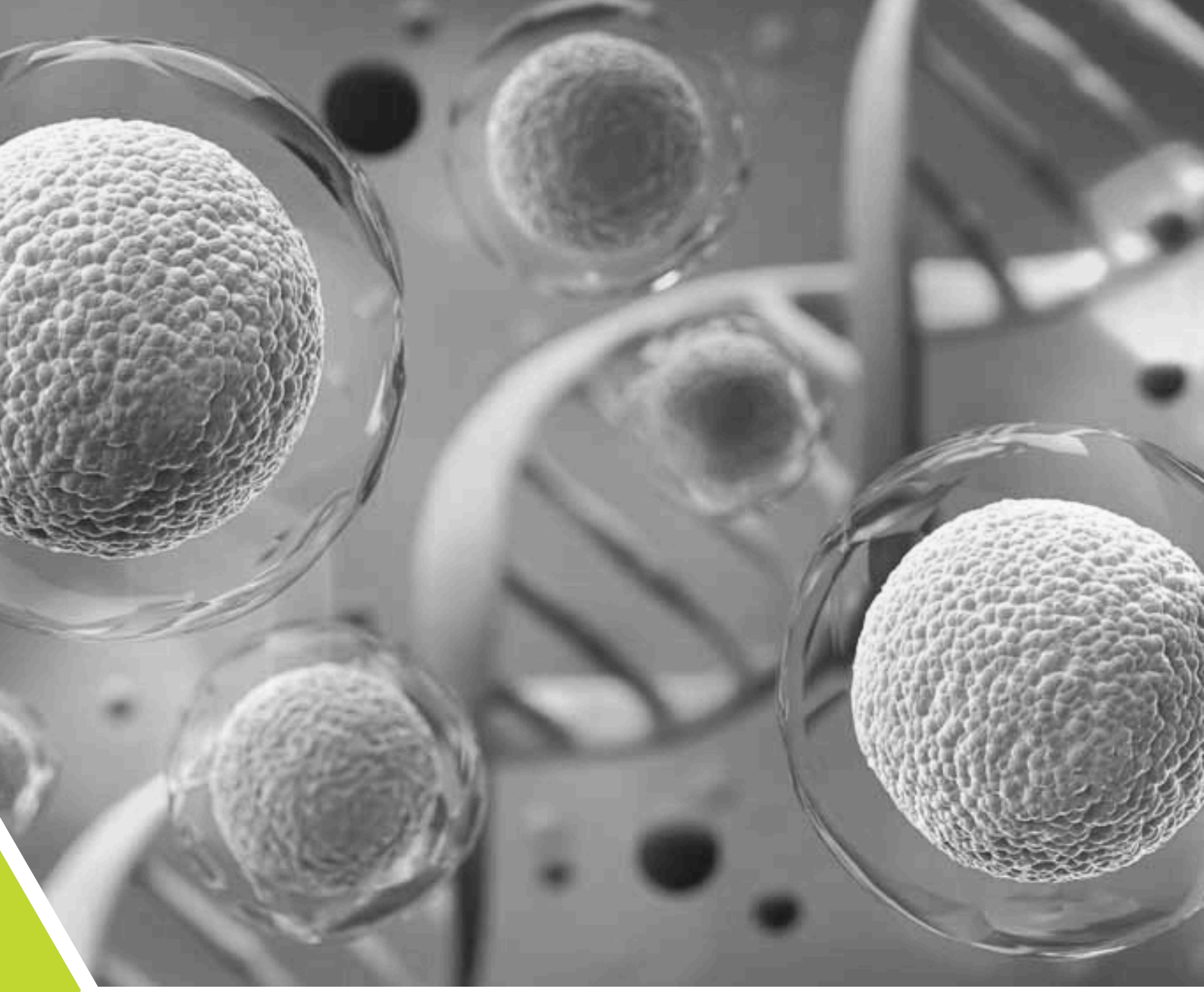


The Potency Puzzle:

Overcoming Challenges in Potency Assays for Cell and Gene Therapy Development

White Paper

solvias

Introduction

Potency assays are an essential aspect of Chemistry, Manufacturing and Controls (CMC) in the release of pharmaceutical product batches at drug substance and drug product stage. The Critical Quality Attributes (CQAs) of a drug are often tightly defined with regards to potency, to provide formal assurance that the drug exhibits a desired activity or function at a given concentration, to produce the intended effect in patients. Potency assays are important in the development and assessment of efficacy and safety for Advanced Therapy Medicinal Products (ATMPs) and are therefore necessary parts of CMC dossiers in marketing license applications.

