August 28, 2024

Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Platform Technology Designation Program for Drug Development
Draft Guidance for Industry

Dear Sir or Madam,
On behalf of the Alliance for mRNA Medicines (mrnamedicines.org), we are pleased to submit comments on the FDA's "Platform Technology Designation (PTD) Program for Drug Development Draft Guidance for Industry." We know that FDA is quite familiar with the role that mRNA played in the response to COVID-19, with millions of Americans having received at least one dose of a COVID-19 vaccine. The amazing story of mRNA's role in the COVID-19 response paved the way for mRNA to be used in other vaccines and treatments. We are only at the beginning of the benefit mRNA will deliver to patients and the public health through the revolution in vaccine development and future treatments for cancer, rare diseases, and other areas of unmet medical need. The technology's agility and flexibility make it well suited to a platform approach, and therefore we are pleased to see FDA's draft guidance and eager to work with the Agency as you move towards a final guidance implementing the PTD program.

About AMM

The Alliance for mRNA Medicines (AMM) is an organization dedicated to advancing and advocating for mRNA and next-generation encoding RNA therapeutics and vaccines for the benefit of patients, public health, and society. Our mission is to propel the future of mRNA medicine, improve patients' lives, and advance scientific knowledge by convening and empowering mRNA industry leaders, innovators, scientists, and other key stakeholders.

AMM officially launched in November 2023 and has become the leading voice of the mRNA community, representing 60 members from North America, Europe, Asia, and Oceania. Our members demonstrate the diversity of the mRNA community, which includes biotechnology companies, pharmaceutical companies, academic institutions, service providers, contract development and manufacturing organizations (CDMOs), and the patients who have and will benefit from mRNA vaccines and therapeutics.

The Promise of mRNA Technology

While the first mRNA vaccines for COVID-19 were issued an Emergency Use Authorization in 2020, this was preceded by more than 25 years of research about how to use RNA.

In awarding the Nobel Prize for Physiology or Medicine in December 2023 to Drs. Katalin Karikó and Drew Weissman for their work on mRNA, the Committee noted the "impressive flexibility and speed with which mRNA vaccines can be developed pave the way for using the new platform also for vaccines against other infectious diseases. In the future, the technology may

also be used to deliver therapeutic proteins and treat some cancer types." We share the Committee's great hope for the future of this technology for vaccines and therapeutic uses.

As the Foundation for mRNA Medicines board chair Deborah Barbara recently wrote, "mRNA offers for the first time the ability to harness the patient's own cellular machinery to express a gene in vivo. This gene may be a simple antigen to elicit an immune response like the COVID-19 mRNA vaccines, or it could encode complex sequences such as those of a therapeutic monoclonal antibody. This molecular flexibility allows mRNA to potentially treat a wide range of diseases as a prophylactic vaccine, a personalized cancer vaccine, a protein replacement therapy, a therapeutic protein, and/or as a critical technology enabling gene-editing and gene modulation (e.g., based on CRISPR). These molecules have the potential power to protect the world from malaria, HIV, and other deadly pathogens, provide cures for cancer, treat sickle cell anemia (like newly approved CASGEVY), and other diseases/conditions where there is a significant unmet need."[1]

The applications of mRNA include:

- Prophylactic vaccines
  Traditionally vaccine development has hinged on introducing the immune system to a weakened or inactivated piece of a particular bacteria or virus, triggering an immune response. For more than a decade prior to the development of the COVID-19 vaccine, scientists had been exploring the possibility of using messenger RNA encoding just a surface protein rather than exposing a patient to all or part of an actual bacteria or virus. mRNA is necessary for protein production, and once cells finish making a protein, the mRNA is broken down without entering the nucleus or altering the genome. mRNA vaccines work by introducing mRNA that corresponds to a microbial protein. When the immune system is introduced to it through a vaccine, it recognizes it as foreign and produces antibodies that will protect the body and mount an immune response when it is exposed to the pathogen in the future.[2]

  The COVID-19 vaccine was just the first approval in what we expect to be a wave of mRNA-based vaccines. The speed and cost savings associated with developing vaccines using mRNA technology make it an attractive tool. In addition, it is possible to make mRNA vaccines that encode for more than one protein, which could, for example, allow vaccines that protect against multiple strains of flu or COVID-19.[3] In the history of medicine, there are only 26 diseases for which prophylactic vaccines are available.[4] mRNA vaccine development presents an incredible opportunity to vastly expand this list.

