# Clinical Holds in Cell & Gene Therapies

## Strategies to mitigate risk and accelerate approval

White Paper

solvias

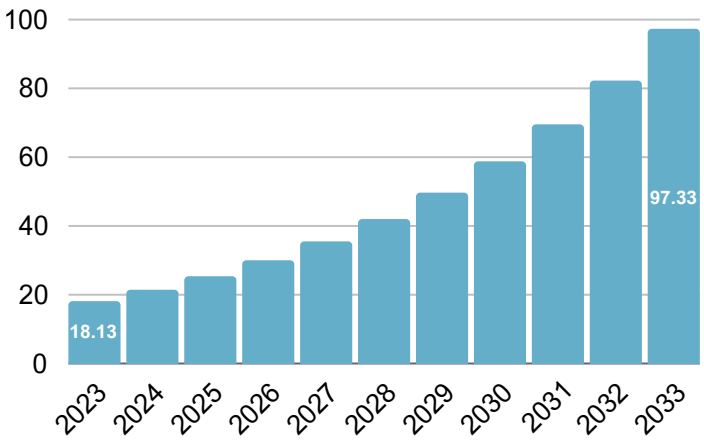
# Executive Summary

Cell and gene therapies (CGTs) are transforming the therapeutic landscape, offering new hope for patients with previously untreatable conditions. However, the path to market for CGTs presents significant challenges. With CGT studies expanding rapidly, regulatory scrutiny has intensified, leading to an increase in clinical holds, many of which are due to deficiencies in Chemistry, Manufacturing, and Controls (CMC). Potency testing is among the most complex CMC requirements. Clinical holds related to potency assay issues can cause severe delays and financial setbacks, making early assay development a critical factor in avoiding these costly interruptions.
This white paper explores the complexities of potency assay development, underscoring the FDA's recommendation for early initiation as part of the Investigational New Drug (IND) process to allow adequate time for testing, refinement, and regulatory alignment. Given the technical hurdles and unique requirements of CGTs, a well-defined strategy that begins early can significantly reduce the risk of clinical holds, enhance product quality, and ensure smoother progression through regulatory milestones.

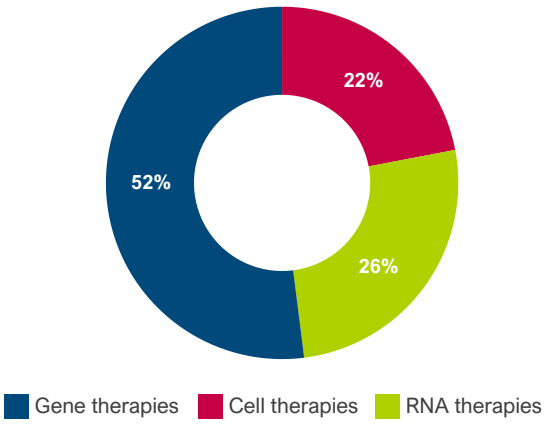
# The Roadblocks to IND: Clinical Holds and the Path Forward

Cell and gene therapies (CGTs) represent a beacon of hope for patients worldwide, promising to transform the way we treat — and potentially cure — a range of previously untreatable diseases. As the fastest-growing area in therapeutics, CGTs are driving unprecedented innovation, with over 4,000 therapies advancing through stages from early research to regulatory approval as of April 2024, fueling a market projected to surge from USD 18.13 billion in 2023 to USD 97.33 billion by 2033, at a compound annual growth rate (CAGR) of 18.3%.[1]

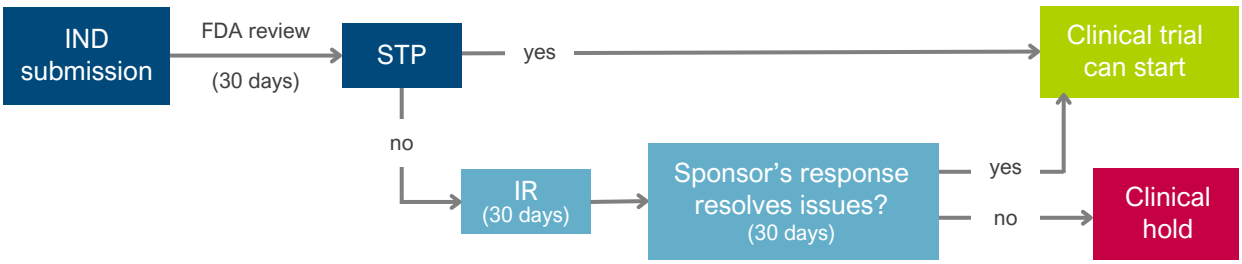
**Cell and Gene Therapy Market Size (USD Billion)**




**Advanced Therapies in Development**



A major bottleneck in the development of CGTs is the risk of a clinical hold following the investigational new drug (IND) submission. An IND includes preclinical data, details on chemistry, manufacturing, and controls (CMC), and clinical protocols. Once submitted, the FDA has 30 days to conduct a comprehensive review to determine if the proposed clinical trial is safe to proceed (STP). If deficiencies are identified, the FDA issues an information request (IR) for further data or modifications. If these issues remain unresolved, the FDA may place the trial on clinical hold. Upon imposing a hold, the FDA provides a written explanation within 30 days, allowing sponsors to address the issues. Once a sponsor submits their response, the FDA has another 30 days to review it and decide whether to lift the hold.