The diverse nature of indications, and drug modalities of cell and gene therapies (CGTs) often leads to bespoke assays developed de novo for each specific ATMP. In this context, inherent variability of results, sample volume, drug stability and testing time constraints, as well as a need for strategic testing approaches to assess complex mechanisms of action provide significant challenges for manufacturers and CMC testing labs. A review of ATMP Marketing Authorization Applications (MAAs) at the European Medicines Agency (EMA) found that nearly 50% had issues related to potency[1]. Peter Marks, Director of the FDA's Center for Biologics Evaluation and Research (CBER), similarly noted that “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.” [2]

Inherent Variability of Cell-Based Products

The inherent variability of cell-based products poses significant challenges for the development and validation of potency assays. Cellular components and biological materials used in ATMPs can vary significantly between batches due to differences in donor or starting material, culture conditions, and manufacturing processes. Furthermore, the heterogeneity and dynamic nature of cell cultures, where populations may exhibit varying phenotypes and functionalities complicates the development of potency assays. This variability may lead to an apparent inconsistency in results, making it difficult to establish robust and reproducible potency measurements for CQAs.

1) Nature - Bloomberg - http://tinyurl.com/55udmamm
2) Alliance for Regenerative Medicine - https://tinyurl.com/3dcxys67

Limitations of Autologous Sample Volume and Time-Associated Pressure

For autologous CGTs, where the drug substance or drug product are derived from the patient's cells in a limited, finite volume, the material available for the testing regime is limited. This often necessitates the use of simple markers or surrogate, reductionist assays for potency. While this approach is acceptable in the EU when there is a functional potency assay for characterization purposes and the results of the assays correlate with each other, it nevertheless presents significant challenges[3]. The limited shelf life of fresh autologous products further complicates potency testing, as the time required to obtain results may exceed the product's viability window, impeding timely administration to patients.

Developing a Comprehensive Potency Testing Strategy

Another critical issue for potency testing of ATMPs is that biological activity is influenced by numerous factors, making it difficult for a single marker or assay to fully capture the product's functionality. The failure to develop adequate assays to address complex mechanisms of action has been proven to delay product licensure. The licensure of lifileucel, an autologous tumor-infiltrating lymphocyte (TIL) therapy, experienced difficulties during regulatory review as the testing scheme relied on a single potency assay[4]. After initially aiming for filing in 2020, pre-BLA discussions with the FDA prompted the manufacturer to further develop and validate a potency assay matrix including a proprietary cell co-culture assay, and lifileucel was approved in February 2024[5].

The FDA's 2011 Potency Tests for Cellular and Gene Therapy Products guidance states that “a single biological or analytical assay may not provide an adequate measure of potency” and emphasized the importance of an assay matrix[6]. The new Potency Assurance for Cellular and Gene Therapy Products draft guidance released in December 2023 suggests that it is not necessary to test each step in a biological cascade directly and there is advice against “assay redundancy” [7]. Nonetheless, the development of multiple assays to measure known or potential potency related CQAs is desirable, some of these assays may not ultimately be part of the CMC release regime but may play a significant role in the characterisation of a novel drug.

3) Frontier in Medicine – https://tinyurl.com/367m9y49
4) Iovance Therapeutics - https://tinyurl.com/px7n77pc
5) FDA - https://tinyurl.com/5cj8utky
6) FDA - https://tinyurl.com/zxxmxkj5
7) FDA - https://tinyurl.com/mrpzf5v

Industry Feedback and the Need for Clear Guidance

Feedback from the Alliance for Regenerative Medicine (ARM) and manufacturers of cell and gene therapies highlights a pressing need for more detailed guidance on potency assays. Many manufacturers view potency testing as a "black box" due to the absence of clear, standardized approaches. ARM quotes a CGT manufacturer stating, “the sector, as a whole, doesn’t exactly know what it’s looking at in terms of potency” [8]. During a workshop in 2023, developers noted that their interactions with the FDA led them to believe that an assay matrix is required for essentially all CGT products. However, determining where in the cascade to measure in a manner acceptable to regulators often leads to the proliferation of assays. FDA staff clarified that an assay matrix is not a universal requirement [8].