[1]Barbara, D. D. (2024, April 26). , mRNA: The Fourth Pillar Of Pharmaceutical Innovation And Intervention. Advancing RNA. https://www.advancingrna.com/doc/mrna-the-fourth-pillar-of-pharmaceutical-innovation-and-intervention-0001

[2] Medline Plus. What are mRNA vaccines and how do they work? MedLinePlus. https://medlineplus.gov/genetics/understanding/therapy/mrnavaccines/

[3] Hamzelou, J. (2023, January 5). What's Next for mRNA Vaccines. *MIT Technology Review*. https://www.technologyreview.com/2023/01/05/1066274/whats-next-mrna-vaccines/

[4] The Immunization, Vaccines and Biologicals Department. Vaccine Preventable Diseases (including pipeline vaccines). World Health Organization. https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases

In May 2023, a review conducted of clinical trials registered at clinicaltrials.gov showed trials underway using mRNA for vaccines targeted at respiratory syncytial virus, seasonal influenza, HIV, Lyme disease, cytomegalovirus, malaria, Zika, Nipah, and others.[5]

This PTD guidance is important because it will enable development of vaccine platforms where new target pathogens can easily be swapped in, reducing duplicative or unnecessary steps for sponsors and easing review for the Agency. For example, in the sequence design space, there are more than a million coding sequence design options for the COVID-19 vaccine. Developing a platform framework that enables a developer to test out multiple sequences in the same trial to pick out the lead sequence to advance towards phase 2 and phase 3 will vastly speed development.[6]

Finally, many vaccines are viewed as low-margin commodities, which endangers the stability of the vaccine development enterprise.[7] So the scientific advancement mRNA offers, the time savings and scale which can be achieved in manufacturing mRNA vaccines compared to traditional egg-based vaccines, and the streamlined regulatory approach of the PTD framework are critical to enabling continued development of new vaccines to protect public health.

- Therapeutic vaccine
  mRNA is also being explored to treat a range of cancers through "vaccine therapeutics," where our immune systems could be trained to recognize proteins on cancer cells. Companies are exploring off-the shelf, indication-specific mRNA cancer vaccine platforms, as well as personalized treatments, where a custom-made vaccine is developed and aimed at stimulating a highly-specific adaptive immune response against the patient's unique tumor.[8] "Given the evidence supporting the effectiveness and safety of clinically approved mRNA vaccines, coupled with growing interest in mRNA-based therapeutics, mRNA technology is poised to become one of the major pillars in cancer drug development."[9] A platform approach to regulating these personalized vaccines will essentially become a regulatory necessity, given the challenge of reviewing a BLA or NDA for each patient-specific vaccine.

[5] Skerritt, J.H., Tucek-Szabo, C., Sutton, B., and Nolan, T. (2024, May 11). The Platform Technology Approach to mRNA Product Development and Regulation. *Vaccines*, 12(5), 528. https://doi.org/10.3390/vaccines12050528
[6] Alliance for mRNA Medicine (AMM). (2024). [Comments made during summit]. Global Regulatory Summit. Washington D.C.
[7] Board on Health Care Services. (2003). Financing Vaccines in the 21st Century: Assuring Access and Availability. National Academies Press. Chapter 5, online. https://www.ncbi.nlm.nih.gov/books/NBK221811/
[8] Hamzelou, J. (2023, January 5). What's Next for mRNA Vaccines. *MIT Technology Review*. https://www.technologyreview.com/2023/01/05/1066274/whats-next-mrna-vaccines/
[9] Liu, C., Shi, Q., Huang, X., Koo, S., Kong, N., and Tao, W. (2023, June 13). mRNA-based Cancer Therapeutics. *Nature Reviews Cancer*, 23, 526 – 543. https://doi.org/10.1038/s41568-023-00586-2

Clinical trials for mRNA vaccines in a phase 3 melanoma trial[10] and pancreatic ductal adenocarcinoma (PDAC)[11] trial have already shown impressive results. Clinicaltrials.gov also lists phase 2 trials in other forms of cancer including malignant melanoma, uveal melanoma, lymphoma, solid tumors, pulmonary osteosarcoma, prostate cancer, head and neck cancers, gastric cancer, ovarian cancer, and biliary tract cancer.[12] One of the potential advantages of mRNA-based personalized cancer vaccines is the compressed end-to-end development time.

- Protein replacement therapy
  There are a variety of diseases in which the aim of medical treatment is to substitute or replenish specific protein deficiencies where the protein is absent or mutated in affected patients. There are many ways to achieve this protein replacement, however, mRNA-based approaches could have advantages compared to more invasive or permanent procedures.[13] mRNA protein replacement therapeutics are being developed for a number of genetic diseases including cystic fibrosis and rare metabolic diseases, type 2 diabetes, cardiovascular disease, and other fibroses. As Skerritt. et al write, "There are also potential safety advantages for mRNA therapeutics over gene therapies because there is no genome integration or permanent modification of the genome. mRNA therapeutics bring manufacturing advantages compared with the production of recombinant proteins in that much smaller quantities are typically required."[14] Another area that's being explored is delivery of mRNA encoding proteins that can promote cellular regeneration and/or rejuvenation, for example VEGF-A for heart failure. Other therapeutic proteins that can be generated by mRNA technologies are therapeutic antibodies, which may replace traditional protein antibodies. smRNA technology generated antibodies eliminates the cumbersome process of the current in vitro protein expression and extends the functional half-life of short-lived proteins, which significantly reduces the cost and duration of antibody production. Thus, smRNA based therapies could be a highly effective therapeutic approach to deliver monoclonal or bispecific antibodies.

