Alliance for Regenerative Medicine

NIIMBL The National Institute for Innovation in Manufacturing Biopharmaceuticals

"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

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 cell and gene therapy (CGT) developers, FDA staff, and other key stakeholders. The session focused on identifying building blocks and/or platform technologies that could be leveraged to improve the time and resource efficiency of CGT development and regulatory review. The facilitated discussion was webcast to allow a broader audience to gain important insights on this important topic. Key discussion points from the meeting are included below. A comprehensive whitepaper will be published in early 2024.

The Challenge

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, validate, manufacture, and review than traditional therapeutics and even biologics. The components of CGT programs are at the frontiers of modern medicine and are being invented in real-time. This results in many bespoke solutions, each of which necessitates its own regulatory review—requiring time and resources from developers and regulators alike. To meet patient demand and make the pursuit of additional disease targets sustainable, the CGT industry must improve the time and resource efficiency of drug development. This motivates a search for reusable 'building blocks.'

"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

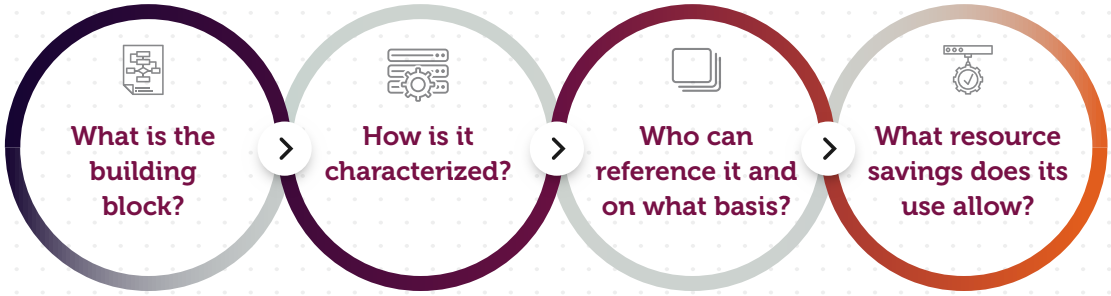
Meeting the Challenge

The Consolidated Appropriations Act of 2023 includes provisions for the FDA to consider requests to designate platform technologies that can serve as building blocks for future programs. Such Designated Platform Technologies have distinct limitations, as they must be linked to a licensed product and can be most readily used by the original developer. In line with Congress' intentions during their crafting of the Act, these limitations suggest that the industry should explore a broader set of approaches to building blocks that may allow dissemination beyond the original developer without compromising patient safety or freezing in place the state of the art in CGT innovation. Such approaches may range from sharing existing best practices/prior knowledge amongst developers to achieving sector-wide alignment or investment into building blocks that can be shared.

> "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**

Key Work of the Day

Developers and FDA representatives were divided into breakout groups according to three technology areas in CGTs: induced pluripotent stem cells (iPSCs), adeno-associated virus (AAV), and lipid nanoparticles (LNP). Prior to the meeting, industry participants were asked to propose potential building blocks for their technology of focus, utilizing the following framework:



The goal of the small group discussions was for the FDA to offer a non-binding appraisal of the viability of proposed building blocks and the evidentiary needs required for their use.

Developers presented 13 ideas for potential building blocks during the breakout sessions: 4 related to iPSCs, 4 to AAVs, and 5 to LNPs. Ideas for building blocks included, but are not limited to, the generation of cell banks, biodistribution studies, toxicology studies, release or characterization assays (e.g., potency, detection of residual cells), full drug products, stability studies, and processes comprising one or more unit operations (e.g., bioreactor process).

Next Steps

Several potentially valuable and viable building blocks were identified during this meeting, the specifics of which will be further detailed in the upcoming whitepaper. Common themes emerged from FDA feedback across the groups: the need to understand variability in the part of the process/product being proposed, the need to demonstrate appropriate control and validation of any process, and the need to provide full justification (e.g., supportive data or scientific literature) for the development and dissemination of any proposed building block.

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

Participants agreed that sponsor-specific building blocks may be most feasible, as the need to protect intellectual property and investments could limit sharing across developers. However, opportunities for pre-competitive work between developers (e.g., workshops, whitepapers, consensus standards, coalitions), partnerships between sponsors and academia, and further discussions with the FDA emerged.

> "Some of the older technologies are less proprietary or sensitive than they used to be. What's truly proprietary is the product itself. I do think that there's opportunity to look into what is nonproprietary versus what leads to a true competitive advantage."
>
> **–Tim Charlebois, Senior Fellow and Viral Vector Program Lead at NIIMBL**

Overall, this working session represented an important first step toward increasing efficiencies and capacity within the CGT industry. In addition to coming up with the potential building blocks mentioned above, participants generated ideas for technologies that could be reusable across modalities in CGT. There was broad consensus that building blocks are a promising way to address a substantial need, but the vision of making them a reality requires further work and clarity.