development and enable access to durable, potentially curative, treatments for thousands of disorders. We commend the Agency on taking such a critical step and offer some suggestions that we believe will strengthen the program and widen its impact.

The aggregate impact of the platform technology designation program proposed in the draft guidance will depend on the scope of its targeted beneficiaries. While the program will almost certainly improve the commercial opportunity for some disorders and sponsors by improving efficiency for additional filings on the same platform, many rare and ultra-rare disorders (including N-of-1 cases), will remain of minimal commercial interest. It has been estimated that 40% of all rare disorders affect 50 patients or less. This tremendous area of unmet need is where academic and other mission-driven organizations, referred to here as "N-of-few drug developers" are best positioned to have an impact.

Unfortunately, in its current form, the draft guidance is heavily dependent on access to information within an approved or marketed ANDA/NDA/BLA, explicitly stating that "designation of a platform

technology does not give third parties additional rights to reference information from an approved product application containing that platform technology if they do not own or have full rights of reference to it." This renders the designation largely inaccessible to N-of-few drug developers—and by extension to the patients affected by ultra-rare disorders. ***We therefore urge the Agency to enable academic/nonprofit sponsors who do not hold a BLA or NDA to obtain or benefit from platform technology designation***, guided by "platform logic" that is anchored in industry-wide prior knowledge and scientific literature, and not intrinsically linked to a developer's historic BLA's. This would be the 'rising tide that lifts all boats', supercharging the development of medicines for rare disorders.

As drug developers and scientific investigators, we recognize that the details of a specific 'parent' platform are important to the safety and efficacy of the related 'daughter' products on that platform. For example, there may be variation due to specifics of the mechanism of action, off-targets, cell viability, and other factors such as with different Cas proteins that each have different safety profiles. Likewise, antisense oligonucleotides may have different chemical modifications that impact its pharmacokinetics, biodistribution, and safety. Despite these differences, there are still important efficiencies that can be gained from the target programmability that is inherent to DNA/RNA targeting platform technologies. We recommend that these properties be used to accelerate N-of-few drug development using oligonucleotide therapeutics, even in the absence of a formal platform designation based on a specific approved therapeutic. With a favorable benefit/risk in such rare disease populations without any approved treatments, this provides both an opportunity for treatment development, as well as for the Agency and the field to continue learning from real-world data of platform medicines in use to further inform best practices of platform designations.

Below we outline several reasons why this is critical to better enable the participation of N-of-few drug developers (whether academic, non-profit, or for-profit) using the platform designations:

1. **Academia already engages in nonclinical studies, clinical trials, and CMC development, contributing critical knowledge to therapeutic platforms.** A large proportion of all CGT INDs (e.g., especially CAR-T cell treatments) are obtained in the academic setting, highlighting that the requirements of the program - that the technology be essential to the structure or function of the drug or biological product, that it can be adapted for use by more than one product, and that it facilitates manufacture or development through standardized processes – apply to products developed in the academic setting. Indeed, many rare disease patients have only ever been able to receive transformative therapies in the context of an academic clinical trial, a reality that is unlikely to change without the kind of system-wide innovation that the platform technology designation program offers. The dramatic cost reductions catalyzed by the platformization of drug development enable the investigation of more candidate products, including those for ultra-rare disorders. Few, if any, of these products will be submitted for BLA/NDA approval. Thus the as-written Platform Designation would not be applicable on these treatment platforms, even as the platform logic is already effectively utilized to streamline

treatment development. Meanwhile, FDA and industry continue to learn from these academic efforts. Thus, incorporating N-of-few drug developers as important stakeholders in the platform technology designation would be beneficial to patients, the Agency, and industry alike.

2. **As academic sponsors are more likely to openly share their findings, iterative use of platforms in early-stage clinical trials could de-risk more candidate products that could be transferred to industry for commercialization.** The FDA could implement a platform technology designation, after safety has been established in a Phase 1 or 2 trial, rather than at BLA/NDA approval. Platform efficiencies are typically gained from addressing new targets and diseases with the same platform technology; since many BLA/NDA approvals are strongly dependent on assessing the efficacy of a disease-specific endpoint, evaluating disease-agnostic platform eligibility is better done at an earlier stage. Enabling platform designations prior to full approval is more efficient and would reduce the per-therapy cost of development. Additionally, the natural incentive of publication and data-sharing within academic settings could provide an important pre-competitive data repository to guide future industry and academic efforts. The N=1 Collaborative is in the process of establishing such a knowledge base for protocols, best practices, and preclinical/clinical data across multiple programs, enabling nascent knowledge sharing to improve platform drug development. Not enabling academic participation on platform drug development risks creating significant data silos around each approved BLA/NDA platform (particularly likely if the sponsors are for-profit), fragmenting the ecosystem and ultimately limiting the transformative potential of such treatments.

