Alliance for Regenerative Medicine

NIMBL

Unlocking the potential of building blocks to expedite cell and gene therapy development:

Takeaways from a Scientific Exchange between FDA, industry, and independent experts

Lead Author: Lindsay Gasch

Table of Contents:

Executive Summary	03
Introduction	07
Overview of The Challenge	07
Potential Paths Forward: Building Blocks of CGTs	09
Identifying Potential Building Blocks	12
Building Block Ideas by CGT Technology Area	13
Takeaways From The Scientific Exchange	32
Conclusions	36
Appendix	37

"One-off approaches for cell and gene therapies will be very cumbersome, especially if we are to get to 10,000 rare diseases. We need developers to be able to use well-defined manufacturing platforms and established vectors, and what can be leveraged across platforms. We have to do something different to achieve this goal."

–Peter Marks, Director of the Center for Biologics Evaluation and Research (CBER), FDA

EXECUTIVE SUMMARY

Background

On November 1, 2023, the Alliance for Regenerative Medicine (ARM) and The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) co-sponsored a Scientific Exchange between cell and gene therapy (CGT) developers, FDA staff, and other key industry stakeholders. The meeting focused on identifying reusable elements of technologies that could be leveraged to improve the time and resource efficiency of CGT development and regulatory review. Such CGT "building blocks" hold the potential to increase the availability of treatments for rare and ultra-rare diseases and conditions, benefiting patients who otherwise face death or serious disability.

One means of increasing efficiency within CGT programs is via the use of an FDA-designated Platform Technology, as provided for in the Consolidated Appropriations Act of 2023. Such designation allows a developer to reuse certain elements of a licensed product to accelerate the development of other products in its pipeline. Because a Designated Platform Technology may be most readily accessed by the developer of the licensed product, Scientific Exchange participants called for ways to create **building blocks** that could more easily reach beyond the original developer and provide a more complete means of streamlining CGT development.

Building-block proposals

Prior to the meeting, industry participants submitted building-block proposals for 1 of 3 technology areas commonly used to develop CGTs: lipid nanoparticles (LNP), induced pluripotent stem cells (iPSC), and adeno-associated virus (AAV). During the meeting, technology-specific breakout sessions were held, allowing FDA and other participants to offer a nonbinding appraisal of the value and viability of the proposed building blocks and the evidentiary needs required for their use. A brief summary of each building block and a preliminary assessment of its value and viability is provided below (additional details are included in the main body of the whitepaper):

	Building block	Scope	Value	Potential viability: Developer-specific	Potential viability: Cross-developer
LNP	Drug product formulation	Drug product for transient expression of a large mRNA therapeutic construct, within the context of a genome-editing product for a potentially large patient population	●●●	●●●	●
	Biodistribution studies	Leveraging extensive biodistribution data from first product across subsequent products	●●●	●●●	●●
	Release and characterization assays	Common/standardized, product-agnostic analytical testing methods for drug product quality attributes	●●●	●●●	●●●
	Toxicology studies	Leveraging extensive toxicology data from first product across subsequent products	●●●	●●●	●●
	Potency strategy	Using platformed potency assays when assessments are performed similarly across products	●●●	●●●	●
iPSC	Unedited MCB	Collecting donor material, reprogramming cells, creating unedited MCB	●●●	●●●	●●
	Gene-edited MCB	Starting with gene-edited, single-cell clone and moving to fully characterized, banked, and released MCB that contains all product-specific traits but remains undifferentiated	●●●	●●	●
	AI/machine-learning–based assay	Assay for characterizing a non–gene-edited banked iPSC or cryopreserved cellular intermediate for subsequent differentiation	●●●	●●	●
	ddPCR assay to detect residual PSCs	Demonstration of the absence of residual PSCs in the final drug product (to potentially reduce/replace *in vivo* tumorigenicity studies)	●●●	●●	●●
AAV	End-to-end manufacturing process	Full AAV-manufacturing platform consisting of various modules and unit operations	●●●	●●●	●
	Suspension bioreactor process	Suspension bioreactor operations following shaker-flask expansion for an AAV transient triple-transfection process	●●	●●	●
	Partial manufacturing process; critical raw materials & fill-finish	Common parts of the manufacturing process that are well-characterized and consistent regardless of serotype/product nature	●●●	●●	●
	Umbrella trial design	Infrastructure to study therapies from multiple developers intended for a disease or group of similar diseases	●●	●	●

Relative ranking: High ●●● Medium ●● Low ●

Key takeaways

Participants discussed these proposals in the context of questions such as: (1) who develops the building block?; (2) what event or approval is needed before the building block can be used?; and (3) what is the vehicle for disseminating the building block?. Given the current regulatory framework and the desire to protect proprietary information, participants agreed that it will be most straightforward for the original developer to leverage building blocks and/or Designated Platform Technologies. Other industry and regulatory takeaways are provided below:

Key industry takeaways:

01 **Developers appear more willing to share building blocks in less mature technology areas with less existing proprietary investment,** perhaps reflecting the need to protect intellectual property, legacy investments, and competitive tensions.

02 The ability to utilize **fixed and well-characterized starting materials and/or reference standards could ease the process** of moving any building block forward. This could involve coordinated efforts across the industry.

03 **Nonclinical testing (e.g., biodistribution and toxicology, including on/off-target assessments) is one of the most viable areas for building block creation.** Because industry may have more expertise in this area than regulators, a public-private collaboration could advance this concept.

04 **Product-agnostic analytical assays represent another highly viable building block idea.** Though identity and potency assays may need to be tailored for each drug product, data from other analytical assays may be leverageable across products when the factors impacting assay output (e.g., formulation and storage conditions) are kept constant.

05 For some technologies, **a building block that is specific to a single unit operation (e.g., a bioreactor process) rather than a full manufacturing platform may lack feasibility,** as variable inputs or processes within other unit operations could affect drug-product quality.

Key regulatory takeaways:

- **FDA designation of a 'Platform Technology' is not the only avenue forward for reusable technologies** in CGT development.
- Information from a cross-referenced DMF or IND can be used quite liberally throughout early stages of development. However, **when a program reaches BLA filing, all manufacturing information needs to be included in the application.**
- Developers must be able to **demonstrate appropriate control and validation of any process** being proposed as a building block.
- Developers must **understand variability in the part of the process/product being proposed** as a building block or platform.
- Developers must provide **full and defendable scientific rationale** (e.g., supportive data and/or published literature) for the development and dissemination of any proposal.

Underlying these takeaways is the general guardrail that no platform technology or building block may compromise patient safety.

Conclusion

The Scientific Exchange represented an important first step toward increasing efficiencies and capacity within the CGT industry. There was broad consensus that building blocks are a promising way to address a substantial need, but making this vision a reality requires further work and clarity. The Scientific Exchange generated excitement for exploring additional paths forward, both within and across developers.

INTRODUCTION

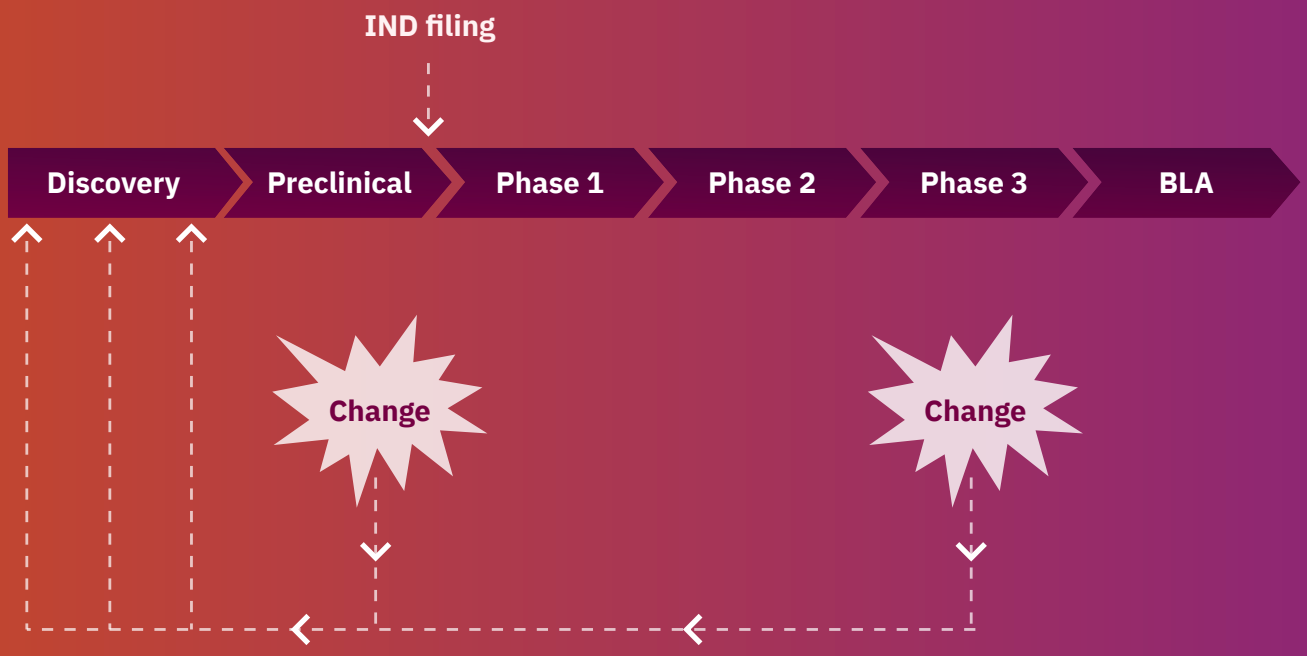
Cell and gene therapies (CGTs) offer the promise of significant patient benefit across a broad range of diseases, including rare genetic conditions, acquired diseases, and cancers. These transformative therapies are much more complex to develop, manufacture, and review than other biologics and small-molecule drugs, posing distinct and often unique challenges for getting potentially life-saving therapies to patients. On November 1, 2023, the Alliance for Regenerative Medicine (ARM) and the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) co-sponsored an all-day working session that included CGT developers, FDA staff, and other key stakeholders. The goal of the session was to **identify potential building blocks** and/or platform technologies that could be leveraged across development programs to improve the time and resource efficiency of CGT development and regulatory review, ultimately enabling these potentially life-changing therapies to reach patients more expediently. This whitepaper provides an overview of the challenges facing the CGT sector, discusses potential regulatory paths toward establishing reusable technologies, and provides the framework developed for the session's interactions. The majority of the whitepaper focuses on specific building block proposals and regulatory feedback.