- Gene-editing delivery (e.g., CRISPR or ZFN, etc.)
  Gene editing is one of the most exciting frontiers in medicine, and one strategy currently being explored for delivering gene editing enzymes includes mRNA delivery. "One key advantage [of utilizing mRNA-based systems] is the ability to achieve transient expression, offering a controlled and time-limited therapeutic effect. This minimizes the

[10] Carvalho, T. (2023, August 16). Personalized Anti-cancer Vaccine Combining mRNA and Immunotherapy Tested in Melanoma Trial. *Nature Medicine,* 29, 2379-2380. https://doi.org/10.1038/d41591-023-00072-0
[11] Reynolds, S. (2023, May 23). An mRNA Vaccine to Treat Pancreatic Cancer. NIH. https://www.nih.gov/news-events/nih-research-matters/mrna-vaccine-treat-pancreatic-cancer
[12] Skerritt, J.H., Tucek-Szabo, C., Sutton, B., and Nolan, T. (2024, May 11). The Platform Technology Approach to mRNA Product Development and Regulation. *Vaccines*, 12(5), 528. https://doi.org/10.3390/vaccines12050528
[13] Vavilis, T., Stamoula, E., Ainatzoglou, A., Sachinidis, A., Lamprinou, M., Dardalas, I., and Vizirianakis, I. S. (2023, January 3). mRNA in the Context of Protein Replacement Therapy. *Pharmaceutics*, 15(1): 166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9866414/
[14] Skerritt, J.H., Tucek-Szabo, C., Sutton, B., and Nolan, T. (2024, May 11). The Platform Technology Approach to mRNA Product Development and Regulation. *Vaccines*, 12(5), 528. https://doi.org/10.3390/vaccines12050528

risk of off-target effects, allowing for a more precise delivery. Moreover, mRNA-based systems eliminate the potential for genomic integration and maintain the integrity of the host genome. This intrinsic safety profile, coupled with the reduced immunogenicity compared to viral vectors, enhances the overall safety of mRNA-based therapies. Collectively, these factors highlight the growing interest and potential of mRNA-based gene editing systems."[15]

- In vivo chimeric antigen receptor (CAR): encoding chimeric antigen receptors using mRNA and delivering the mRNA to T cells (and/or other immune cells) in vivo using LNPs.
  This in vivo approach has a number of advantages over the ex vivo approaches currently used in clinical practice, including their being naturally autologous and not requiring complicated/expensive cell therapy manufacturing.

Relevance of Platform Designation to mRNA

In section 2503 of the *Food and Drug Omnibus Reform Act*, Congress directed FDA to create a "platform technologies" designation program. The benefit of reviewing a platform technology include more nimble development of product by sponsors, streamlined regulatory submissions and review by regulators, and ultimately faster patient access to future products. While many other technologies will also potentially fit under the definition of "platform technologies," mRNA-based products are an especially good fit for this concept.

The COVID-19 experience proved that regulators already have leveraged sponsors' prior knowledge of non-clinical toxicity data for mRNA-based vaccines to move to phase 1 clinical trials. However, the range of flexibilities and extraordinary devotion of FDA staff resources that went into these reviews cannot be expected to occur regularly moving forward. Therefore, detailing the ways in which sponsors can use prior knowledge in regulatory submissions will have major benefits to both sponsors and regulators alike.

During the COVID-19 pandemic, vaccine manufacturers demonstrated the capability of the mRNA-LNP platform to produce high quality, consistent results. As new COVID-19 variants emerged, the vaccines were updated to reflect these new targets corresponding to sequence variations in the RNA while maintaining the same LNP drug product formulation and FDA was able to review these revisions with efficiency. We can imagine a future scenario where these same, proven, mRNA-LNP vaccine platforms are used to target new infectious diseases, and again where prior knowledge enables the potential of streamlined review. In these circumstances, the mRNA sequence may be changed to a new target. However, the product would be the same in many other ways including similar non-coding sequences, and in particular the lipid nanoparticle (LNP) or other delivery method, analytical test methods, and manufacturing methods. If the elements have been reviewed as part of a platform technology designation request, FDA could conduct an efficient review rather than duplicate the regulatory process and sponsors would be spared replicating redundant data sets.

[15] Popovitz, J., Sharma, R., Hoshyar, R., Kim, B. S., Murthy, N., and Lee, K. (2023, September). Gene Editing Therapeutics Based on mRNA Delivery. *Advanced Drug Delivery Reviews*, 200. https://www.sciencedirect.com/science/article/abs/pii/S0169409X23003411

These same concepts apply beyond infectious disease use cases to the therapeutic applications of mRNA. For example, PTD would allow quicker implementation of individualized neoantigen cancer vaccine therapies[16] and vaccine manufacturing. If LNPs secured PTD (as we advocate for as a possibility in the section below on "Applicability of PTD concept to individual aspects or a combination of them"), then sponsors who keep the key characteristics of the mRNA the same and the LNP formulation, composition, and characteristics the same, then that should constitute a platform where a sponsor can interchange different medical targets. In this scenario, the sponsor can leverage a vaccine technology by switching in and out different antigens, even if they are looking at different infectious diseases or tumor types in the oncology space. In an analogous way, the sponsor can leverage an mRNA-based protein replacement therapy or gene editing therapy for a rare disease by switching in and out different transgenes or gene targets defined by the mRNA or guide RNA sequences alone.

