

A Comprehensive Blueprint for *In Vitro* Glycoengineering Adoption

Source: Roche CustomBiotech

In Vitro Glycoengineering (IVGE), a technology for **precisely modifying a protein's glycosylation profile** after it is produced, offers reliable, direct control over the final glycopattern, thereby eliminating the batch-to-batch variability and costly process excursions that can result from fluctuating upstream cell culture conditions. By separating glycosylation from their strategies for optimizing product yield, developers have the operational freedom to maximize fermentation output while achieving a consistent, high-quality glycoprofile downstream.

Nevertheless, while adopting IVGE is a strategic move that can fundamentally improve control over therapeutic protein quality, its successful adoption requires validating the robust clearance of all added enzymatic reagents and executing a phased, risk-minimized integration plan into the existing downstream purification train. Understanding these considerations helps transform IVGE from a novel research concept into a validated, manufacturable solution, allowing developers to confidently unlock new levels of product quality and process flexibility while meeting rigorous regulatory expectations.

The Business Case for IVGE

Innovation and change are fundamental to the pharmaceutical industry's mission, yet the high regulatory and financial risks naturally make adopting new technologies intimidating. This critical move is necessary, however, to ensure that the therapeutic potential unlocked by science can translate into new, life-changing medicines.

IVGE's ability to profoundly improve safety, efficacy, and stability while optimizing biopharmaceutical workflows **throughout the entire development and biomanufacturing life cycle** make it a viable strategy for achieving pharma's end goal. Yet, novel approaches like IVGE frequently raise concerns rooted in the high stakes associated with regulatory compliance, capital expenditures, and safety. Therefore, a necessary precursor to understanding IVGE integration is a holistic evaluation of not only its scientific capabilities but also its commercial and manufacturing suitability.

Consequently, this necessary assessment is framed by several common concerns typically raised by stakeholders, including:

- **Time and Complexity:**
  While IVGE adds a step to the downstream process (DSP), data indicates the ~5% increase in overall production time is minimal and often offset by time saved in upstream process (USP) optimization.[1]
- **Regulatory Prudence:**
  The risk associated with a new technology can be systematically mitigated by generating robust Quality by Design (QbD) data, validating product stability, and proving the clearance of all enzymatic reagents with sensitive assays.[2]
- **Cost Dynamics:**
  Although high-quality reagents can seem expensive, the long-term economic benefits, such as maximizing upstream yields and creating a superior drug profile, outweigh the initial cost.[1]

Although these concerns would carry significant weight if left unaddressed, proactively validating them with comprehensive data and a clear cost-benefit analysis will ultimately demonstrate the strategic viability of IVGE.

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An IVGE Integration Framework

Phase 1: Lab Scale (Optimization and Feasibility)
This initial phase focuses on determining if IVGE is technically viable for a specific therapeutic protein. Using a small amount of **purified material**, the goal is to define optimal reaction parameters like enzyme-to-protein ratios, incubation times, and buffer conditions. This ensures that the desired glycan structure can be created reliably and efficiently.

Phase 2: Pilot Scale (Process Integration and Validation)
The pilot scale is where the process is integrated into an existing workflow. IVGE is typically performed as a downstream step after an initial capture step, such as Protein A purification, which ensures the starting material is pure enough for the reaction. This phase involves two key process decisions:

1. **Starting Material Purity:**
   The efficiency of IVGE is critically dependent on the purity of the starting material. To overcome the inhibitory effects of impurities found in crude supernatant, an initial simple Protein A purification step is essential. Studies show that using a Protein A purified substrate yields results comparable to using fully purified bulk material.

2. **Two-Enzyme Process Strategy:**
   For sequential modifications (e.g., galactosylation followed by sialylation), the choice is between a faster one-pot reaction or a sequential two-step reaction with an intermediate purification. While the one-pot saves time, the sequential two-step approach with an intermediate Protein A purification is the best practice for quality control, as it is proven to drive the final sialylation levels significantly higher, maximizing the efficiency and homogeneity of the final product.

Pilot runs establish parameters for efficient scaleup, including mixing, temperature control, and – most importantly – validating the robust clearance of all added reagents. Successfully completing this phase means the integrated process is efficient, reliable, and ready for larger-scale validation.

Phase 3: Manufacturing Scale (Commercial Readiness)
The final phase involves scaling up the validated process for clinical or commercial manufacturing. A key consideration here is ensuring that all enzymatic reagents meet the rigorous quality standards required for commercial production. Roche CustomBiotech's enzymes are produced under a quality management system (QMS) according to ISO 13485:2016 and are animal-origin free, directly addressing critical regulatory concerns regarding safety and traceability. This commitment to raw material quality is essential for building the comprehensive Quality by Design (QbD) data packages needed for regulatory submission and product approval.

Case Study: Examining IVGE Integration in Alternative Expression Systems

In a case study demonstrating the value of IVGE technology, a biotech pioneer focused on previously inaccessible biological therapies, successfully integrating IVGE to accelerate development of a protein replacement therapy.

To address specific glycan requirements beyond the native capabilities of alternative plant-based expression system, the company chose IVGE rather than undertaking time-consuming genetic modification. The primary driver for this decision was speed, which significantly accelerated their preclinical phase and enabled a faster path to clinical trials.

The company ensured a robust and scalable implementation of a non-standard technology by:

- Optimizing process parameters to maximize specific activity and reduce enzyme loading, supporting cost-effective manufacturing
- Characterizing and optimizing the purification strategy to efficiently remove enzymes and substrates after IVGE
- Working closely with suppliers to support regulatory readiness and establish methods for quantifying residual enzymes

Despite the work involved, the process was scaled successfully without major issues, demonstrating the technology's robustness from milligram to gram scale. The company's structured implementation of IVGE proved its value as a powerful approach to de-risk and accelerate clinical development.

The Key to Successful IVGE Integration

Realizing the profound benefits of IVGE – from eliminating batch variability to optimizing USP yield – begins with expert guidance. Integrating IVGE is a strategic shift that requires a reliable partner with deep manufacturing experience. Roche CustomBiotech offers decades of experience providing high-quality raw materials and fit-for-purpose solutions for biotherapeutics manufacturing.

We have the capabilities and expertise to support every phase of your process integration by supplying a complete **IVGE toolbox**, including well-characterized enzymes and activated sugars. These reagents can be scaled from milligram to kilogram amounts and provided in GMP grade upon request, ensuring a seamless and fully supported transition from lab optimization to commercial readiness.

***Contact** your local Roche CustomBiotech team to schedule a technical consultation and begin charting your path to predictable glycan control.*

References

1. Roche CustomBiotech. (2025, May). *In Vitro* Glycoengineering (IVGE): Taking Control of Glycosylation. Retrieved from **https://www.bioprocessonline.com/doc/in-vitro-glycoengineering-ivge-taking-control-of-glycosylation-0001**
2. Sebastian, Malik & Thomann, Marco. (April 2016). *In vitro* glycoengineering – Suitability for Biopharma manufacturing. **https://go.roche.com/IVGE_Biopharma_Manufacturing**

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Published by
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Signature Page for MC--20040 v1.0

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Regulatory Approval	Gina Chang Regulatory Approval 09-Feb-2026 13:36:08 GMT+0000

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