For a full list of participants and definitions of abbreviations used in this whitepaper, please see the appendix.

OVERVIEW OF THE CHALLENGE

The components of CGT programs are at the frontiers of modern medicine and are being invented in real time. This results in a large number of bespoke (and generally proprietary) solutions that each require their own development program and regulatory review, demanding significant time and resources from both developers and regulators. Though inherently different from other drugs, CGTs are subject to traditional drug-development timelines **(see Box 1)**. A change to an existing drug product (e.g., even a small nucleotide sequence) could result in a return to early stages of the development program, as the resulting drug product will be considered a "new" drug product.

Box 1: Potential impact of a change on the drug-product lifecycle



The impacts of a change on development timelines and costs are challenging for any disease targeted by CGTs. However, these impacts may be particularly unworkable for extremely rare diseases, where the CGT may benefit a small number of patients (or even a single patient), especially those with a small window of opportunity for treatment. High costs and long development times lead to a significant drag on additional therapeutic innovation, as the expenses of developing therapies for small populations are insufficiently offset by expected commercial returns.

> "A child could be born with a point mutation that is actionably editable, but when you change a single thing in an existing IND, you are back to a new product that will take about 4 years and $7 million to develop. But that child only has 8 months to live."
>
> **–Fyodor Urnov, Professor of Molecular Therapeutics and Scientific Director for the Innovative Genomics Institute at the University of California, Berkeley**

Many of the technologies relevant to CGTs are similar across investigators/drug developers and rely on similar raw/starting materials (e.g., cells, reagents, media). Despite this, leveraging commonalities across programs (by a single developer or across developers) is difficult within the current regulatory framework. For example, the editing of genes with CRISPR/Cas9 technology has existed for nearly 15 years and has evolved into a well-understood, reliable, and replicable tool across users, albeit with some remaining uncertainties around the long-term impact of potential off-target editing. With the relatively straightforward replacement of a 20-nucleotide sequence, hematopoietic blood stem cells have essentially become editable, with edits showing durability over time.[1] Between the broad use of CRISPR/Cas9 technology and the existence of proven delivery mechanisms such as LNPs, many of the 100,000+ children born every year with inborn errors of immunity or metabolism could theoretically receive life changing treatments within their first 3 to 12 months of life.[2] Yet, despite the existence of relevant technologies, there is only 1 approved CRISPR/Cas9 genome-edited therapy in the U.S. today.[3]

To make the pursuit of additional disease targets sustainable, the CGT industry must evolve past traditional drug-development approaches and timelines, particularly when the disease being treated is rare and the inherent value of the therapy lies in its ability to reach patients who have little time. Streamlining the technological foundations of CGT development will also lower the costs for both rare and more common indications.

POTENTIAL PATHS FORWARD: BUILDING BLOCKS OF CGTs

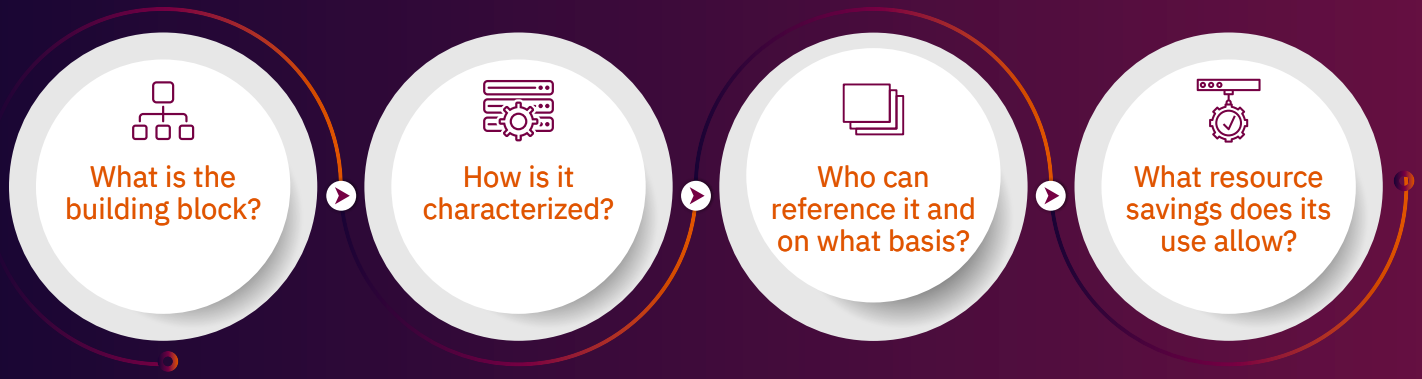
The challenges facing the CGT industry motivate a search for reusable technologies (or '**building blocks**') that can be leveraged across programs where additional data generation can be minimized, thus allowing developers to increase time and resource efficiency while also enabling an efficient regulatory process. The pursuit of reusable approaches has yielded significant savings and increased reliability in other industries (e.g., aerospace, software) and within life sciences (e.g., monoclonal antibodies, vaccines), and similar principles could likely be utilized across other novel drug-development technologies.

For the purposes of this Scientific Exchange, a '**building block**' was defined as:

An element of development, manufacture, or delivery that can be reused across development programs by the original creator and potentially by other developers.

To enable a fruitful discussion at the Scientific Exchange, organizers developed a common framework for describing building blocks in a way that facilitates understanding, discussion, and comparison:

Box 2. Framework for proposed building blocks



01

What is the element of development, manufacture or delivery that can be re-used across development programs?

02

What are the CQAs or other measurable parameters that define that building block and ensure that future uses correspond to the original? What parameters must be fixed?

03

What is the vehicle for the original developer or the broader industry to reference a building block? How does this inform industry and developer practice?

04

What steps in development can be omitted or done more efficiently? What is the impact of 'streamlined' development on developers, the Agency, and patients?

Pre-workshop discussions with developers, experts, and FDA staff revealed multiple pathways for the creation and dissemination of building blocks, each of which has implications for the required investment, the key actors in its creation, and how the building blocks are accessed and/or shared. Discussions revealed the following four approaches (while acknowledging that other approaches may also be possible):

Box 3. Potential approaches for creating and disseminating building blocks

	Who develops	Needed for use	Vehicle for dissemination
Create / codify: Sector-wide effort to develop shareable building blocks	• Coalition • Association	• Publication	• Any developer or CDMO
Share: Existing best practice /prior knowledge	• Coalition • Association	• Regulatory clarity • Voluntary info sharing	• Any developer or CDMO (?)
Use: Developer's prior knowledge, expertise, DMF	• Medicine developer • CDMO	• Meet guidance • Review decision	• Regulatory guidance, historic reviews
Designated Platform Technologies	• Medicine developer	• Approved drug • FDA-designated platform	• Original developer • Licensee

One new means to increase efficiency within CGT programs is via FDA designation of a Platform Technology **(see bottom left in Box 3**). The Consolidated Appropriations Act of 2023 includes provisions for the FDA to consider requests to designate Platform Technologies that were part of an approved drug, and that can be reused in future programs without having to recreate all of the evidence that led to the initial designation.[4,5] Legislative requirements for a Designated Platform Technology are established[†], and the FDA is working on a Draft Guidance that is expected to clarify the process of applying for a designation.

[†]A technology is eligible for designation as a designated platform technology under section 506K of Chapter V of the Federal Food, Drug, and Cosmetic Act if: (1) the platform technology is incorporated in, or utilized by, ... a biological product licensed under section 351 of the Public Health Service Act; (2) preliminary evidence ... demonstrates that the platform technology has the potential to be incorporated in, or utilized by, more than one drug without an adverse effect on quality, manufacturing, or safety; and (3) data or information ... indicates that incorporation or utilization of the platform technology has a reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process. Full legislative wording and description of actions that may be undertaken by the Secretary of Health and Human Services can be found via the following link: https://www.congress.gov/bill/117th-congress/house-bill/2617/text

Because access to a Designated Platform Technology is tied to a licensed product,[4] it is most readily used by the original developer (additional licensing is required for dissemination beyond the originator) and it is not clear how CDMOs may contribute. These limitations create an opportunity for the CGT industry to explore building blocks that enable sharing beyond the original developer and provide a more complete solution to streamlining development. As shown in **Box 3 on page 11**, such approaches may range from sharing of existing best practices/prior knowledge among developers to achieving sector-wide alignment or investment into shareable building blocks.

> "Not everything has to be part of the Platform Technology designation program. It is one avenue forward for technologies that meet the statutory requirements, but it does not have to be the only way that the FDA uses platforms."
>
> **–Phillip Kurs, Senior Advisor to the Center Director in CBER, FDA**

IDENTIFYING POTENTIAL BUILDING BLOCKS

Pre-meeting work

Prior to the meeting, industry participants were asked to submit case studies detailing potential building blocks across 1 of 3 technologies commonly used to develop CGTs: LNPs, iPSCs, and AAVs. Participants were asked to utilize the developed 4-part framework **(see Box 2 on page 10)** to describe their proposal. It was stressed that proposals should: 1) not compromise patient safety; 2) support CGT innovation; and 3) ideally allow the dissemination and use of productive platforms. FDA participants reviewed these case studies prior to the Scientific Exchange.

Technology-specific workshop discussions

During the meeting, developers and FDA representatives were divided into breakout sessions according to their area of expertise. These sessions provided an opportunity for participants to offer a nonbinding appraisal of the viability of proposed building blocks and the evidentiary needs required for their use.

To encourage structured discussions, participants were asked to identify key features of each proposed building block, including promising and limiting aspects and readiness for deployment. Participants also considered the various avenues for creating and disseminating a building block **(see Box 3 on page 11)**, ranging from formal FDA designation as Platform Technologies (viable for the original developer or their licensee) to broader, sector-wide efforts to promote information sharing between developers and, potentially, CDMOs.