John Skerritt, who recently retired from his position of Deputy Secretary Health Products Regulation Group, Therapeutic Goods Administration, and colleagues wrote "Providing a predictable development pathway for academic and commercial groups so that they can know in detail what product characterization and data are required to develop a dossier for regulatory submission has many potential benefits. These include: reduced development and regulatory costs; faster consumer/patient access and more agile development of products in the face of pandemics; and for rare diseases where alternatives may not exist or to increase survival and the quality of life in cancer patients. Therefore, achieving consensus around platform approaches is both urgent and important."[17]

While we are very supportive of a platform approach for many mRNA medicines, we recognize that the framework will need to account for different classes of mRNA therapeutics and their associated delivery systems, which carry different risks and different benefits. We have products like the COVID-19 vaccines that have already been widely used, but many more, especially therapeutic mRNA products, are newer and still in early development, so it may not yet be known which of their aspects may be appropriate for a platform approach.

In fact, because of the heterogeneity of issues that relate to mRNA-based vaccines and therapeutics, including personalized gene-editing RNA drugs and therapeutics for rare diseases, one **overarching request from AMM is that FDA develop follow on guidance(s) specifically focused on mRNA-specific platforms and their related delivery systems.** We recognize the Agency has limited resources to draft guidance documents but feel that, given the wide range of potential platforms addressed in this first guidance, more specificity will be needed to provide the level of clarity and detail needed to optimize mRNA platforms to speed development.

As an organization able to gather the relevant players in the community in a pre-competitive space, we are eager to partner with FDA on scientific meetings, workshops, or other information exchanges needed to tease out the issues of relevance for such a guidance. This letter raises some of those issues, and at the same time we recognize there is substantially more to discuss.

[16] We recognize that different terms are used, with some preferring "individualized neoantigen therapy" instead.
[17] Skerritt, J.H., Tucek-Szabo, C., Sutton, B., and Nolan, T. (2024, May 11). The Platform Technology Approach to mRNA Product Development and Regulation. *Vaccines*, 12(5), 528. https://doi.org/10.3390/vaccines12050528

For that reason, AMM looks forward to working with FDA as the Agency continues to develop its regulatory approach to mRNA.

Specific Considerations for Guidance

AMM offers the following comments on specific aspects of the draft guidance.

I Introduction (page 1, line 13)

Issue: Use of terms "platform technology" and "designated platform technology"
In the introduction to the guidance FDA acknowledges that "the term 'platform technology' has been used by both industry and FDA to describe technologies in ways that differ from the definitions of **platform technology** and **designated platform technology** that are outlined in statute and this guidance. Some technologies that industry and FDA have historically considered to be platform technologies might not meet the statutory definition and statutory eligibility factors and, if not, would not be eligible for the designation program. According to FDA, ineligibility for designation does not preclude a sponsor from leveraging prior knowledge across applications. FDA has allowed sponsors to leverage prior knowledge from previously submitted applications when authorizing or approving drugs in an application submitted by the same sponsor."
AMM appreciates FDA's affirmation of the ability of sponsors to use "prior knowledge" across applications even when not eligible for a "designated platform technology." However, we are concerned that the full benefits of the PTD will not be realized if FDA employs this narrower application of what products and sponsors are eligible to participate in the PTD process.

AMM Recommendation:
As noted in more detail later in these comments, AMM is concerned with the guidance's document's narrow approach on which "sponsors" and what products or processes are eligible for PTD. In the interest of patients and public health, we encourage FDA to utilize its authority under Section 505 of the Food, Drug and Cosmetic Act (FD&C Act) to broaden the scope of eligibility.

II PLATFORM TECHNOLOGY DESIGNATION REQUEST

A. Eligibility for the Platform Technology Designation Program (Page 4, Line 101)

Issue: Use of "approved drug" framework
FDA's draft guidance indicates that it will determine whether a technology is eligible for designation as a platform technology by FDA if (1) it is incorporated in, or used by, an approved drug (i.e., FDA reviewed and approved an application for a product incorporating or using the platform technology); (2) preliminary evidence demonstrates that the platform technology has the potential to be incorporated in, or used by, more than one drug without an adverse effect on quality, manufacturing, or safety; and (3) data or information submitted by the applicable person indicates that incorporation or usage of the platform technology has a reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process."

We are concerned that the first criteria, which requires a platform technology to be incorporated in an approved drug, will significantly limit the utility of the platform designation. In the case of mRNA there are currently only a small number of approved drugs, however there are many more potential "mRNA platform technologies" with sufficient evidence and allowing these to receive designation prior to approval of the first NDA or BLA will significantly speed FDA review without sacrificing quality.

AMM Recommendation

AMM recommends that FDA take a broader view of which technologies are relevant to be considered as platform technologies and allow sponsors with sufficient evidence to apply for platform technology designation prior to approval of a drug or biologic. Currently, there are only two sponsors that could apply for an mRNA PTD based on having approved COVID-19 vaccines. This excludes all the other mRNA-based products these companies and others are developing. In addition, because so many of the companies in the mRNA space are small start-ups, they are not likely to have the prior approvals and data that larger companies likely will have in order to follow the requirements of the current draft guidance.

