Navigating the Complexities of Early Drug Development

Ensuring Quality and Efficiency from the Start

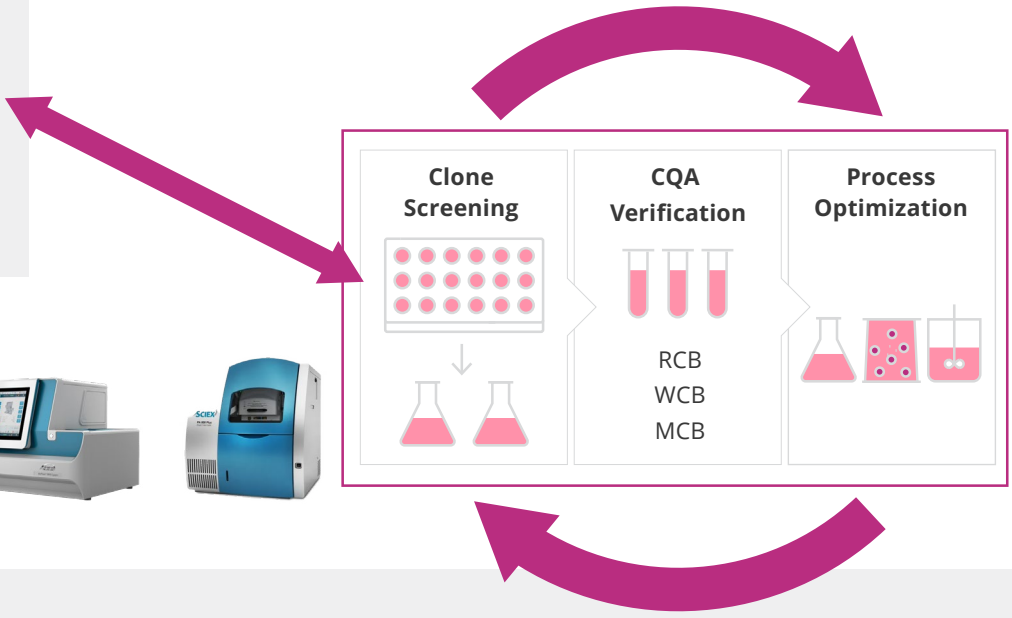
The journey from initial concept to a fully developed therapeutic is marked by a series of rigorous scientific and logistical milestones that involve multiple labs, teams and analytical strategies. At the heart of early drug development lies cell line development and the verification of critical quality attributes (CQA), essential steps for understanding the molecular structures of the protein therapeutics being produced. This stage relies on several analytical assays, including CE-SDS for cell line purity, capillary isoelectric focusing for charge variant monitoring, integrated icIEF-UV/MS workflows for charge variant and post translational modification identification, and peptide mapping via LC-MS for sequence confirmation.

During this early stage of cell line development, there are key challenges and considerations to address in order to keep the development timeline moving, reduce risk and late-stage failures.

Gain insights on CQA faster

Target Identification → Drug Discovery → Preclinical → Upstream Development → Downstream Development → Production → Clinical Development → Commercialization

- Clone characterization and CQA verification
- Can take from 8 weeks to more than 20
- Information can be used to drive process optimization



Includes:

- Cell line purity assessment – CE-SDS
- Charge variant monitoring – cIEF
- Charge variant identification – icIEF UV/MS
- Charge variant confirmation – peptide mapping