BUILDING BLOCK IDEAS BY CGT TECHNOLOGY AREA

Developers reviewed 13 potential building blocks during the breakout sessions: 5 related to LNPs, 4 to iPSCs, and 4 to AAVs. A brief summary of each building block and a preliminary assessment of its value and viability is provided in **Box 4**. Viability is assessed on both a developer-specific level (i.e., technology being reused by the originator for a new product) and cross-developer level (i.e., technology shared from the originator with a new developer for a new product). The ensuing sections (by technology area) provide a more detailed description of each building block, including where each proposal lies on the CGT development map and any applicable FDA feedback.

Box 4. Summary of building block proposals across technology areas

	Building block	Scope	Value	Potential viability: Developer-specific	Potential viability: Cross-developer
LNP	**Drug product formulation**	Drug product for transient expression of a large mRNA therapeutic construct, within the context of a genome-editing product for a potentially large patient population	●●●	●●●	●
	Biodistribution studies	Leveraging extensive biodistribution data from first product across subsequent products	●●●	●●●	●●
	Release and characterization assays	Common/standardized, product-agnostic analytical testing methods for drug product quality attributes	●●●	●●●	●●●
	Toxicology studies	Leveraging extensive toxicology data from first product across subsequent products	●●●	●●●	●●
	Potency strategy	Using platformed potency assays when assessments are performed similarly across products	●●●	●●●	●
iPSC	**Unedited MCB**	Collecting donor material, reprogramming cells, creating unedited MCB	●●●	●●●	●●
	Gene-edited MCB	Starting with gene-edited, single-cell clone and moving to fully characterized, banked, and released MCB that contains all product-specific traits but remains undifferentiated	●●●	●●	●
	AI/machine-learning–based assay	Assay for characterizing a non–gene-edited banked iPSC or cryopreserved cellular intermediate for subsequent differentiation	●●●*	●●*	●*
	ddPCR assay to detect residual PSCs	Demonstration of the absence of residual PSCs in the final drug product (to potentially reduce/replace *in vivo* tumorigenicity studies)	●●●	●●	●●
AAV	**End-to-end manufacturing process**	Full AAV-manufacturing platform consisting of various modules and unit operations	●●●	●●●	●
	Suspension bioreactor process	Suspension bioreactor operations following shaker-flask expansion for an AAV transient triple-transfection process	●●	●●	●
	Partial manufacturing process; critical raw materials & fill-finish	Common parts of the manufacturing process that are well-characterized and consistent regardless of serotype/ product nature	●●●	●●	●
	Umbrella trial design	Infrastructure to study therapies from multiple developers intended for a disease or group of similar diseases **	●●	●	●

Relative ranking: High ●●● Medium ●● Low ●

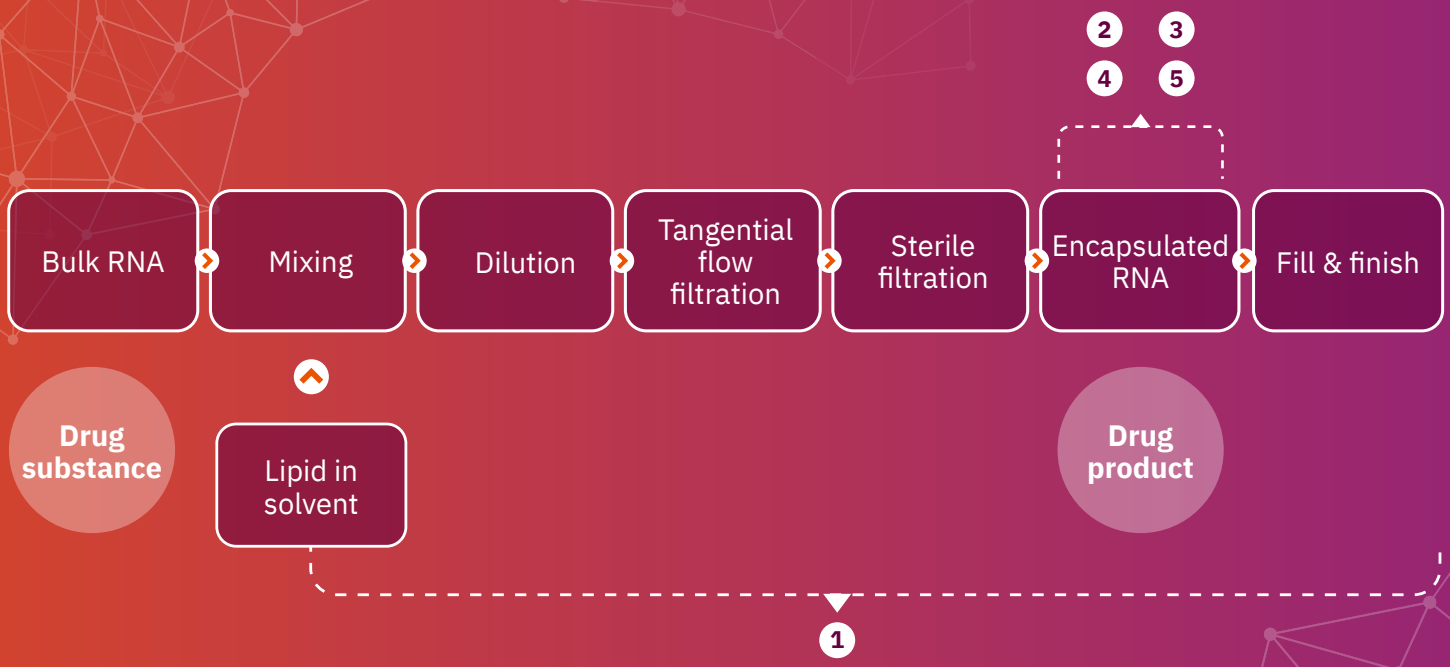
*FDA noted that too many unknowns exist regarding the inherent abilities of/ variabilities within AI to fully understand its value and viability at this time.

** Generated discussion but is out-of-scope for an AAV-specific building block.

LNPs

LNPs are mixtures of cationic, ionizable, and other lipids that are increasingly used as nonviral delivery vehicles for small molecules and RNA. Most notably, LNPs are used to deliver antigen-specific mRNA in two authorized COVID-19 vaccines.[6,7] Other LNP RNA formulations are under investigation for the prevention and/or treatment of other viral infections, cancers, and genetic diseases.

Box 5. LNP building block ideas within a simplified manufacturing schema



Simplified manufacturing schema adapted from: BioPhorum Operations Group Ltd. Overview of end-to-end mRNA drug substance and drug product manufacturing processes and scale-up considerations, 2023.[8] 1 2 3 4 5 in the schematic refer to the various proposed LNP building blocks.

1 Drug product formulation

The first building block proposal related to an intravenously administered LNP drug product for transient expression of a large mRNA therapeutic construct and associated RNA guide(s). This idea was presented within the context of a single-administration, gene-edited therapeutic for a relatively large patient population (i.e., not an extremely rare or 'n of 1' disease). The proposal starts with combining fully characterized drug substances (i.e., RNAs) and lipid components in a defined process, moving through to the addition of a drug-product buffer and freezing. To make the leveraging of this building block across programs most feasible, the entire drug product manufacturing process would remain as fixed as possible (i.e., only the sequence of the RNA molecules would vary). Properties of the lipid components and starting ratios of RNA to cationic or ionizable lipids would be kept constant, as would the composition, manufacturing process, and manufacturer for all raw, critical, and starting materials. Additional fixed aspects would include release specifications and methodology for off-target evaluation (either for release or characterization). Notably, ratios of mRNA: guide RNA may change based on the product—in those cases, additional data may be required to support the change. The level of comparability data required to support any change would be determined by an assessment of the risk imparted by the change and by the scale of the drug product.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Low

2 Biodistribution studies

As an extension to the first proposal, biodistribution studies were presented as their own building block idea. In the genome-editing LNP space, biodistribution of drug product, lipids, guide RNA, mRNA, and assessment of on-target/off-target gene editing efficiency in various tissues all need to be considered, resulting in extremely large study-related costs. This is especially true when NHP testing is involved. The proposed building block would reflect an iterative process, where biodistribution studies would be streamlined over time and could be leveraged for subsequent products (i.e., products using the same LNP formulation and similar RNA payload). Eventually, this building block could deliver a large package of biodistribution data that could be fully leveraged across analogous programs. Streamlining of biodistribution studies could come in the form of foregoing certain time points, limiting the number of tissues evaluated, or limiting the number of components evaluated (e.g., only RNA vs protein expression).

This could occur if the developer was able to demonstrate consistency in biodistribution for at least 2 products with same LNP formulation and similar RNA payload. Streamlining or foregoing the need to conduct future biodistribution studies would materially lower costs and development time, regardless of program scale.

To make biodistribution studies viable as their own building block, several issues need to be resolved: 1) the appropriate dose for biodistribution studies (which can be below the MTD per the ICH guideline[9]); 2) when the use of mice rather than NHPs could be appropriate (the FDA is open to non-NHP studies); and 3) frameworks for assessing the acceptable risk of off-target editing (perhaps more flexibility/risk could be tolerated in very rare or very lethal diseases). In addition, the pharmacologic activity required to characterize certain parts of distribution (e.g., lipid, mRNA, guide RNA, protein) may depend on the LNP application. Participants agreed that assessing mRNA distribution is generally less informative than assessing the distribution of the protein expressed by the mRNA.

Given that the FDA has data from extensive biodistribution studies across developers, the idea of pooling such data to issue guidance to developers was proposed. Agency representatives noted that some concepts of biodistribution (e.g., the use of surrogate drug products and the appropriate leveraging of existing biodistribution studies) are already covered in the FDA Guidance on genome editing and in ICH S12.[9,10] They encouraged developers to talk with the Agency (perhaps under the auspices of a Pre-IND or INTERACT meeting) about cross-referencing data from previous CGT development programs.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Medium

3 Release and characterization assays

The third building block introduced common, product-agnostic analytical testing methods for LNP drug product quality attributes (e.g., compendial methods for examining microbiological sterility, fluorescence and/or absorbance assays for assessing RNA encapsulation, and/or chromatographic assays for assessing lipid content and purity). The USP is already working to compile testing recommendations for LNP-based mRNA vaccines.[11] Accelerating those efforts and encouraging the inclusion of other standard-coordinating bodies (e.g., NIST) may be a logical path forward. Of note, the FDA has published a Guidance on standards development that could aid these efforts.[12]

Alignment on standardized assays may be more challenging among genome-editing LNP applications than vaccine applications due to the more complex mechanism of actions. Nevertheless, alignment on testing methods and the threshold for depth of analyses (e.g., read counts, depth of sequencing) would be meaningful, as there is significant uncertainty regarding what will be accepted by the FDA. Membership organizations, consortia, and other industry stakeholders should strive to play a role in these efforts.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	High

4 Toxicology studies

The fourth proposal encompassed toxicology studies as a building block for LNPs. To make this building block viable, several drug-product criteria must be fixed:

- The resultant protein would reside intracellularly (rather than be secreted into systemic circulation)
- The resultant protein would be endogenous (and therefore have innate mechanisms in place to prevent overexpression)
- Protein expression would be limited to the same organ (e.g., liver)
- Protein expression would be transient
- The type of payload would be fixed

Similar to biodistribution studies, a building-block comprised of toxicology studies would likely take an iterative approach, where accumulated data could be used to scientifically justify less robust testing going forward.

