

BUILDING A MECHANISM-BASED POTENCY STRATEGY FOR BISPECIFIC ANTIBODIES

A biotechnology company developing a bispecific antibody was advancing its program toward late-stage development. Unlike conventional monoclonal antibodies, this therapeutic relied on two simultaneous target-binding events to recruit immune effectors cells and mediate drive tumor cell killing. During early development, several functional assays were established to understand the molecule's biological activity, including potential mechanism of action. However, as the program matured, a critical question emerged: which assay should ultimately define product potency for regulatory submission? While a single cell-based cytotoxicity assay captured the overall biological response, it provided limited insight into the responsible mechanism if potency shifted. Validating multiple complex cell-based assays for commercial release would significantly increase analytical burden, biological variability, and lifecycle management.



THE CHALLENGES

Complex and Multimodal Mechanism of Action Driving Clinical Activity

Unlike conventional monoclonal antibodies, bispecific antibodies rely on the coordinated interaction of two binding domains to mediate their therapeutic effect. Demonstrating that both biological functions remain intact requires a potency strategy that adequately reflects the molecule's mechanism of action.

Limited Understanding on the Cause of Potency Changes

An integrated cell-based cytotoxicity assay may successfully measure the final biological outcome. However, when potency changes, the assay alone cannot always distinguish whether reduced potency results from impaired target binding, reduced immune cell activation, altered binding affinity, or another mechanism.

Multiple Cell-Based Assays Increase Complexity

Implementation of each additional functional assay introduces its own cell lines, biological variability, assay controls, reference standards, and qualification requirements. An increased number of assays can lead to longer development timelines, increased operational complexity and greater long-term maintenance planning.

Regulatory Justification

Global Regulatory agencies require scientifically justified potency assays that are phase-appropriate, suitable for release and stability testing, reflective of the mechanism of action, relevant to clinical efficacy, and capable of supporting comparability and lifecycle management.



OUR COLLABORATIVE APPROACH

Mechanism-of-Action Assessment

We collaborated with the client to map the bispecific antibody's biological mechanisms and identify critical functions that contributed to clinical activity. This framework established the foundation for potency strategy.

Orthogonal Functional Characterization

Rather than relying exclusively on a single endpoint assay, Solvias developed a panel of complementary analytical and functional assays to characterize distinct functional attributes, including target-binding assays, reporter assays, and cell-based functional assays. This approach provided a comprehensive understanding of each functional component and its impact on the overall biological activity.

Phase-Appropriate Potency Strategy

The broader assay panel provided mechanistic insight during development while helping identify which assays most accurately reflected overall potency. This supported the transition toward a streamlined commercial testing strategy without sacrificing scientific confidence.

Regulatory-Ready Scientific Justification

By correlating orthogonal assay results with biological function, Solvias helped establish a robust scientific rationale supporting the proposed potency strategy for later-stage development and regulatory submission.



THE RESULTS

- Comprehensive functional characterization of the bispecific antibody's clinically relevant biological functions.
- Clear understanding of mechanistic contributors of potency.
- Development of a phase-appropriate potency strategy balancing scientific rigor with operational practicality.
- Reduction in long-term analytical complexity while maintaining product quality.
- Confidence in regulatory interactions through a mechanism-based scientific justification for potency testing.



CONCLUSION

This case demonstrates that for complex biologics such as bispecific antibodies, potency cannot be demonstrated by a single assay without mechanistic understanding. By integrating orthogonal analytical methods with carefully selected cell-based assays, Solvias enabled the development of scientifically robust, phase-appropriate potency assays that met regulatory expectations. This approach empowered the biotech company to advance complex biologics through late-stage development, regulatory approval and long-term commercial quality control.

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