Specifically, in the final guidance, we recommend FDA consider allowing sponsors to leverage data from platform programs still under development (pre-approval) as well as those already approved. FDA should specify that companies can submit for a designation at an earlier stage in the development process (e.g., pre-IND, EOP2 or a Type C meeting for a first approval) where companies can demonstrate that the platform technology has the potential to be incorporated in or utilized by more than one drug without adverse effect on the quality, manufacturing, and safety.

This approach would be consistent with the currently available Fast Track or Breakthrough designations wherein the potential is recognized before definitive proof is available, and only obligates the FDA to provide more direct interactions with the sponsor; it does not limit subsequent FDA review or requirements, nor do these earlier designations guarantee final regulatory approvals. What they do provide, which is invaluable to small, early-stage companies, is recognition that the investigational agents are recognized by the key regulatory body as having potential merit. In a similar manner, having a "pre-step" to platform technology designation would encourage companies and their funding backers to track key developments for patients in parallel, such as multiple related viral family vaccines or variants in rare genetic diseases (e.g., a multi-arm study of all the filoviridae viruses or various point mutations underlying a single neuromuscular condition, wherein utilizing the same manufacturing and LNP system, and vector for a srRNA, or processing for a circRNA would be possible).

The validation of the PTD during development would encourage studies of viral families or variants in rare genetic diseases where a common "backbone" technology could be acknowledged by FDA to only require one regulatory submission package for Module 3 and a more limited Module 4. In the absence of the earlier stage designation, the practical solution would be for a company to only develop one product, and only following successful regulatory review and commercialization would subsequent products be developed. For indications with a small patient population, a PTD could make a commercial case possible and thus bring new medicines to patients with rare diseases who are currently often underserved. Additionally, allowing a PTD to be granted in development prior to full product approval could potentially enable more parallel development programs where multiple small indications could be developed at the same time.

For example, we believe that non-clinical safety, CMC, and clinical data could all be leveraged earlier than the BLA stage. Under the current guidance what would the procedure be for leveraging such data and how would an applicant lacking an already approved product seek FDA feedback? Likewise, under the current construct of draft guidance, CDMOs are not allowed to meet with FDA nor apply for PTD. Non-sponsor innovators (e.g. delivery system technology providers, manufacturing process technology providers, etc.) under the current construct of draft guidance are not provided a mechanism to engage with the FDA and apply for PTD

We recognize that FDA will require sufficient data and experience with a potential platform technology before granting a designation, and practically this will often mean, at least initially, that it is part of an approved NDA or BLA. However, we think it is important for FDA to approach this issue flexibly, recognizing that the range and volume of mRNA products may be significantly different in the future. Creating a designation process which allows for the possibility that a platform may be designated based on sufficient data available for the Agency to review, even before it is part of an approved product, will create a pathway for innovators to efficiently develop multiple products simultaneously. For example, a prophylactic vaccine platform could be used to develop several vaccines at once to meet public health needs by leveraging clinical proof of concept, non-clinical toxicity, biodistribution, genotoxicity, developmental and reproductive toxicology (DART) results, and CMC analytical method and method validation.

If companies need to wait until after approval of the first product to leverage this platform designation, it will not result in the efficiencies that may be gained through platform designations, given the long timeframe to approval relative to when similar platform programs would be in development and similar processes would be most relevant to leverage.

Finally, we suggest incorporating language around evaluating similarities between programs in a phase-appropriate context. Since manufacturing processes are likely to mature over the lifespan of a product's development prior to filing, it should be clear that, for a second platform program, evaluation of similarities should use phase-dependent considerations.

In principle, programs at later stages of clinical development would also serve as a reference to support and enable a platform development approach for follow-on molecules. Including this option would help to streamline follow-on platform products in development with more temporal proximity to the lead platform product—which is more likely to occur (and more practical) from a sponsor's perspective versus waiting until the first product is approved to leverage the platform technology.

Our understanding is that for mRNA technologies, any "platform technology" needs to be reproducible and it may include a nucleic acid sequence, molecular structure, mechanism of action, delivery methods, vector, or a combination of any such technologies that FDA determines to be appropriate where it is incorporated or utilized by a drug and is essential to the structure or function of such drug. If a sponsor receives a platform technology designation, information from the platform technology can be leveraged in subsequent application from the same sponsor. Creating a predictable path to using prior knowledge would reduce the work needed to get to a future IND (for example, by eliminating the need for certain IND-enabling toxicology studies by leveraging prior studies). This broader view will truly leverage the "platform technology" approach and facilitate innovative development and save lives. This is critical for mRNA medicine development in general, and specifically for mRNA cancer vaccines.

