Alliance for Regenerative Medicine

American Society of Gene + Cell Therapy

"I think there's pretty uniform agreement that one of the key things that has delayed a fair number of approvals over the course of time has been issues related to potency."

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

On October 19th, 2022, the Alliance for Regenerative Medicine (ARM) and the American Society of Gene and Cell Therapy (ASGCT) organized an all-day working session including senior FDA staff, gene and cell therapy developers, and academic experts. The session focused on development challenges related to potency assay requirements. As a facilitated discussion among participants that was also webcast to a broader audience, the session represented a novel way for participants to engage on a topic that has been a source of growing pains for the sector. Key ideas discussed at the meeting are listed below. A comprehensive whitepaper will be distributed later this year.

The Challenge

Cell and gene therapies represent a class of therapeutics that are typically an order of magnitude more complex than small molecules and other biologics. This creates a variety of manufacturing challenges, among them the task of ensuring the potency of drug products delivered to patients. In 2011, the FDA issued guidance for potency tests for cellular and gene therapies and acknowledged some of the modality-specific challenges developers face. For example, cell and gene therapy products may rely on heterogeneous starting materials like donor-derived cells, they may incorporate multiple active components that must each be tested independently, or tests of critical product attributes (e.g., infectivity, expression, or functionality) may be performed in different experimental systems. Furthermore, the mechanism of action of the drug may be incompletely understood:

"We know that we want the product to kill a target cell. That's not so hard to understand. But there are other aspects that we're not really sure about, in terms of trying to understand what pieces are important for the practical efficacy of the drug down the road."

- CGT Developer

In addition, the final drug product may be the result of a biological cascade, and determining where in that cascade to measure potency can be difficult:

> "If you measure things right at the end of the cascade, can you dispose of steps before that?"
>
> **- CGT Developer**

Developers expressed a desire for clarity and modality-specific direction on how and when to prune the assay matrix.

Areas for Improvement

For both developers and regulators, a central theme was the need for improved communication with FDA staff and transparency as to regulatory expectations. Developers also challenged regulators to consider the scientific basis for multiple assays within an assay matrix that yield highly correlated results. They suggested that it may not be necessary to perform potency assays on every stage of a therapeutic cascade (such as infectivity – expression – activity) if, for example, the last stage of the process can only come about if all previous stages were completed successfully.

The 2011 guidance was designed to provide flexibility to developers. In practice, this flexibility can lead to ambiguity that is difficult to resolve absent regulatory interactions. Developers desire more opportunities for informal, live feedback (in lieu of written exchanges) early in the therapeutic development timeline – while acknowledging that FDA resourcing has not always made this possible.

> "It's very hard to get to the crux of the issue and the real topics that will allow the proper development to take place, and it could set a company on the wrong path, depending on how a written response is interpreted."
>
> **- CGT Developer**

Developers recognize that sharing information on therapies that share essential characteristics could de-risk and accelerate potency assay development. However, little of this information has historically been shared:

> "At the point when the product reaches the level of marketing, you don't find any information about the potency assays."
>
> **- CGT Developer**

Given that developers invest significant time and resources into developing potency assays, discerning a successful approach is a competitive advantage. While it is unclear how pre-competitive potency assay information could be shared, developers expressed a desire to try:

"I think that collaboration between the industry associations and the FDA would be beneficial, where the detailed information is not provided, but we have the opportunity to talk about different modalities and talk about expectations of what a potency assay might be."

- CGT Developer

For their part, regulators acknowledged developers' frustration and agreed that addressing communication issues is one important next step toward improving potency assay development:

"I very much think we hear the need for more live interaction, and feedback that's more consistent"

- Peter Marks

Next Steps

"We planted a seed here today, and now we just need to keep watering it. I think we can make a difference in the field, that's what I'm taking away from today."

- CGT Developer

This working session was seen as an important step towards developing a more consistent and clear approach to potency assays. ARM, ASGCT, and developers are actively discussing next steps to address this challenging set of issues, and will include ideas supporting progress in the whitepaper. The whitepaper will focus on specific challenges faced by developers and provide a roadmap for future discussions and progress.

"At the end of the day, we're all here because we think potency assays could be improved both by us and by the regulators. We understand that they are a hurdle to getting these drugs rapidly to patients, and we ultimately serve the patient."

- CGT Developer