> “The sector, as a whole, doesn’t exactly know what it’s looking at in terms of potency”

The recent FDA draft guidance, recommends evaluating the utility of assays in parallel during early clinical investigations, enabling selection of the most relevant assays for phase-specific validation and eventual commercial testing, and the redundant assays can be discontinued at an appropriate stage[7]. Despite this, developers have expressed a need for clearer guidance around criticality. Delineating what is critical, helpful, redundant, or unnecessary for characterization or batch release is not just blurry but unknown. As one developer remarked, “It’s very hard to develop these unique, product-specific assays. It’s a huge competitive advantage when you know what worked” [8].

> “It’s very hard to develop these unique, product-specific assays. It’s a huge competitive advantage when you know what worked”

7) FDA - https://tinyurl.com/mrpzf5v
8) Alliance for Regenerative Medicine - https://tinyurl.com/2yjaurr9

Choosing the Right External Testing Lab for Batch Release and Potency Testing

Selecting a lab for external batch release or potency testing of drug substances/products is crucial for efficient testing, involving several key evaluation aspects by manufacturers. The scientific depth of the testing lab, especially in constructing cell-based assays with diverse mechanisms of action, assay conditions, and endpoint technologies for more bespoke assays, is crucial for timely issue resolution during assay development. It also ensures appropriate criteria for phase-specific validation, often paralleling process validation.

The experience of the testing labs in transforming an R&D-level assay to an efficient scalable GMP process capable of supporting significant volumes of samples during commercial manufacture is also a key consideration. Such transitions from a few samples a month to multiple samples weekly, or even daily, requires operational resilience and experience in resource allocation. Furthermore, a mature Quality Management System enabling detailed, yet rapid resolution of quality events and appropriate corrective and preventative actions underpins such transitions from pre-clinical, through clinical and into commercial stage operations.

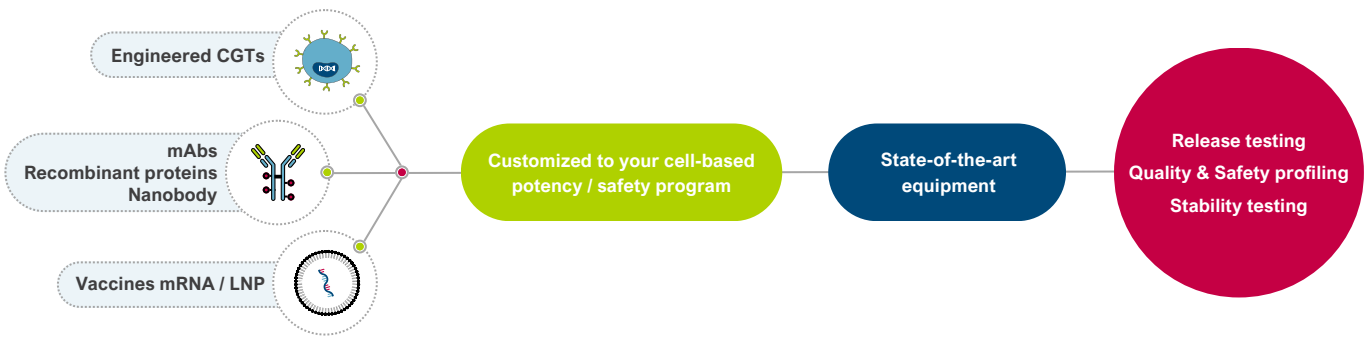
The deployment of a team well versed in the regulatory guidance for phase-specific transition through assay qualification into formal GMP validation, typically at the time of validation of the manufacturing process, is a valuable asset for any testing lab, and this constitutes a differentiating aspect in the service offering of testing labs, providing confidence to the manufacturer of reliability in execution.

Solvias' Expertise in Cell-Based Potency Assays

At Solvias, our cell-based potency assay services are tailored to each customer's individual needs. We understand that cell-based bioassays are unique to each product and our extensive experience allows us to rapidly develop, transfer, and validate cell-based assays in compliance with ICH Q2(R2), ICH Q14, and USP <1033/1210>. Our capabilities span the entire product lifecycle, from late-stage research, pre-clinical development through commercial release, with expertise in potency, stability, and safety assessment of biologics and cell & gene therapies.