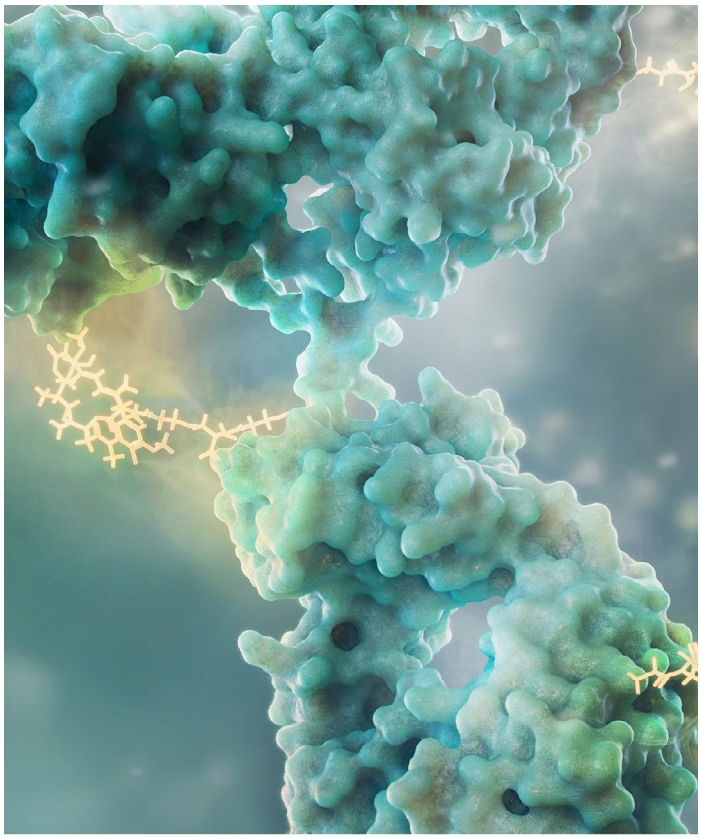
Early Development: Cell Line Development

Goal: Identify stable cell lines capable of consistently producing high-purity protein therapeutics.

Key Challenge: With thousands of potential cell lines, a solution is needed to efficiently identify those that best reduce the pool of optimal clones.

Considerations:

- **Volume and Diversity:** Early development involves screening thousands of cell lines, each with unique characteristics that can be inherent or induced by the environment. Selecting the "best" line is both a technical and logistical challenge.
- **Analytical Precision:** Demonstrating a comprehensive understanding of the candidate, including factors like primary sequence, quality attributes, and charge heterogeneity, is crucial, as these can compromise downstream processes and the safety of the final product.
- **Resource Management and Risk Reduction:** Investing heavily in non-viable cell lines delays progress and inflates costs.



Workflows to Use:

Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS)

- CE-SDS is the standard method for assessing protein purity. By separating proteins based on their molecular weight, this workflow helps identify cell lines that yield the correct product form with minimal contaminants or degradation products, ensuring that only those with optimal purity profiles advance to further development. Intabio technology can enhance this process by providing precise and rapid analysis.

Capillary Isoelectric Focusing (cIEF)

- cIEF separates proteins based on their isoelectric points (pI). This enables the identification of variants that arise due to differences in charge caused by changes in sequence, glycosylation and other post-translational modifications. cIEF helps select those candidates that produce the desired main isoform with minimal charge variants to ensure product consistency and quality. Intabio can be utilized to improve the accuracy and efficiency of cIEF, helping to select those candidates that produce the desired main isoform with minimal charge variants to ensure product consistency and quality.

SCIEX Solutions:

BioPhase 8800 system with NF: Accelerate time to answer with parallel processing, and enhanced sensitivity for CE-SDS, CZE, and cIEF.

Impact on Timeline and Resources:

- Accelerates decision making by quickly identifying high-quality candidates.
- Minimizes resource allocation by focusing efforts on viable cell lines.

BioPhase 8800 system >

Assessing Protein Purity–The Role of CE-SDS

Workflow Spotlight: CE-SDS

- **Efficiency:** CE-SDS can screen dozens to hundreds of samples rapidly, delivering reproducible purity profiles for each candidate. This enables the focus of resources on the most promising cell lines, accelerating selection and minimizing later-stage failures.
- **Risk Reduction:** Early identification of high-quality cell lines ensures fewer surprises during scale-up and manufacturing, reducing the risk of costly setbacks.

Learn more

Early Development: Candidate Characterization and Verification of Quality Attributes (product or critical)

Goal: Support efficient downstream development by establishing a comprehensive understanding of each potential candidate's makeup, stability, and ability to reliably express target proteins.

Key Challenge: Balance sensitivity and specificity in analytical screening to detect subtle differences in protein variants, post-translational modifications (PTMs), and impurities that could impact safety or efficacy.