Ultimately, it is the developer's responsibility to put forward 'defendable scientific rationale' to support any narrowing of nonclinical testing. The level of rationale required remains a matter of debate, though the FDA noted an increased Agency focus on flexibility. One developer has demonstrated reproducibility of toxicology data with a similar route of administration and at a similar dose level and dose frequency, utilizing the information from an initial package across multiple other products to show that toxicology is independent of LNP payload. In this sense, when minor changes (e.g., a change in a 5' or 3' untranslated region) or even major changes (such as in the open reading frame) are not expected to affect the nonclinical risk assessment, an argument could be made to forego repeating some toxicology studies (or only performing a small bridging study). The onus lies on the developer to provide sufficient justification for such an approach.

Industry participants agreed that the LNP itself (rather than its cargo or payload) is the largest driver of LNP drug product short-term ("acute") toxicity (and biodistribution). In fact, developers estimated that biodistribution data across LNP developers would look nearly identical, with only subtle differences with uncertain impacts on toxicology. The leveraging of toxicology information pre-competitively (e.g., through a publication) and its use as 'common knowledge' across the industry is a promising opportunity. However, it is unclear how to pool and publish such data, as even the supplements of traditional scientific articles rarely include full data from animal toxicology studies. Though the FDA encouraged such sharing of knowledge, they noted that coordination of such efforts would need to come from outside of the Agency (e.g., from an industry association or consortium).

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Medium

5 Potency strategy

Participants noted that potency assessments could be too product-specific to include within a building block. However, they agreed that individual developers may be able to use platformed potency assays when assessments are done in a similar way across products. This could save significant time and cost by potentially reducing the number of assays that need to be developed. The FDA Draft Guidance on potency assurance for CGT products can be consulted for recommended approaches to potency-assay development and overall potency strategy.[13]

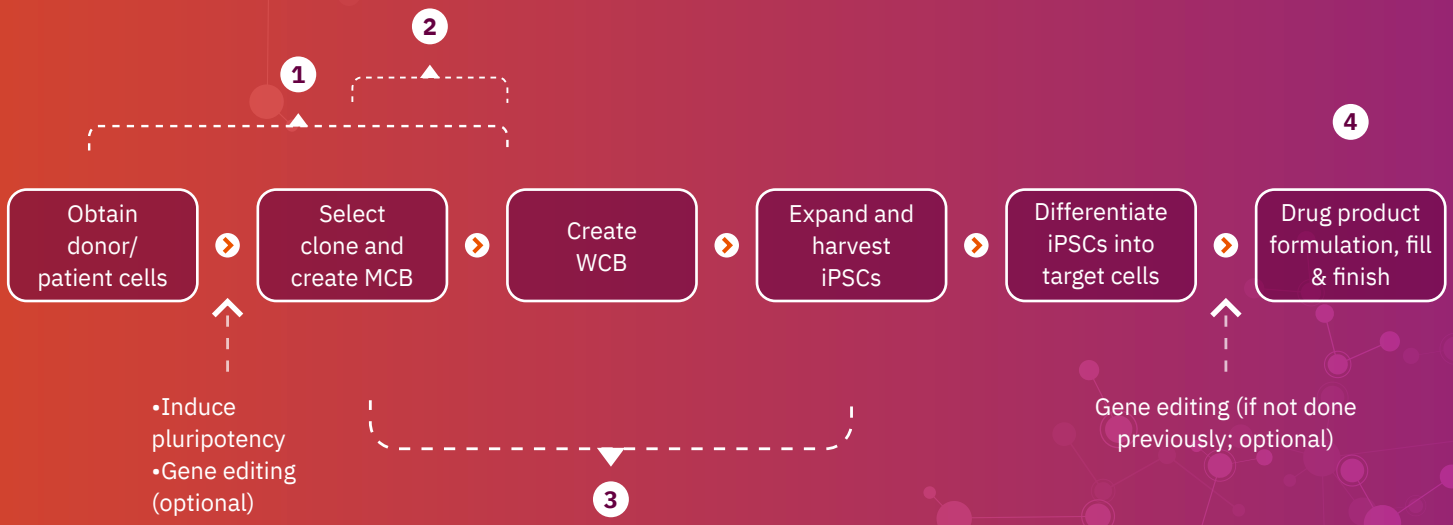
For rare conditions, it can be difficult to show correlation between the activity of a drug product, a potency assay, and a clinical outcome. As such, the FDA will need to see a potency assay that demonstrates the biological activity of the drug product. For gene therapies, this generally involves looking at the functionality (or loss of function) of the gene being edited. For a metabolic disease that can arise from a single mutation in one of many genes, a potency assay that measures the same change in the disease outcome, regardless of the path (e.g., editing of a different base pair or different gene), could be leveraged across multiple products. In addition, previous potency assay validation data could be leveraged for future products, provided that there is preliminary evidence showing that a change to the product does not change the utility of the potency assay.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Low

iPSCs

iPSCs are human cells that have been reprogrammed back into a pluripotent state, are capable of indefinite self-renewal, and can become one of many types of effector cells when cultivated under specific conditions and exposed to tailored microenvironments. These effector cells can be administered into a patient's body to grow, replace, or repair damaged tissues. Increasingly, iPSCs are being gene-edited (e.g., via CRISPR/Cas9 technology) to incorporate features that have the potential to target and treat diseases. Due to their virtually unlimited replicative potential, gene edits can be performed sequentially, enabling the development of highly engineered cell therapies to meet specific needs. Genetic enhancements can be made via knock-in or knock-out of specific genes, and the genome can be characterized for on-target placement using genetic sequencing methods. iPSC products are being edited to include tumor- or autoreactive-cell targeting, tumor-microenvironment targeting, safety, and immune-evasion features. After differentiation of the edited iPSCs into the desired cell type (e.g., NK or T cells), these final products are then used to treat hematologic, oncologic, and autoimmune diseases.

Box 6. iPSC building block ideas within a simplified manufacturing schema



Simplified manufacturing schema adapted from: BioPhorum Operations Group Ltd. Cell therapy process manufacturing maps, 2020.[14] 1 2 3 4 in the schematic refer to the various proposed iPSC building blocks.

1 Unedited MCB

The first building block encompasses the process of collecting donor or patient material, reprogramming cells into a stem-cell state, and creating a MCB of nonengineered (unedited) iPSCs. This process could yield a common starting point for all iPSC-derived therapies (autologous or allogeneic), regardless of final differentiation state, and may enable the standardization of donor eligibility requirements and reagent qualification. Characterization of the proposed building block would involve testing of donor material (subject to 21 CFR 1271 requirements[15]) and testing (via compendial and/or other methods) of reprogrammed iPSCs for such traits as viability, identity, purity, sterility, and genetic stability. Further alignment would be required on mandatory versus optional testing at the MCB stage and on appropriate specifications. Promising aspects of this proposed building block include its broad applicability. Potential limiting aspects include the variability of iPSCs at the undifferentiated stage and the lack of a compendial assay to determine comprehensive genetic stability.

An FDA representative noted the need for a baseline assessment of the genetic stability of the starting material (i.e., parental somatic cells such as fibroblasts) before the start of the reprogramming process. Participants agreed that an unedited cell bank appears more reproducible than an edited bank, though variability in unedited clones was acknowledged. To move such a building block forward, developers would need to standardize the parameters required to generate an iPSC MCB. Related to genetic stability studies, the FDA does not recommend any particular assays but noted that developers may save valuable resources if the genetic stability and safety of starting materials are evaluated before the start of the reprogramming process (especially for allogeneic approaches). Any manufacturing and testing strategy should be planned early and should involve the use of qualified reagents. FDA Guidances on CMC information for human somatic cell therapies and characterization of cell banks can be consulted during planning.[16,17,18]

The most viable existing path for moving this building block forward is via the DMF, in which a developer could reference the particular process and their collaborator (e.g., a CDMO) or another developer (if given permission by the originator) could then cross-reference it. This path could be plagued by a general lack of transparency surrounding DMFs, which often contain proprietary information. Other regulatory paths forward remain less clear, but if a developer were to create a new unedited iPSC MCB based on another developer's program, they would need the associated protocols and testing methods to demonstrate that their manufacturing and testing processes are the same.

The possibility of sharing the process of creating an unedited iPSC bank across the industry (e.g., via a whitepaper or 510[k]-like approach) seemed feasible to participants. Developers collaborating to put forward a voluntary consensus standard for producing a qualified or validated MCB "appeared to be a good idea," to FDA staff, and the recent FDA Guidance on voluntary consensus standards in regenerative medicine therapies could be leveraged.[19] Possible interaction avenues to discuss such a building block idea with the FDA include, but are not limited to, INTERACT, Type B, Type C, or CATT meetings.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Medium

2 Gene-edited MCB

The second building block idea centered around a more downstream cell-banking process managed by a CDMO, specifically starting with a gene-edited single-cell clone and moving to a fully characterized, banked, and released iPSC MCB that contains all of the product-specific traits but is still undifferentiated. The possibility of looking for residual gene-editing components earlier in the process (i.e., at the MCB stage) rather than at the final drug product stage (as per current FDA gene-editing Guidance[10]) was raised. FDA staff did not see much difference in testing for gene-editing components early versus late, provided that a clear plan, with justification, is presented to the Agency. The Agency noted that if a number of products are derived from the same genetically engineered MCB, a sponsor can likely leverage safety data related to the gene-editing components for one product in support of another similar product. This would be considered on a case-by-case basis, and sponsors should provide justification for their approach.