3. **Requiring that the designation depend on a BLA slows the uptake of innovative technologies.** For a given platform technology, in most instances reaching a BLA/NDA approval may take years and will cost significantly more than establishing platform safety. An earlier platform designation based on safety would enable faster utilization of the platform designation to develop more innovative therapies. Furthermore, if academics could leverage the platform technology designation, innovative technologies could be de-risked in the academic setting in multiple indications and then made available to industry sponsors.

4. **We encourage FDA to collect and publish data on the impacts of the program across the ecosystem and engage stakeholders continuously to strengthen the program.** As the Agency learns from the implementation of the program, especially as it relates to specific modalities, such as CRISPR or ASOs, the field would benefit greatly from FDA developing additional guidance documents that reflect such nuances.

Case Studies: Recommendations for specific platform designations

We encourage the Agency to include specific discussions of several platform modalities in the final guidance, such as:

CRISPR

The draft guidance does not explicitly address in any way the current field-leading approach that allows for one-time targeted genetic modification for treatment: CRISPR-Cas gene editing. We believe that the mechanism of action of CRISPR-Cas gene editors, in which a small change to the drug substance yields a therapeutic for a different disease indication (e.g., changing the 20 nucleotides in a guide RNA), makes it the poster technology for a platform designation. It would be appropriate, thus, to represent this in the draft guidance in some way.

Ex-vivo gene editing

A platform for *ex vivo* gene editing in hematologic disease could enable the reuse of drug product manufacturing equipment, of a protein or mRNA active pharmaceutical ingredient for the gene editing enzyme, and the nucleic acid composition of the guide RNA, with solely the mutation-specific 20 nucleotide region to be altered between patients. The platform would thus comprise a set of manufacturing solutions for the excipients and active pharmaceutical ingredients and for the cell product; a standardized approach for assessing potency by measuring the efficiency of desired genetic change in the drug product; and a standardized approach to assess the genotoxic potential of the gene editing process.

In vivo gene editing

Separately, a platform for *in vivo* gene editing of the liver could comprise all of the above along with a standardized way to assess biodistribution that could, under appropriate circumstances, be a set of studies performed once for a given *in vivo* delivery modality (e.g., LNP to the liver) and represent a platform dataset that does not need to be generated *de novo*. For the LNP-based gene editing platform, while there is no BLA approved, the collective knowledge over dozens of patients dosed across multiple products have provided important safety information that may make it already useful in treating other rare metabolic diseases of the liver. In both cases, the introduction of a novel patient-specific 20 nucleotide stretch of the guide RNA into the drug product would enable the sponsor to leverage the sum total of nonclinical manufacturing, efficacy, toxicology, and biodistribution data that were generated for a previous such drug product.

Supporting an expanded program

We recognize that the statutory language in Public Law 117-328, adding Section 506K of the Food, Drug and Cosmetic Act is prescriptive and may not authorize broader interpretation as we propose here (especially in light of the recent *Loper Bright Enterprises v. Raimondo* Supreme Court ruling)**.** Thus, we would be eager to engage in educational efforts on this issue with Members of Congress to advance conversations about the appropriateness of more permissive language. Additionally, we appreciate that FDA may use its regulatory flexibility

to effectively enable use of the framework presented in the draft guidance for academic/nonprofit developers without formally labeling it as a designated platform technology. In this case, we ask that the Agency clearly communicate to N-of-few stakeholders that such a pathway could be explored in direct consultation with review staff.

Additionally, we acknowledge that expansion of the program to N-of-few developers could present resource challenges for the Agency. We propose that FDA leverage outside expertise (akin to Advisory Committees) to evaluate how to designate proposed platforms. While the specifics of the evaluation process should be developed by FDA in consultation with stakeholders across the ecosystem, we suggest that determinations should be made based on, at least, the following: (a) the applicability of the proposed technology to other disorders; (b) its benefits to patients with unmet medical need, with priority given to disorders of little or no commercial interest; and (c) estimated development and/or manufacturing cost savings.

Conclusion

We are excited by the concerted efforts at FDA to implement a Platform Technology Designation Program, recognizing advances in the drug development field and the potential of platform-based technologies to address the thousands of rare diseases and cancers with high unmet medical need. We encourage the Agency to strengthen the program by enabling N-of-Few drug developers to leverage platform efficiencies and contribute to the ecosystem without having to rely on BLAs/NDAs. We further ask that the Agency discuss modality-specific considerations in the final guidance.

We are grateful for FDA's commitment to advancing treatments for rare and ultra-rare disease patients and look forward to seeing the potential of platform technologies realized through this revolutionary program.

- - -