**Roundtable Session 1 – Table 2 – Setting Specification (Including Potency) for Not Well-Characterized Biological Products, e.g., Cell and Gene Therapy Products**

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**Abstract:**

Demonstration of potency for ATMPs presents many challenges from a regulatory and technical perspective. Having the appropriate control strategy for potency has been shown to delay FIH studies and has been one of the most common reasons for clinical hold for late phase studies.

It is becoming evident that the traditional paradigm of a cell-based potency assay that is representative of the MoA of the product may not be always achievable, or the strongest indicator of potency. Regulators have tried to provide guidance on expectations around potency with regulations, workshops, townhalls and by attending conferences, but more clarity is needed around global expectations of potency requirements in ATMPs.

**Discussion Questions:**

- What are the main differences between a potency strategy for ATMPs and a potency strategy for biological products?
- What are the common elements, and what can we learn from well characterized biologics experience to design a potency control strategy appropriate for ATMPs?
- What systems / technologies / standards would be needed to reduce the burden of potency testing development for ATMPs?
- What are some of the lessons learned that can be shared with the group with regards to best practices and strategies?

**Notes:**

Overall, while developing a robust and reliable potency assay for ATMPs remains a significant challenge, manufacturers can only partially draw on lessons from traditional biologics to better define potency expectation and strengthen regulatory submissions. It will be critical for the manufacturers to align with multiple regulatory bodies to ensure potency strategy meets regulatory expectations globally. The main challenges identified in our discussion are: 1) selecting the right assay, and 2) selecting an acceptable acceptance criteria.

Points discussed:

Potency assays for ATMPs need to: 1) prove lot-to-lot consistency, 2) be able to reasonably predict the product's activity, and 3) reflect the product's mechanism of action (MoA). However, ATMPs often feature complex MoAs, such as gene or cell therapies, which may not have well-established, easily quantifiable biomarkers. This can

complicate the creation of traditional potency assays, which are typically based on cell-based systems that measure specific biological activity reflective of the MoA. In many cases, these traditional assays may not be feasible or effective.

- For ATMPs, regulators face the challenge of ensuring potency assays effectively represent the product's activity, even when the MoA may not be fully understood, in an effort to minimize the risks to patients, since often time the CGTPs medicines involved severe medical regimen and procedures to prepare for the dose(s). However, especially when the canonical potency assay requires development of artificial, engineered cell lines to ensure detectability of a biological effect, the artificial conditions used to generate the functional potency assay can create artificial biases. In such cases, assessing the direct biological effect may be a better indicator of potency .

- A key discussion point is how to map out a potency assay that satisfies regulatory requirements globally. For example, the European guidelines on potency assays for ATMPs differ from those in the U.S in terms of timing of implementation of a release potency assay, and requirements for a "functional" potency assay. Draft guidance by FDA may help provide flexibility once finalized. Japan has a well-established regulatory framework for regenerative medicine, and it is highly stringent in regard to what assay is an acceptable evidence of clinical benefit, as we were reminded at this conference during the regulatory panel. There is a concern about the lack of alignment across countries, as the manufacturers will need to align with the most stringent requirement anyway. All jurisdictions offer (and some may require) a different array of meetings to gain alignment on critical topics such as potency.

- An important point highlighted in the discussion is the potential for better collaboration between preclinical, CMC and clinical data. Often, assays used in preclinical studies may offer some insight into the expected efficacy, although may not be suitable for routine release. The preclinical models may also not be fully representative of clinical outcomes, for example in the case when therapies involve human genes that are not conserved among species. Novel technologies such as organ-on-chip models, which aim to replicate human tissue behavior, were mentioned as able to provide more relevant insights into human response, although these technologies are still evolving and may not be widely accepted yet.

- The variability between batches, especially for autologous products, means that potency assay specifications need to be carefully managed. Starting with broader acceptance criteria and then narrowing them based on real-world data and production experience is suggested as a pragmatic approach, especially with not-so-well characterized products, where the correlation between various CQAs and potency is not yet fully understood. The traditional approach may however not be applicable to autologous products, where with increased manufacturing experience the variability of the source (e.g. donor) may provide grounds for expanding the acceptable specifications, rather than tightening. In cell therapies, it is common to use clinical efficacy data with lots that do not conform to approved specifications to apply for broadening of such specifications post approval.

Key points for further discussion:

- The role of functional potency assays in ATMP development.
- How research and CMC teams can better align their efforts in potency assay development.
- Strategies for managing the variability of autologous therapies and setting appropriate potency specifications.
- The evolving regulatory landscape and how different regions, such as the U.S., EU, and Japan, handle potency requirements for ATMPs.
- The need to integrate advanced technologies, like organ-on-chip systems, to enhance the predictability of potency assays for ATMPs.