This statement may apply best when the only change imparted after MCB creation is in the differentiation of cells (e.g., into a T cell or NK cell). However, it may also be possible to leverage the full characterization of early gene-editing components (e.g., for HLA editing) across products, even when additional gene edits are performed downstream from the MCB to generate individual product types. The viability of a building block that encompasses the entire iPSC process from donor-material selection to differentiated HSC (or even beyond) was also considered. Similar to the CRISPR/Cas9 idea previously presented, inserting a CAR expression cassette post-differentiation (with only the therapeutic payload in the cassette changed) was discussed. If a developer could show that the cassette always resulted in single-copy insertion into one specific locus in the gene, it might it be possible to leverage pharmacology/toxicology studies for similar products and provide supporting safety and pharmacology studies related to the payload. The initial reaction from the FDA was that such an idea seemed reasonable if the developer could provide adequate justification.

As materials, reagents, and processes appear largely similar across developers, there is a clear role for CDMOs to advance standards for the quality of banked iPSCs as starting materials. Though most meetings are generally held in the context of specific products, CDMOs may request meetings with the Agency, such as to discuss specific facility-related concerns. The meeting request may be converted to another applicable meeting type at the Agency's discretion. Other paths forward for CDMO involvement in the iPSC space involve less formal interactions with regulators through workshops. Notably, the ability of the Agency to provide feedback may always remain, at least in part, tied to knowing what the final product will be. As such, viability of such a proposal by a CDMO may be limited, and the product-specific and proprietary nature of a gene-edited MCB would appear to limit cross-developer viability.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	Medium	Low

3 AI/machine-learning–based assay for the characterization of banked iPSCs

The third building block proposal was for an RNA-Seq and AI/machine-learning–based assay for characterization of a non–gene-edited banked iPSC or cryopreserved cellular intermediates that can be differentiated into an intended cell type. Though developed for an autologous approach, where a cell bank must be produced for each individual patient, this technology could be applied to allogeneic settings and could potentially be expanded to include in-process control testing.

One example of this approach is the PluriTest™ (Aspen Neuroscience, Inc.), which is being used alongside orthogonal analytical assays to assess the identity, pluripotency, and genomic stability of iPSC banks.[20] The developer's vision is to use next-generation sequencing technologies to develop a new version of this genome-wide transcriptional platform for characterization and testing of safety and purity. Additionally, this new version will be able to rank clones for pluripotency (with the aim of moving forward a single clone per patient or product) and will enable expansion to diverse patient genotypes. Ultimate goals are to understand how greater diversity in donor genotypes influences pluripotency and to determine whether standard characterization assays can be replaced with more efficient methods that reduce labor costs, require less cell material for testing, and expedite product release.

Though the overall plan for this building block appeared interesting to the FDA, the Agency is still working to understand how machine-learning-based technologies will play into regulatory review and decision-making processes. It was too early for the Agency to comment on this technology, but developers were assured that the Agency is aware of academic and other efforts in this area. Though collaboration between developers and the FDA on this topic may not be practical, a Type C meeting to discuss how it relates to a specific product may be feasible. An understanding of the variabilities within machine learning, and eventual validation of these methods, will be essential for any future use of such technology.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High/ Unknown	Medium/ Unknown	Low/ Unknown

4 ddPCR assay to detect residual pluripotent stem cells in final drug product

The fourth building block proposal centers around the use of a ddPCR assay to significantly reduce, or potentially eliminate, the *in vivo* tumorigenicity studies currently used to demonstrate the absence of residual iPSCs in the final (fresh or frozen) drug product. The *in vivo* animal studies currently relied upon are plagued by a lack of sensitivity, significant (up to 18 month) time requirements, the number of animals required, and the limited volume of cells that can be administered to an animal. In both academics and industry, ddPCR-based assays have been shown to be substantially more sensitive for detecting residual iPSCs than *in vivo* assays.

The FDA views ddPCR as a highly sensitive assay type with established utility for detecting residual iPSCs. It remains to be seen whether the proposed assay would be specific for one type of differentiated cell product or be applicable across multiple types of differentiated cells. Validation of the entire process via ICH guidelines will be essential for demonstrating the robustness of this assay to the FDA.[21] Other requirements for making this building block viable include the setting of standards for target sequences (e.g., OCT4, NANOG) that represent pluripotent stem cells and the development of a qualification matrix. Eventually, such efforts could lead to a scalable assay that a CDMO could run.

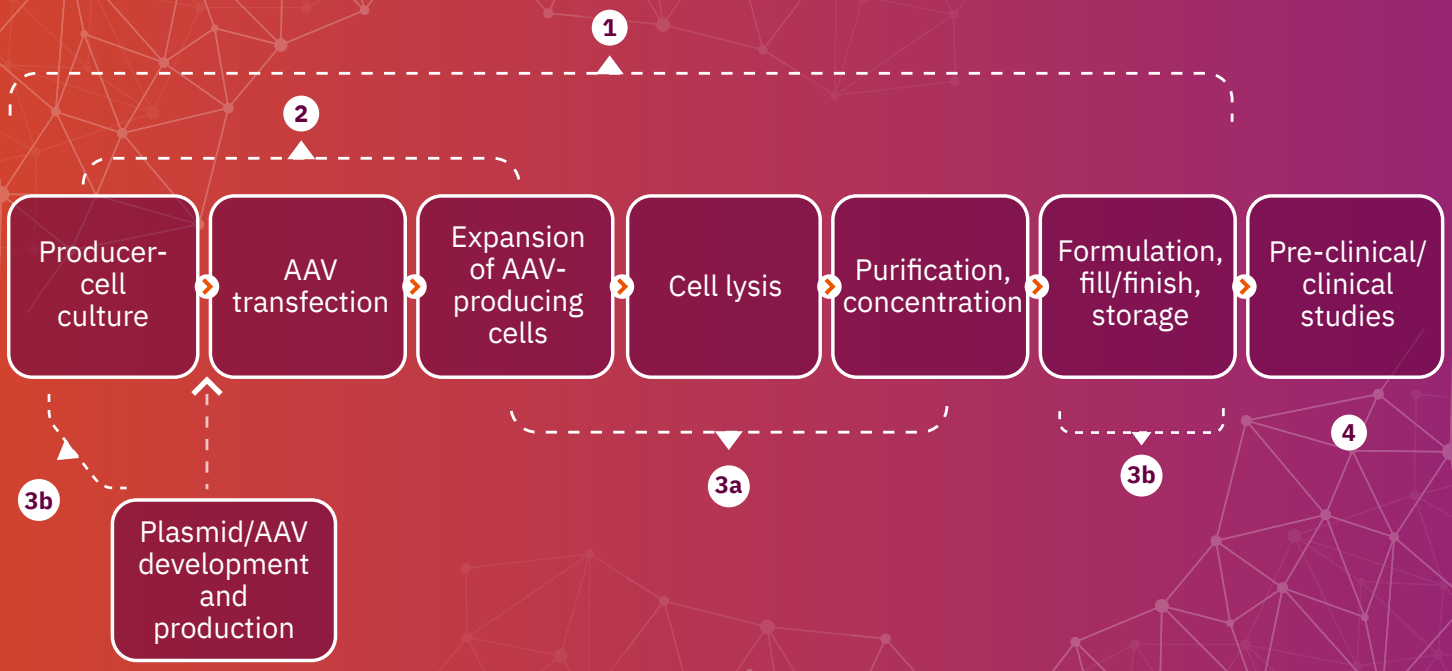
Theoretically, this proposed building block could be combined with other traditional, but less time-consuming, *in vivo* studies (e.g., MOA, POC, or biodistribution) that may have greater bearing on the overall tumorigenicity potential of a drug product. From a pharmacology/toxicology standpoint, the FDA stated that a ddPCR assay to detect residual iPSCs would not replace the role of longer-term *in vivo* studies for a number of product-specific traits that could impact tumorigenicity (e.g., fate of the cells, durability of the effect, or the presence of any partially differentiated cells). For a differentiated cell type that is not expected to survive long-term in the body (e.g., an NK cell), shorter-term *in vivo* studies, in conjunction with *in vitro* analyses, may be sufficient if supported by scientific justification. At this time, there is no prescriptive FDA Guidance for how long *in vivo* studies should last in relation to the expected duration of cell survival. Agency views on this will be influenced by the robustness of justifying data provided by the developer, which could come from pilot studies or previous product experience. Moving forward, developers called for guidance from the FDA regarding iPSC spiking standards.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	Medium	Medium

AAVs

AAV vectors can be used to deliver, *in vivo*, new genetic material to human cells. *Ex vivo*, AAVs can also be used alongside gene-editing tools (e.g., CRISPR/Cas9) to genetically modify human cells that are then transferred back into the body. AAV-based gene therapies have demonstrated significant promise for the treatment of numerous diseases, including rare conditions with substantial unmet needs.