Issue: Concept of "sponsor" for PTD
Related to the issue raised above, since FDA's draft guidance defines a platform technology as hinging on an approved NDA or BLA, the term "sponsor" is used throughout the guidance. Under the FD&C Act, the term "sponsor" means "a person who takes responsibility for and initiates a clinical investigation."[18] The use of the term sponsor in this guidance is problematic because it precludes other entities, such as delivery system technology providers, manufacturing process technology providers (e.g., CDMOs), companies pre-IND, or academic researchers, from applying for a PTD for the aspects of their process which may be appropriately reviewed as platform technologies. The mRNA field has utilized CDMOs extensively and they will continue to be critical partners to achieve the federal government's oft-stated goal of 100-day vaccine development timelines. Since many parts of a potential PTD may be within the remit of the CDMO or other partner, it stands to reason that those technologies and designations should not be restricted to a specific drug or vaccine company sponsor.

AMM Recommendation:
AMM recommends that FDA clarify in the guidance that the PTD is not just relevant for sponsors of an approved BLA/IND, but also, IND sponsors or other entities and that a PTD can apply to sections of a compound development such as a specific LNP and manufacturing process for RNA+ LNP formulation.

Since FDA uses the term "sponsor" in the guidance, to avoid confusion in AMM's response we too will use this term. However, in our usage, we are referring more broadly to any entity that is eligible to submit a PTD request, not the narrower concept as described in the guidance. We would recommend that FDA adopt terminology such as "Platform Technology Innovator" to avoid confusion with the use of the term "sponsor" in other contexts.

If FDA adopted this broader view, a non-sponsor innovator which has developed methods that have been successfully reviewed by FDA for a given drug product formulation (e.g. a defined mRNA manufacturing process or LNP delivery system) could then consider it as having a PTD for the efficiencies it provides to a different sponsor and new program. One example of this might be that a CDMO or LNP delivery system provider has biodistribution data and an FDA approved method for making mRNA vaccines with a specific LNP, so all that work would be considered in the context of a PTD accelerating a different sponsor's work on a different viral family that needs vaccines, which is supported by the non-sponsor innovator's technology. While not directly analogous, it might be modeled after some of the biosimilar review requirements wherein FDA does not require the new sponsor to redo all the work of the original NDA or BLA. Further exploration and explicit guidance in this area is requested.

Issue: Applicability of PTD concept to individual aspects or a combination of them
In describing eligibility for the PTD program, FDA indicates that "under section 506K(h)(1) of the FD&C Act, a platform technology is a well-understood and reproducible technology, which may include a nucleic acid sequence, molecular structure, mechanism of action, delivery method, vector, or a combination of any such technologies that FDA determines to be appropriate." We agree that a platform technology may be any of these individual things or a combination of

[18] Title 21 Food and Drug, Chapter I Food and Drug Administration, Subchapter D, Drugs for Human Use, Part 312 Investigational New Drug Application, Subpart A general provisions. Sec 312.3 Definition and interpretations

them, but request that FDA provide additional specificity about a sponsor's flexibility to apply for a PTD for specific modules separately or together as a master file.

AMM Recommendation:
AMM recommends that each applicant be permitted to apply for its specific platform technology module separately or use a "platform technology master file" mechanism for each module. For example, any of these elements could stand alone as a platform technology, or an applicant could bundle them together in a master file.

Examples:

1. Tumor biopsy analysis, (neo) antigen selection, algorithm for personalized cancer vaccine.
    A. Once an analysis and antigen selection algorithm is established, the use across tumor types or lines of therapy should be able to reference the PTD master file.
2. Manufacturing advantage: mRNA, vector, LNP, plasmid DNA.
    A. Manufacturing processes that achieve CQA's that are independent of the other components of the drug product (e.g. double stranded RNA impurity in the manufacture of mRNA) can be applied across drug products.
3. In vivo delivery and biodistribution e.g. organ or tissue specific targeting.
    A. As it is recognized that key aspects of quality and biodistribution are common and independent of specific RNA payload, PTD master file components related to those areas should be covered by the PTD and accelerate development in other use cases.
4. Ex vivo immune cell delivery: DC, CAR-T, NK.

Issue: Further clarity around "minimal differences" (page 5, line 133)
In describing the information that a sponsor must submit to sufficiently demonstrate the potential for a platform to be incorporated in, or used by, the drug under investigation without adversely affecting quality, manufacturing, or safety, FDA indicates there "should be minimal differences between the approved or licensed drug(s) using the platform technology and the drug(s) under investigation as part of an IND application that proposes to use the same platform technology. Such information could involve establishing that there are minimal differences in aspects of structure, mechanism of action, biological effect, or manufacturing processes that could affect quality or safety."

This framework is highly subjective and we would appreciate further engagement with FDA to better understand the Agency's intent. We hope that further guidance on this topic would provide clarity to industry and ensure overall consistency in the Agency's approach.

AMM Recommendation:
AMM recommends the final guidance include some examples of what similarities/differences would be considered in versus out of scope for a designated platform program. We recognize that not all possible permutations can be captured in the guidance, but some key examples and additional clarification from FDA would be helpful to establish expectations. Consistent with other regulatory schemes, we recommend FDA apply a risk-based approach to evaluate the potential impact of the differences; if the risks are assessed to be low, the platform concept could be applied.