> Rapidly develop, transfer, and validate cell-based assays in compliance with ICH Q2(R2), ICH Q14, and USP <1033/1210>

We emphasize a thorough understanding of the product's mechanisms and foster a collaborative relationship with our clients to target the right cellular outcomes and adapt to product-specific needs. We provide cGMP-compliant services which deliver reliable and reproducible results using a broad range of endpoint assessments, including qPCR, chemiluminescence, absorbance, fluorescence, flow cytometry (FC), capillary electrophoresis, ELISA, LC-MS, and molecular-based techniques. By leveraging our expertise in both physical chemistry and biology, we deliver advanced scientific solutions. Our team excels in phase-appropriate consultation, defining acceptance criteria, and supporting routine testing with robust data, ensuring efficient resource use. We've successfully developed potency assays from functional protein readouts to sophisticated assays for several approved ATMPs. Our personalized approach ensures clients receive the exact support they need, driving their products from development to clinical phases and through to commercial success with confidence and clarity.



Navigating the complex transition of a developed potency assay to Good Manufacturing Practice (GMP) can be a daunting challenge, especially for smaller biotech companies. Our expertise lies in seamlessly converting assays into GMP-compliant processes, ensuring every step of development aligns with regulatory standards. We understand the unique hurdles faced by our cell and gene therapy clients, from the need of consistent cell culturing and securing GMP-grade serum supplies to developing sophisticated readouts for complex products. Our hands-on approach, coupled with deep industry knowledge, ensures our customers' potency assays are set up for a seamless transition into late and commercial phases.

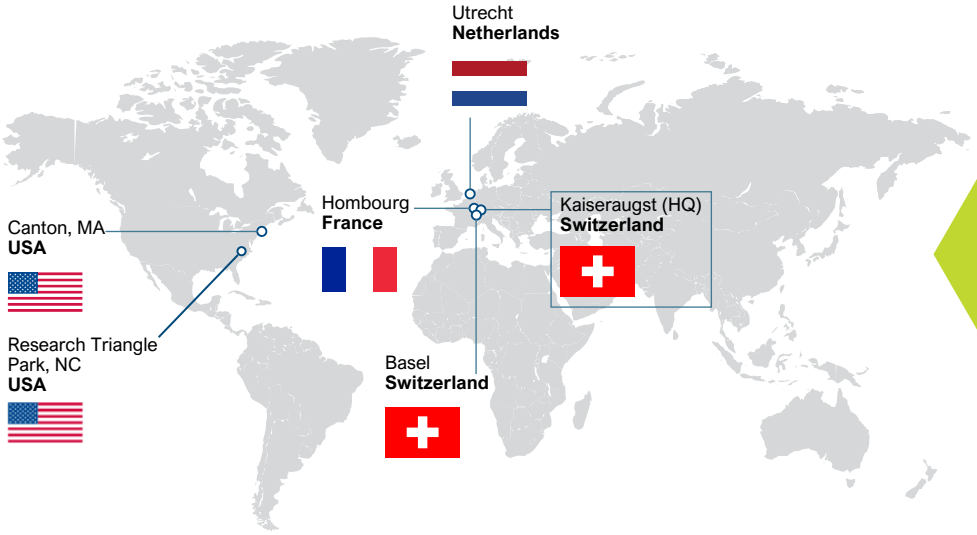
Understanding the critical importance of turnaround time for autologous therapies, we emphasize rapid and efficient processes to align with patient treatment timelines. Our logistics and testing protocols are designed to be timely and reliable, ensuring no time is wasted in delivering life-saving treatments. Additionally, by prioritizing quick time-to-qualification and smooth transitions to commercial production, we help our clients bring their therapies to market faster without compromising quality or compliance.

Key Takeaways

Developing reliable potency assays is vital for the successful commercialization of CGTs. Despite the significant challenges posed by the intrinsic variability of cell-based products and the limitations of autologous samples, a strategic approach can robustly evaluate potency. Despite recent regulatory advice providing more comprehensive guidance than before, industry feedback highlights the necessity for further clarity. By leveraging Solvias' expertise, clients can overcome the challenges associated with potency assays, ensuring effective testing of CGTs, and providing a suitably granular dossier of data to support submission of regulatory filings for marketing license. We provide the necessary support and guidance to enable the successful translation of ATMPs from the laboratory to the clinic.

Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence



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