Box 7. AAV building block ideas within a simplified manufacturing schema



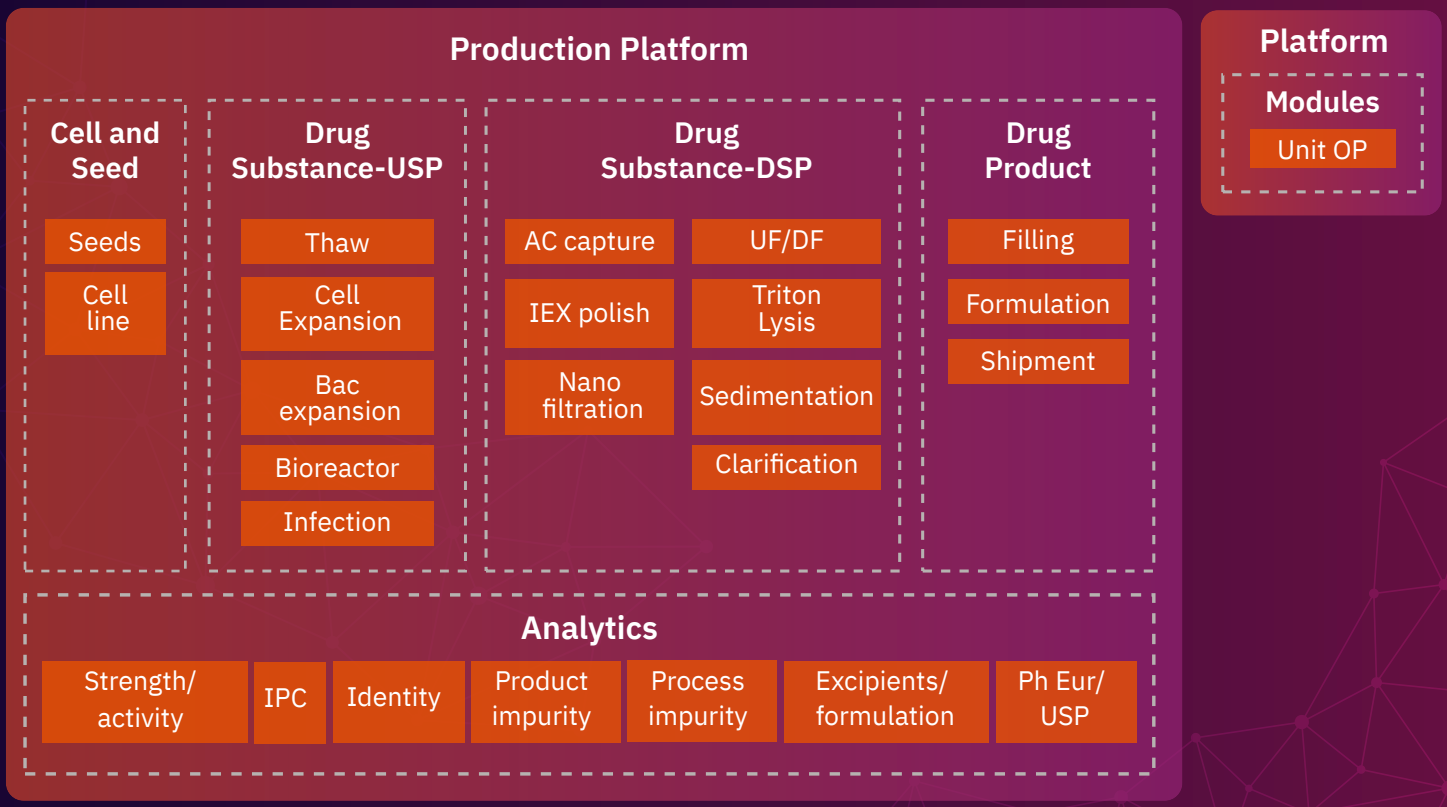
Simplified manufacturing schema adapted from: Alliance for Regenerative Medicine. Project A-Gene, 2021.[22] 1 2 3 4 in the schematic refer to the various proposed AAV building blocks.

1 End-to-end manufacturing process

The first proposal encompasses a full AAV-manufacturing platform consisting of various modules and unit operations. Modules are defined as packages of individual unit operations that can be upgraded independently, whereas unit operations are defined as individual process steps and analytical operations with a module. Each module is operated with its appropriate CPPs as inputs, while the CQAs are defined and specified as outputs. Therefore, an operating space is designed to show control of the process of each unit operation and module, and (finally) of the full process.

This end-to-end manufacturing process is designed to be usable across multiple transgenes. By design, the manufacturing platform is kept stable and only the transgene-specific variability is adjusted. As an example, the module “analytics” is comprised of testing methods (unit operations) that are common across all AAV components except the transgene. Potency or identity methods must be redeveloped, while several other analytical methods can be reused by capitalizing on know-how and data generated from previous programs. For every new program, an assessment is conducted to define what can be reused and what must be redeveloped or adjusted. Ultimately, data are generated to confirm that the full manufacturing process and analytical strategy are providing full control.

Box 8. Proposed full production platform[23]



This platform is already in use by the developer who proposed this idea (with updated iterations in progress), and this proposal generated significant participant feedback. A platform that incorporates every module and/or unit operation into a fixed manufacturing process may be viable as it would limit variability within the resultant products. The platform is referenceable by the original developer, though referencing across developers seems unlikely unless there is an intention to pursue a licensing-focused business model by the originator.

Though the platform represents a substantial proprietary investment, it may enable the leveraging of prior knowledge (e.g., stability and nonclinical safety data), reduce risk, and save substantial time when applied across products. Related to this discussion, the FDA noted increasing tolerance for the leveraging of nonclinical safety data from previous programs, though this tolerance may be greater for products destined for adult vs pediatric indications. Additionally, the FDA expanded on the ability to leverage stability information across a development program: if the same formulation, capsid, and storage conditions used for a Phase 3 product are then used for an earlier-phase product, the developer could leverage some of the stability data to support the Phase 1 trial for that newer product.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	High	Low

2 Suspension bioreactor process

The second building block idea involves a consortium-based approach to a manufacturing process that would eventually consist of individual, but intersecting, process and analytical platforms. As a first step towards this goal, the building block chosen for focused discussion was suspension bioreactor operations following shaker flask expansion (i.e., inoculation, cell expansion, transfection, and harvest) for an AAV transient triple-transfection process.

The building block includes comparability studies to demonstrate that boundaries for target operating conditions (e.g., PARs and NORs) relevant to a product's CQAs could be maintained across various production scales and equipment. It remains unknown if any flexibility in cell line, media, plasmids, and process-performance attributes could be tolerated while maintaining sufficient levels of reproducibility within the building block. Participants questioned whether such a proposal could include bioreactors from multiple companies, if it could accommodate adherent-based production platforms, and if it could be viable as a sole unit-operation (i.e., without being part of larger upstream and downstream processes and controlling for all inputs).

The FDA pointed out that certain process parameters (e.g., plasmid ratios or growth rates) will likely be changed to suit individual products. The need to test for the impact of such changes on PPQ results and drug product CQAs could partially negate the efficiencies of a building-block approach. The threshold for the extent and/or reproducibility of data that would increase Agency comfort with a process sufficiently for developers to skip certain testing was difficult to define. The willingness of the developer to invest in DoE work to determine the acceptable operating parameters of a process would likely influence this comfort level. A publicly available DMF (or a proprietary DMF

made available to other developers upon request) for a bioreactor-based building block could certainly be cross-referenced in an IND application. Information from a cross-referenced DMF can be used quite liberally throughout early stages of development. However, when a program reaches BLA filing, all manufacturing information needs to be included in the application. Notably, this inclusion could be enabled via licensing from the owner of the DMF.

Overall, challenges remain significant for a consortium to put forth a platform or building block idea, though a publicly available DMF could be a path forward. However, participants noted a role for collaborative, consortium-based efforts (e.g., between the USP, NIST, and/or NIMBL) to put forth analytical testing standards and integrated reference materials in service to all AAV developers. As an extension of this discussion, there could be a role for a consortium (or a CDMO) to develop a well-qualified, or perhaps even validated, product-agnostic analytical testing panel for product characterization, batch release, and stability. The FDA saw value in this idea, particularly given that less experienced developers may lack a full understanding of how to manufacture their product in alignment with regulatory expectations.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
Medium	Medium	Low

3 Partial manufacturing process (3a); critical raw materials and fill-finish (3b)

The third building block was presented by a CDMO that possesses a DMF for a robust AAV manufacturing process. This DMF is currently being referenced under INDs to support multiple applications. The larger process piece of this building block (3a) would likely exclude discrete operating units that are product- and/or serotype-specific, such as the upstream transfection step and the downstream formulation step. To generate something more broadly applicable to multiple manufacturers, the CDMO is also attempting to identify other parts of the AAV manufacturing process that are already well-characterized and that will be consistent regardless of serotype/product nature. Specific ideas (3b) included critical raw materials (i.e., MCBs, WCBs, helper plasmids) and the final fill/finish process. Cost savings for any part(s) of a manufacturing process leading to reliable CQAs would be significant to any program.

Though achieving a Platform Technology designation for such ideas could be beneficial in terms of both regulatory review and attracting new clients, the path to such a designation remains unclear for a CDMO. This may be clarified within an upcoming FDA Draft Guidance. Theoretically, there may be an opportunity for co-ownership (and broader or nonexclusive licensing) of a reusable technology between CDMOs and developers. When an employed technology was largely (or completely) generated and validated by the CDMO, ownership could lie largely with the CDMO and could enable sharing across clients. However, when a technology is employed as part of a developer's larger proprietary process, more of the ownership may lie with the developer.

If a CDMO was to leverage an existing DMF, Designated Platform Technology, or prior knowledge (e.g., viral clearance and impurity clearance validation), all could speed the time to IND but, in the absence of additional licensing, would face the same bottleneck in later-stage development: the need for complete manufacturing data to be included in a BLA filing by the developer. Related to earlier discussion, the FDA noted that there could be a role for CDMOs and consortia to build a 'playbook' for developers explaining key manufacturing concepts (e.g., GMPs) that could speed development time and minimize regulatory hurdles regardless of whether a CDMO is used or not.