We agree with Skerritt et al. that “The extent to which platform approaches can be utilized in regulatory submissions depends on the degree of similarity between the structural composition, intended effect, manufacturing process and product quality, and proposed context of use between mRNA products. To effectively utilize platform approaches in regulatory submissions, sponsors are required to have sufficient information to understand the relevance of differences between a new mRNA product and preceding platform products.”

For example, if a sponsor has several mRNA vaccines and needs to change a critical raw material, today they would typically have to do a comparability study for each program the material is used in. Under a PTD, we would expect that the comparability study could be completed for the platform as a whole, and then applied to each of the approved products using that platform without necessitating a similar study for each product. Our view is that "minimal differences" should generally be defined broadly as long as the safety and efficacy of a base technology has not changed.

For CMC, some of the areas that we believe are suitable for PTD are:

- Specific aspects of mRNA design, associated manufacturing processes, methods (release and characterization) and control (except for product specific method such as potency assay or mRNA identification method) LNP composition, lipid testing methods and controls.
- mRNA LNP DP manufacturing, in-process controls, methods and controls (including impurities) except for product specific methods, such as potency assay or mRNA identification methods.
- Analytical method validation for some aspects of drug substance and drug product.
- Stability data for drug substance and drug product if a comparable manufacturing process is used. For example, if the sponsor wants to leverage stability testing, the preliminary evidence should demonstrate the similarities of the molecules, and the manufacturing process, such that leveraging stability data would be justified.
- PPQ manufacturing for drug substance and drug product.
- GMP inspection for drug substance and drug product manufacturers.
- Technology to deliver mRNA into target cells to rapidly manufacture gene and cell therapies, vaccines, and therapeutic antibodies (e.g., electroporation, LNP, viral vectors, etc.).

- In terms of manufacturing and CMC, the platform technology developer should define a design space[19] for each unit operation in which the product can be manufactured, also providing evidence that within that design space, multiple products can be manufactured with the required

[19] We are using this term as FDA defines it in the guidance “Q8(R2) Pharmaceutical Development” accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8r2-pharmaceutical-development

CQAs. Based on this evidence, the regulatory authorities should designate this as a platform technology within the characterized design space.

B. Potential Benefits of a Platform Technology Designation (page 6, line 166)
Issue: Applicability of right of reference
In describing the benefits of a PTD, FDA indicates "Information about a designated platform technology may be leveraged in a subsequent application when supported by sufficient preliminary evidence. The application should be from the sponsor that was originally granted the platform technology designation. Alternatively, it can be from a sponsor that has full rights of reference to that information."

AMM Recommendation:
We agree with FDA that it is appropriate to allow a different sponsor to leverage a platform technology designation if they receive a full right of reference to leverage data under a business agreement with the originator of the platform technology. As discussed earlier, we believe FDA should take a broader view of "sponsors," and as suggested by AMM, create a new terminology to be used in this guidance in order to advance public health.

D. Meetings to Discuss a Planned Designation Request (page 8, line 279)

Issue: Which entities are eligible to request meetings
In describing the process for requesting a meeting, FDA indicates that such requests should be "submitted as an amendment to the drug product's IND" and that "sponsors can have a preliminary discussion with the Agency regarding a planned platform technology designation request at any pre-submission meeting."

This construct limits the ability to request a meeting to only drug sponsors in the context of an IND. As indicated earlier in our comments, we are concerned that this limits the scope and utility of the PTD significantly. In addition, this section on meetings precludes a CDMO from requesting a meeting.

AMM Recommendation:
AMM recommends that FDA create a process for IND holders and other entities, beyond the traditional construct of a "sponsor" to seek a PTD and also to request meetings with the Agency related to such requests. For example, CDMOs play an important role working with their sponsor partners in development of mRNA products, however they rarely have the chance to interact directly with FDA. Since these CDMOs work with many sponsor partners, having a PTD on their elements of the process would streamline development, but to do so, they need to have a similar ability to meet and ask questions. If a CDMO is reliant on their sponsor partner for all specific regulatory details, information may not filter down properly. For example, the process performance qualification (PPQ) and process characterization effort for similarly sized mRNA could be the same and make reduced effort for BLA approval.

E. Submitting (Page 9, line 301-307)

Issue: Additional clarity on Module 1
Information is provided on how to submit a designation request, including what to include in Module 1 if designation is requested as part of an IND. However, it is not clear where to provide

the non-clinical and CMC data/rationale to justify the platform request, including potential efficiencies that could be achieved under a platform designation.

AMM Recommendation:
AMM recommends that the final guidance include additional detail regarding where the non-clinical and CMC data and justifications supportive of the platform designation request should be included (e.g., in specific sections within Module 2 and 3 respectively, or provided elsewhere in an ancillary document).

F. Timing (page 10, line 327)
Issue: Length of review period
FDA indicates it will determine whether the designation meets the eligibility factors and if the platform technology will be designated within 90 calendar days from receipt of the platform technology designation request. Given that the benefit of a platform technology designation is to streamline review of subsequent applications, we recommend this timeline be shortened.