Consequently, a clinical hold results in at least a 60-day delay. The impact of these delays can be significant, potentially reducing investor confidence or seeing programs de-prioritized to conserve resources.

As CGT clinical trials have grown, so too have clinical holds; while CGT trials represent less than 2% of all clinical trials listed by the NIH, they account for approximately 40% of all clinical holds. Over 21% of these holds are triggered by issues in the CMC section, with CMC-related holds taking the longest to resolve — often lasting more than six months.[2] A primary challenge in this area is potency testing. As Peter Marks, director of the FDA's Center for Biologics Evaluation and Research (CBER), explains:

> **"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."**

The following sections will explore why potency testing is so challenging and how developers can reduce the risk of these costly delays.

# The Potency Assay Challenge

Potency measures a drug's ability to produce the desired biological effect, ensuring that the therapy performs as intended and at a strength sufficient for effective patient treatment. Traditionally, potency for biological products is assessed through a quantitative bioassay that evaluates the product's activity based on its ability to achieve a specific effect. These bioassays, often conducted within cell culture systems, must meet several essential criteria:

- Indicate potency (biological activity/activities) specific to the product
- Provide test results for release of the product
- Provide quantitative data
- Meet pre-defined acceptance and/or rejection criteria
- Include appropriate reference materials, standards, and/or controls
- Establish and document the accuracy, sensitivity, specificity and reproducibility of the test methods employed through validation
- Measure identity and strength (activity) of all active ingredients
- Meet labeling requirements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For complex products like CGTs, fulfilling all these criteria in a single assay is often unfeasible. Instead, developers commonly rely on a matrix of multiple assays to capture a comprehensive potency profile.

Potency testing is among the most challenging elements of Chemistry, Manufacturing, and Controls (CMC) for advanced therapies due to the unique characteristics of these products and technical limitations in certain assays. These issues are further explored in our white paper, "The Potency Puzzle: Overcoming Challenges in Potency Assays for Cell and Gene Therapy Development", which delves into the complexities of developing these assays. Proactive planning to develop, optimize, and validate these assays can significantly reduce the risk of clinical holds, helping prevent costly delays or the suspension of potentially life-saving therapies from reaching patients in need.

# Starting Strong: Why Early Potency Assay Development Matters

The FDA advises developers to begin assessing potential potency assays early in the IND process. Custom potency assays require a lengthy development timeline (see next page), so starting early helps prevent delays. Early initiation also allows time to explore multiple assay options, gather data on stability and consistency, and conduct correlation studies.

During the initial stages of an IND, acceptance criteria can be set broadly. As development advances and more manufacturing and clinical data become available, acceptance criteria can be refined and narrowed to reflect a deeper understanding of the product. Although a potency assurance strategy may not be fully developed in the initial stages, it is still important to have a defined approach that includes identifying initial potency-related Critical Quality Attributes (CQAs) and assessing any risks to these CQAs, along with mitigation strategies.

Specifically, the IND submission should include:

- The product's mechanism of action, Quality Target Product Profile (QTPP), and an initial list of potency-related CQAs, with explanations of how these CQAs were identified
- A description and rationale for the current potency assurance strategy
- General plans for enhancing the potency assurance strategy as the product develops

By the later stages of clinical development, this strategy should be comprehensive, covering all essential aspects of potency assurance.

Despite FDA recommendations to begin potency assay development early, some developers may delay this investment, waiting for clearer signs of a therapy's safety and efficacy. However, insufficient early focus on potency assay development can lead to clinical holds, which can have serious implications for timelines and financial viability.

## Typical Timeline for Custom Potency Assays

**4 to 6 months**

### Development and Optimization

- Assay Design: Developing an assay format that best captures the intended mechanism of action and biological activity of the product.
- Parameter Selection: Determining key criteria for assay performance, such as sensitivity, specificity, and reproducibility.
- Reagent Optimization: Testing and refining assay reagents to ensure reliability and minimize variability.
- Preliminary Testing: Conducting initial tests to verify the assay's ability to measure potency and meet quality requirements.