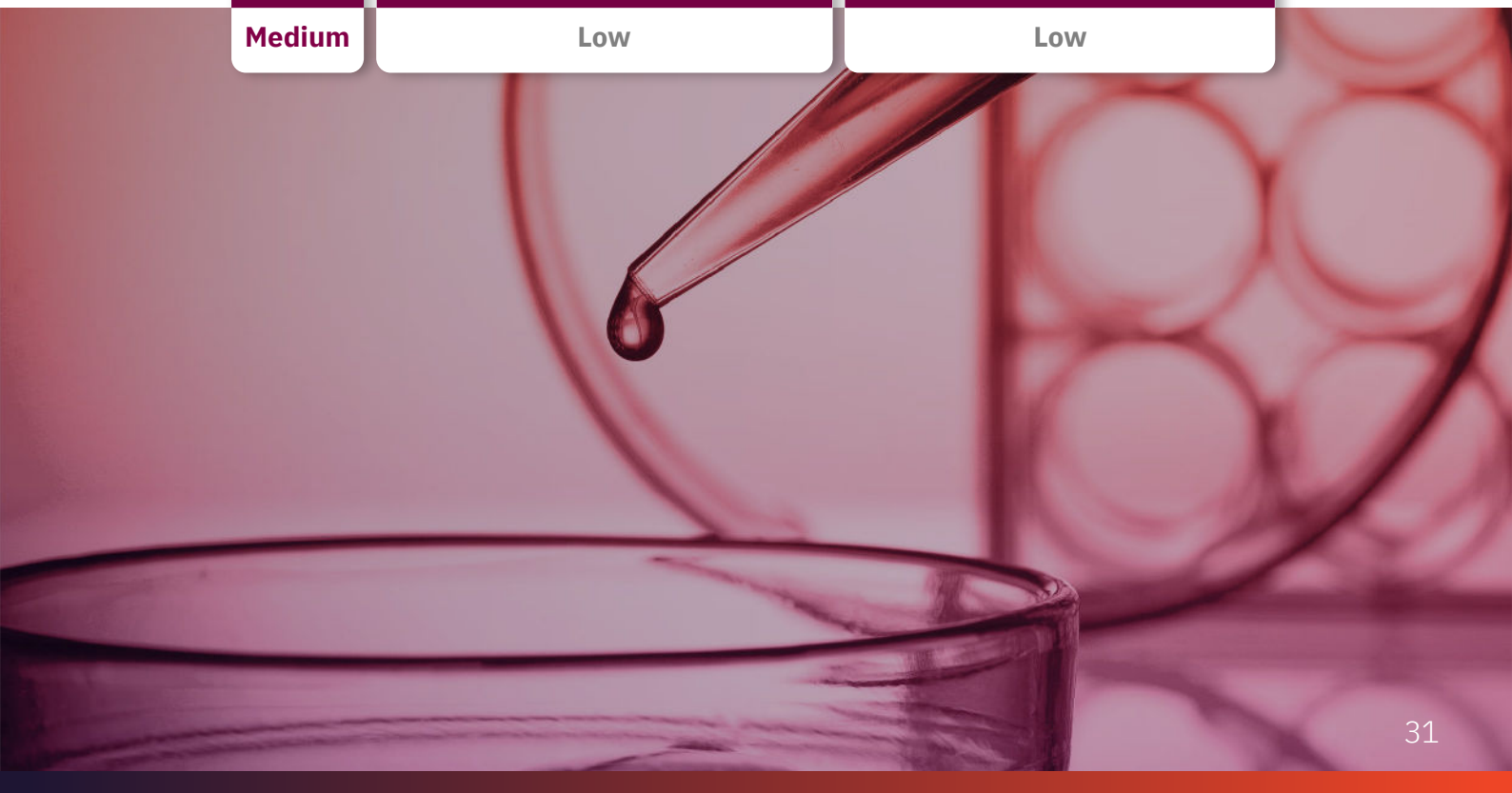
VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
High	Medium	Low

4 Umbrella trial design

Though out-of-scope from the standpoint of a technology-specific building block, the fourth proposal involved an 'umbrella trial' infrastructure that could be used to study therapies from multiple developers intended for a disease or group of similar diseases (e.g., lysosomal storage diseases). Patients with rare diseases are often treated at specific centers, where concentrated efforts could speed study start-up, screening, and enrollment. However, setting up this type of infrastructure would be resource intensive and the idea of governance of such a trial could prove tricky, given the involvement of multiple developers.

In 2022, the FDA published a Guidance on studying multiple highly related versions of a CGT product in a single early-phase clinical trial. The Guidance could theoretically apply to testing multiple different guide RNAs or donor templates for a single disease caused by a mutation in a single gene. However, extension into multiple diseases or into a single disease that could be caused by mutations in multiple genes would be more difficult. A clear path forward for a multi-developer, multi-indication, later-phase trial infrastructure is lacking, but participants felt that a similar idea could be applicable to natural-history studies, particularly at centers where newborn screening for rare mutations is robust. Though the FDA noted that there could be some flexibility in how the Agency would approach a multi-developer and/or multi-indication umbrella trial platform, they added that such an approach would fall outside of existing guidance and would require case-by-case discussions with the Agency.

VALUE	DEVELOPER-SPECIFIC VIABILITY	CROSS-DEVELOPER VIABILITY
Medium	Low	Low



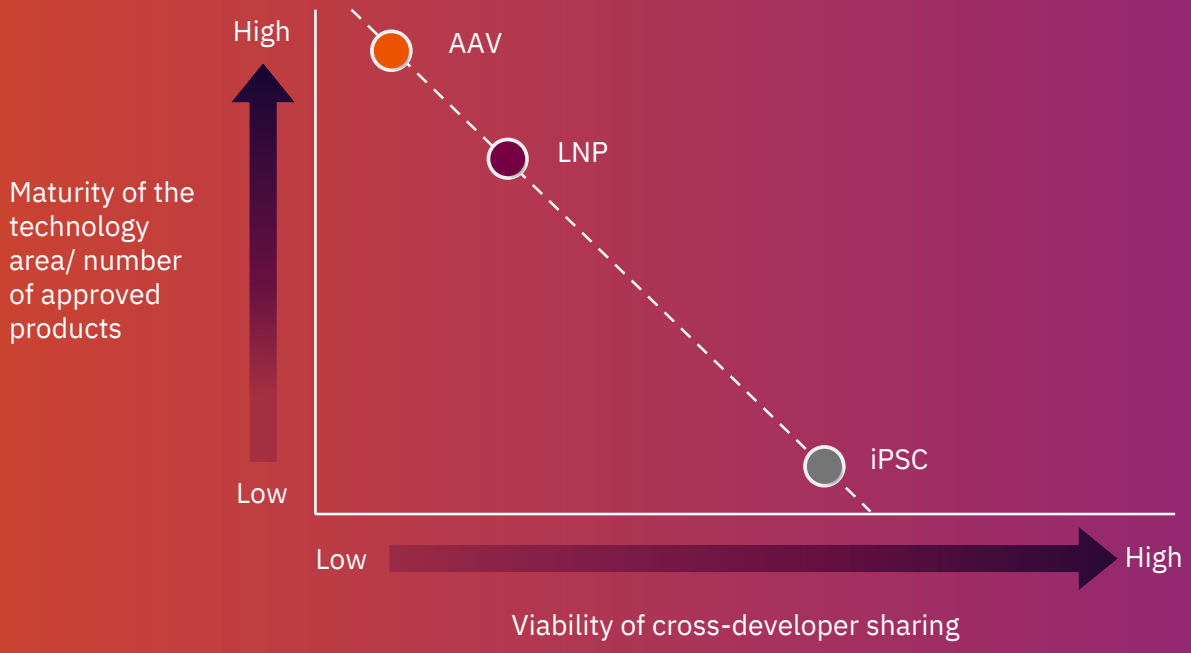
TAKEAWAYS FROM THE SCIENTIFIC EXCHANGE

Following the technology-specific breakout sessions, all participants reconvened to review proposed building blocks, find commonalities across group discussions, and reflect on next steps for moving CGT development forward in a more efficient manner.

Common themes across breakout groups

Participants agreed that it will be most straightforward for the original developer to leverage building blocks and/or Designated Platform Technologies regardless of the specific technology component (i.e., LNP, iPSC, or AAV). The feasibility of cross-developer referencing may be inversely associated with the maturity of the technology area or number of approved products utilizing the technology, perhaps reflecting the need to protect intellectual property, legacy investments, and competitive positioning.

Box 9. Preliminary assessment of the viability of cross-developer sharing by technology area



Regulators encouraged the cross-referencing of DMFs and INDs, as well as the leveraging of prior knowledge. Other key industry and regulatory takeaways from the Scientific Exchange are included below.

Box 10. Industry and regulatory takeaways

Key industry takeaways:

1. **Non-clinical testing (e.g., biodistribution and toxicology, including on/off-target assessments) is one of the most viable areas for building block creation.** A better understanding of the clinical implications of off-target gene editing would help streamline clinical development and regulatory review. Because industry may have more expertise in this area than regulators, there was interest in public-private collaboration (e.g., between academia, industry, and NIST) to advance this concept.

2. The ability to utilize **fixed and well-characterized starting materials and/or reference standards could ease the process** of moving any building block forward. Efforts by industry and/or academia to partner with consortia or standard-setting bodies (e.g., USP, NIST, NIMBL) could be key to creating publicly available information leverageable by multiple developers.

3. **Product-agnostic analytical assays represent another highly viable building block idea.** Though identity and potency assays may need to be tailored for each drug product, data from other analytical assays may be leverageable across products when the factors impacting assay output (e.g., formulation and storage conditions) are kept constant.

4. For some technologies, **a building block that is specific to a single unit operation (e.g., a bioreactor process) rather than a full manufacturing platform may lack feasibility**, as variable inputs or processes within other unit operations could affect drug-product quality.

Key regulatory takeaways:

- Information from a cross-referenced DMF or IND can be used quite liberally throughout early stages of development. However, **when a program reaches BLA filing, all manufacturing information needs to be included in the application.**

- Developers must be able to **demonstrate appropriate control and validation of any process** being proposed as a building block, must **understand variability in the part of the process/product being proposed** as a building block, and must provide **full and defendable scientific rationale** (e.g., supportive data and/or published literature) for the development and dissemination of any proposal.

- The **regulatory path forward for any potentially re-usable technology needs to be defined**, as does the applicable meeting type(s) for Agency engagement.

- The **FDA cannot compel any developer to disclose proprietary information**. As such, any **efforts for public or cross-developer sharing of knowledge or building blocks would need to be driven by industry** rather than by the Agency.

Underlying these takeaways is the general guardrail that no platform technology or building block may compromise patient safety.

"Whatever comes out the other side of the building block needs to be of very high quality and meet FDA standards for safety and efficacy. We may be able to tolerate some increased uncertainty, but we cannot accept building blocks that cause a decrement in the quality of the resultant product."

–Peter Marks

Next steps

Despite the general consensus that developer-specific paths may be most viable for moving building blocks or Designated Platform Technologies forward, opportunities emerged for pre-competitive work between developers (e.g., workshops, whitepapers, consensus standards, coalitions), for partnerships between developers and academia, and for further discussions with the FDA. In line with earlier considerations, motivation for pre-competitive sharing appeared highest among the more nascent technologies (i.e., iPSC and LNP). Opportunities for cross-developer sharing may also emerge when a coalition or consortium (e.g., NIIMBL) is driving building block creation and dissemination **(see Box 3 on page 11)**, even among more mature technologies such as AAV.