AMM Recommendation:
AMM recommends this timeline be shortened to 60 days, to align with other designation types. These other designation types include:

- Fast Track Designation: To be eligible for the fast track program, an applicant must submit a request with supporting documentation for fast track designation for the product and its proposed use.[20]
- Breakthrough Therapy: A process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).[21]

IV Postapproval Changes to A Designated Platform Technology (page 10, line 352)

Issue: Threshold for what requires a postapproval change submission
In this section of the guidance, FDA describes the process for a sponsor to submit changes to an approved application that incorporates the designated platform technology via a postapproval supplement to the application. FDA also indicates "one approved application that uses a designated platform technology may submit a single submission of grouped supplements for CMC postapproval changes and a single supplement per proposed change for nonquality-related changes to that platform technology." While this is helpful, we have many remaining questions about what changes require this process and which could be made without submitting a supplement.

AMM Recommendation:
AMM and its members have many questions about what changes a sponsor could make to a platform that would be within scope of the original designation, and which would require a postapproval change or additional studies or data when the product that is relying on the

[20] FDA. (2024, February 16). Fast Track Designation Request Performance. FDA. https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/fast-track-designation-request-performance.
[21] FDA. (2018, January 4). Breakthrough Therapies. FDA. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

platform is submitted for FDA approval. Below are some examples of these kinds of considerations:

- Since manufacturing processes are likely to mature over the lifespan of a product's development prior to filing, FDA's final guidance should specify that for a second platform program, evaluation of similarities should use phase-dependent considerations.
- If the platform technology developer has characterized a manufacturing design space on a unit operation basis in which it can produce the product with the target CQAs, moving within that design space should not require a post-approval change.
- Specify whether a treatment that has the same composition as an approved platform, but a different lipid/mRNA ratio, may still be considered the same "platform." Our view is such a change would be acceptable if there is no impact on critical quality attributes (CQAs). In that case, clinical data could be leveraged for determining starting doses or tolerable doses.
- Describe when a bridging study is needed to determine the limits of composition change. We anticipate that if a sponsor changes the lipid, they would be deemed to have changed the platform. However, if they change the lipid composition of an LNP comprised of the same lipids, is this change within the parameters of the process that has been designated a platform? One view is that from an LNP perspective, if the sponsor is keeping the mRNA the same and the critical LNP characteristics the same, then that could constitute a platform where they can interchange different medical targets.
- If a change is made in a critical raw material used in the platform, can the sponsor submit a postapproval change, and then assume this change is approved for all subsequent products relying on the platform? If not, what bridging studies would be needed to demonstrate the interchangeability without doing a full toxicology study? We recommend FDA model the specifics as the Agency does for generics or biosimiliars entering the market.
- In the list of general consideration on page 11, line 383, FDA discusses a potential platform technology could be LNPs, with key elements of the technology being "composition, including type, amount, and manufacture of the lipids." If a sponsor makes small changes to the composition, would this still be treated as the same as a platform technology or would it require a new designation? One view is that if the change did not affect safety or efficacy, it should not require a new designation.

V. General Considerations for Eligibility (Page 11, line 381)

Issue: Use of term "mRNA vaccine" in the list of examples is too limiting and potential confusing

This section includes examples of potential platform technologies, with examples of key elements of each technology. The first example listed is "Lipid nanoparticle (LNP) platforms for mRNA vaccine or gene therapy products."

While footnote 38 notes "Although this example includes mRNA vaccine or gene therapy products, this is not intended to suggest that other cell or gene therapy products are not appropriate for the designation program" we believe the reference to mRNA "vaccines" is overly specific.

AMM Recommendation:
AMM recommends the language read "vaccines and therapeutics" or "vaccines and other products" to simplify this example and keep it as broad as possible since LNPs may be used in a variety of mRNA-based products beyond vaccines. This would also align with the footnote, which could then be deleted.

Issue: Quality of materials
In the same example of potential platform technologies where FDA describes LNP platforms, the Agency describes some of the factors to be considered, but does not address quality of raw materials.

AMM Recommendation:

FDA has other guidance documents, including "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)"[22] from January 2020, which outlines standards for ancillary materials. AMM recommends that FDA cross reference section C of that guidance (Control of Materials), which describes the information that must be provided to FDA to describe the quality and grade of materials, and recommends using "FDA-licensed, approved, or cleared materials, or other clinical-grade materials, when they are available. If the material is not FDA-licensed, approved, or cleared (or in the absence of recognized standards), additional information on the manufacturing and/or testing may be needed to evaluate the safety and quality of the material." High quality materials, such as reagents, are necessary to provide assurance to FDA that use of a platform technology is appropriate. Therefore cross referencing this guidance, or providing similar relevant guidance, could provide useful direction to industry.

Conclusion

AMM appreciates FDA's work on this important guidance. We look forward to future discussions with you as you finalize this and other guidance document that will help the mRNA sector move forward in innovating new vaccines and therapeutics to benefit patients and public health. If you have any questions or would like to discuss this further, please contact Clay Alspach at Clay.Alspach@Leavittpartners.com or Sara Singleton at Sara.Singleton@Leavittpartners.com.

Sincerely,

Clay Alspach, Executive Director
Sara Singleton, Managing Director

[22] FDA. (2020, January). Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), Guidance for Industry. FDA. https://www.fda.gov/media/113760/download