**3 to 6 months**

### Qualification

- System Suitability Testing: Evaluating the assay's performance characteristics, such as accuracy, precision, and linearity, to confirm that it meets specifications.
- Reproducibility: Testing across multiple runs, operators, and instruments to confirm consistent results.
- Reference Standards and Controls: Establishing and validating reference standards and controls that provide benchmarks for potency measurements.

**3 to 6 months**

### Validation

- Full Validation: Conducting detailed studies to confirm that the assay meets required performance metrics for accuracy, sensitivity, specificity, robustness, and consistency.
- Documentation and Compliance: Completing extensive documentation of validation processes and results, aligned with regulatory guidelines to support regulatory submissions.
- Ongoing Stability Testing: Using the validated assay to assess product stability over time, ensuring the potency of each batch remains consistent.

# Expanding Excellence: Dedicated CGT Lab in the US

Solvias Cell-Based Bioassay Center of Excellence in Hombourg, France, brings decades of proven experience in potency assay development, from functional protein readouts to advanced assays for advanced therapies. With a personalized, end-to-end approach, we guide clients confidently from early development through clinical phases to successful commercialization.

Building on this solid foundation, we are expanding to the United States with a new, state-of-the-art facility in Research Triangle Park (RTP), North Carolina. Expected to be fully operational by 2025, this 50,000-square-foot facility will serve as our North American hub for large molecule analytical services, providing essential support for CGT and other advanced therapeutic modalities.

At our new RTP Center of Excellence, we will apply our extensive experience to customize cell-based assays, offering tailored, phase-appropriate solutions that streamline drug development and help mitigate risks early on.

- **Pre-Clinical:** We help you fully understand your molecule or ATMP to reduce risk.
- **Clinical phases:** We support you at every clinical phase, using our library of techniques we will tailor our approach to meet unique requirements and ensure proper documentation.
- **Regulatory filings:** We support and guide you as you prepare your regulatory filings.
- **Post-commercialization release testing:** Post-approval, we continue to support release testing for drug safety and effectiveness.

With the FDA recommending that developers start potency assay development early, our expertise can help sponsors mitigate the risk of clinical holds by establishing robust assays from the outset. Given the length of development timelines and the high demand for our services, we encourage you to reach out to our experts now to reserve your slot. Contact us at **info@solvias.com** to discuss how we can bring your innovation to its destination.

# Acknowledgements

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# References

1) BioSpace. (2024, April 5). Cell and gene therapy market size to reach USD 97.33 bn by 2033. https://www.biospace.com/u-s-cell-and-gene-therapy-clinical-trial-services-industry-is-rising-rapidly

2) Wills, C. A., Drago, D., & Pietrusko, R. G. (2023). Clinical holds for cell and gene therapy trials: Risks, impact, and lessons learned. Molecular Therapy — Methods & Clinical Development, 31, 101125. https://doi.org/10.1016/j.omtm.2023.101125

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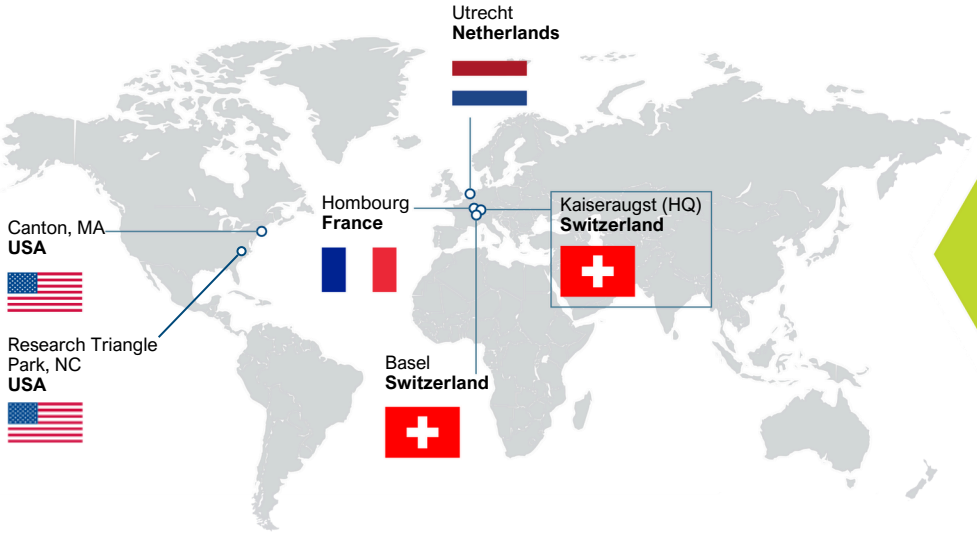


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