Industry participants welcomed FDA's offer to clarify types of formal and/or informal meetings that could be used to move building-block discussions forward, not just between developers and the Agency, but potentially to also include CDMOs. Participants were reminded that CATT meetings have resumed and may be the most appropriate type of meeting to gain nonbinding advice on technologies or approaches to their assessment that could be leveraged across multiple INDs. The upcoming FDA Draft Guidance related to Designated Platform Technologies is eagerly awaited, and the FDA encouraged stakeholders to comment on the draft.

CONCLUSIONS

The Scientific Exchange represented an important first step toward increasing efficiencies and capacity within the CGT industry in order to expedite the delivery of potentially transformative and life-saving medications to patients. In addition to the building-block proposals formulated prior to the meeting, participants generated ideas for other CGT components (e.g., CRISPR/Cas9 gene-editing RNA molecules, CAR constructs/sequences) that could be applied across development programs. There was broad consensus that building blocks are a promising way to address a substantial need, but that the vision of making them a reality requires further work and clarity. This Scientific Exchange generated excitement for exploring additional paths forward, both within and across developers.

> "Coming together to think about how we can leverage building blocks is a really interesting way of thinking about this. If we can start to think about leveraging more as we move from one therapy to another, we could hopefully streamline costs and ultimately get products to more people."
>
> **–Peter Marks**

APPENDIX

Scientific Exchange Presenters and Participants

- **Andrew Bellinger,** Chief Scientific Officer, Verve Therapeutics
- **Stefan Braam,** Chief Technical Officer, Cellistic
- **Danielle Brooks,** Team Lead, Office of Pharmacology/Toxicology, U.S. Food and Drug Administration
- **Andrew Byrnes**, Division Director, Office of Gene Therapy, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Pierre Caloz**, Chief Operating Officer, uniQure
- **Tim Charlebois**, Senior Fellow, National Institute for Innovation in Manufacturing Biopharmaceuticals
- **Anissa Cheung**, Office of Vaccines Research and Review, U.S. Food and Drug Administration
- **Matt Diver**, Co-Founder, Galen/Atlantica
- **Anne-Virginie Eggimann**, Chief Regulatory Officer, Tessera Therapeutics
- **Alyssa Galaro**, Branch Chief, Office of Pharmacology/Toxicology, U.S. Food and Drug Administration
- **Lindsay Gasch**, Technical Writer, Capstone Medical Writing & Communications, LLC
- **Denise Gavin**, Director, Office of Gene Therapy, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Nicholas Gertler**, Co-Founder, Galen/Atlantica
- **Susan Goody**, Senior Director, Head of Toxicology, Moderna
- **Stefan Irion**, Chief Scientific Officer, BlueRock Therapeutics
- **Saran Karumbayaram**, Office of Cellular Therapy and Human Tissue, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Phillip Kurs**, Senior Advisor to the Center Director in Center for Biologics Evaluation and Research, FDA
- **Kim Lamey**, Technical Operations Product Lead, Biomarin
- **Michael Lehmicke**, Senior Vice President, Science and Industry Affairs, Alliance for Regenerative Medicine
- **Josephine Lembong**, Senior Manager, Science and Industry Affairs, Alliance for Regenerative Medicine
- **Peter Marks**, Director of the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Melissa Robb**, Regulatory Strategy, REGENXBIO Inc.
- **Christopher Saeui**, Team Lead, Office of Pharmacology/Toxicology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Christopher Shilling**, Chief Regulatory Officer, Forge Biologics
- **Ana Sousa**, Senior Vice President Global Regulatory Affairs, Quality and Product Strategy, Aspen Neuroscience
- **Aron Stein**, Senior Vice President, Global Regulatory Affairs, Intellia Therapeutics
- **Brian Stultz**, Branch Chief, Office of Gene Therapy, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Tim Taps**, Senior Director, Regulatory Affairs, Head of Regulatory Strategy & Operations, Century Therapeutics
- **Fyodor Urnov**, Professor, Scientific Director at Innovative Genomics Institute, University of California, Berkeley
- **Nicole Verdun**, Director, Office of Therapeutic Products, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Iwen Wu**, Director, Office of Pharmacology/Toxicology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration
- **Wei Zhang**, Director of Analytical Development and CMC Development Lead, Ultragenyx

Term Key

AAV: adeno-associated virus

AC: affinity chromatography

AI: artificial intelligence

ARM: Alliance for Regenerative Medicine

ASGCT: American Society of Gene &

Cell Therapy

BLA: Biologics License Application

CAR: chimeric antigen receptor

Cas9: CRISPR associated protein 9

CATT: CBER Advanced Technologies Team

CBER: Center for Biologics Evaluation

and Research

CDMO: contract development and manufacturing organization

CFR: Code of Federal Regulations

CGT: Cell and gene therapy

CMC: Chemistry Manufacturing and Controls

CPP: critical process parameter

CQA: critical quality attribute

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

ddPCR: digital droplet polymerase chain reaction

DMF: drug master file

DoE: design of experiments

FDA: United States Food and Drug Administration

GMP: Good Manufacturing Practices

HLA: human leucocyte antigen

HSC: hematopoietic stem cell

ICH: International Council for Harmonisation

IEX: ion exchange chromatography

IND: Investigational New Drug

INTERACT: INitial Targeted Engagement for Regulatory Advice on CBER ProducTs

iPSC: induced pluripotent

stem cell

LNP: lipid nanoparticle

MCB: master cell bank

MOA: mechanism of action

mRNA: messenger ribonucleic acid

MTD: maximum tolerated dose

NHP: nonhuman primate

NIIMBL: National Institute for Innovation in Manufacturing Biopharmaceuticals

NIST: National Institute of Standards and Technology

NK: natural killer

NOR: normal operating range

PAR: proven acceptable range

Ph Eur: European Pharmacopoeia

POC: proof-of-concept

PPQ: process performance qualification

PSC: pluripotent stem cells

RNA: ribonucleic acid

RNA-Seq: ribonucleic acid sequencing

UF/DF: ultrafiltration/diafiltration

USP: United States Pharmacopeia

WCB: working cell bank

References

1. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. *N Engl J Med.* 2021;384(3):252-260. doi:10.1056/NEJMoa2031054

2. Urnov F. Developing and derisking an n=1 CRISPR therapy: a tale of two gaps and what we could do about them. Presented at: Unlocking the potential of building blocks to expedite CGT development and review: ARM-FDA Scientific Exchange; November 1, 2023; Rockville, MD.

3. U.S. Food and Drug Administration. Casgevy. December 8, 2023. https://www.fda.gov/vaccines-blood-biologics/casgevy

4. H.R.2617 - Consolidated Appropriations Act, 2023. https://www.congress.gov/bill/117th-congress/house-bill/2617/text

5. PREVENT Pandemics Act (P.L. 117-328, Division FF, Title II. Congressional Research Service. August 15, 2023. https://crsreports.congress.gov/product/pdf/R/R47649#:~:text=The%20PREVENT%20Pandemics%20Act%20addresses,Administration%20for%20Strategic%20Preparedness%20and

6. Spikevax. Prescribing information. Moderna US, Inc.; September 2023. Accessed December 29, 2023. https://assets.modernatx.com/m/7ce607d0bf1f0e20/original/FPI-0717_Spikevax-2023-2024-Formula-Prescribing-Information-PI-12y-US-English.pdf

7. Comirnaty. Prescribing information. BioNTech Manufacturing GmbH/Pfizer Inc.; October 2023. Accessed December 29, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=16351

8. BioPhorum Operations Group Ltd. Overview of end-to-end mRNA drug substance and drug product manufacturing processes and scale-up considerations. 2023. https://www.biophorum.com/download/overview-of-end-to-end-mrna-drug-substance-and-drug-product-manufacturing-processes-and-scale-up-considerations/

9. International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Nonclinical Biodistribution Considerations for Gene Therapy Products S12. March 2023. https://database.ich.org/sites/default/files/ICH_S12_Step4_Guideline_2023_0314.pdf

10. U.S. Food and Drug Administration. Draft Guidance for Industry: Human Gene Therapy Products Incorporating Human Genome Editing. March 2022. https://www.fda.gov/media/156894/download

11. U.S. Pharmacopeia and the National Formulary. Analytical procedures for mRNA vaccine quality (draft guidelines)- 2nd edition. April 2023. https://www.uspnf.com/notices/analytical-procedures-mrna-vaccines-20230428

12. U.S. Food and Drug Administration. Guidance for Industry: Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research. March 2019. https://www.fda.gov/media/124694/download

13. U.S. Food and Drug Administration. Draft Guidance for Industry: Potency Assurance for Cellular and Gene Therapy Products. December 2023. https://www.fda.gov/media/175132/download

14. BioPhorum Operations Group Ltd. Cell therapy process manufacturing maps. 2020. Accessed February 1, 2024. https://www.biophorum.com/download/cell-therapy-process-map/

15. U.S. Food and Drug Administration. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). August 2007. https://www.fda.gov/media/73072/download

16. U.S. Food and Drug Administration. Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs). April 2008. https://www.fda.gov/media/73624/download

17. U.S. Food and Drug Administration. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy. March 1998. https://www.fda.gov/media/72402/download

18. U.S. Food and Drug Administration. Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications. February 2010. https://www.fda.gov/media/78428/download

19. U.S. Food and Drug Administration. Guidance for Industry: Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies. October 2023. https://www.fda.gov/media/159237/download

20. Müller FJ, Schuldt BM, Williams R, et al. A bioinformatic assay for pluripotency in human cells. *Nat Methods*. 2011;8(4):315-317. doi:10.1038/nmeth.1580

21. International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Validation of Analytical Procedures: Text and Methodology Q2 (R1). November 2005. https://database.ich.org/sites/default/files/Q2%28R1%29%20Guideline.pdf

22. Alliance for Regenerative Medicine. Project A-Gene: A case study-based approach to integrating QbD principles in Gene Therapy CMC programs. 2021. https://alliancerm.org/manufacturing/a-gene-2021

23. Caloz P. Presented at: Unlocking the potential of building blocks to expedite CGT development and review: ARM-FDA Scientific Exchange; November 1, 2023; Rockville, MD.

Alliance *for*
Regenerative
Medicine