Considerations:

- Gain in-depth characterization of product quality attributes early, with methods that can be applied to multiple modalities.
- Identify strategies that can minimize resource expenditure during early screening to focus on viable candidates, accelerating timelines, and reducing the risk of late-stage failure.
- Ensure robust data management and traceability for all characterization activities to support process optimization and regulatory submissions.

Workflows to Use:

icIEF-UV/MS (Imaged Capillary Isoelectric Focusing with UV and Mass Spectrometry):

- icIEF-UV/MS integrates CE separation with MS identification on a single platform to accelerate the characterization of proteins. This workflow provides both qualitative and quantitative information on post-translational modifications, sequence variants, and other product-related impurities in hours, enabling critical information to be available earlier in the pipeline to better guide decisions and reduce risk.

LC/MS Characterization:

- As drug candidates progress through development, detailed characterization becomes essential. Liquid chromatography-mass spectrometry (LC-MS) is used to confirm primary protein sequences as well as to identify and localize PTMs. Thorough characterization ensures that all CQAs are understood and controlled, reducing the likelihood of late-stage failures. Common LC-MS characterization workflows are intact protein analysis, subunit analysis, or peptide mapping.

Impact on Timeline and Resources:

- Provides a complete molecular understanding, supports informed decision-making, and enhances the ability to manage complex therapeutics and evolving modalities with confidence.
- Reduces risk with early identification of changes to secondary structure, sequence variants, and impurities, enabling informed decision-making throughout the development process.
- Continuous monitoring and adaptation mitigate unexpected issues, enhancing process reliability and reducing regulatory risk.

SCIEX Solutions:

Intabio ZT system: Integrated icIEF-UV/MS platform for confident charge variant and PTM identification, reducing project time from weeks to just hours.

Intabio ZT system >

SCIEX Solutions:

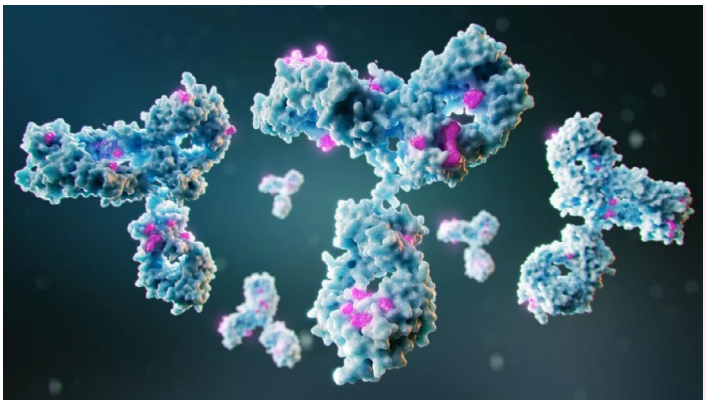
ZenoTOF 7600+ system and ZenoTOF 8600 system: Enable identification of challenging PTMs with the sensitivity and power of EAD. Take advantage of biopharma data analysis with Biologics Explorer software, supporting therapeutic characterization from the peptide level to the intact level.

ZenoTOF 8600 system >

Reducing Risk: The Role of Integrated icIEF-UV/MS

Traditionally employed for charge variant analysis, icIEF is commonly used for variant detection to support regulatory submissions, release testing, and product stability. However, further mass spectrometry analysis is necessary to identify peak composition, and preparing icIEF samples to be mass spectrometry compatible is time-consuming and laborious. The integrated icIEF-UV/MS workflow on the Intabio ZT system reduces identification time to under an hour, enabling timely feedback during cell line development and informing product strategy decisions.

Having PTM and quality attribute information available quickly and reproducibly enables a rapid feedback loop to address potential issues at critical time points in the process. The information obtained can help guide decisions and formulate an effective analytical strategy to move a product to market.



From Detection to Mitigation: Managing Sequence Variants in Biotherapeutics

Free on-demand virtual event

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Conclusion

At multiple points in the drug development pipeline, core assays provide crucial data that guide analytical decisions, file regulatory submissions, and enable faster and more informed decisions about which clones to advance. The ability to implement and streamline these workflows early is key to accelerating timelines and reducing risk.

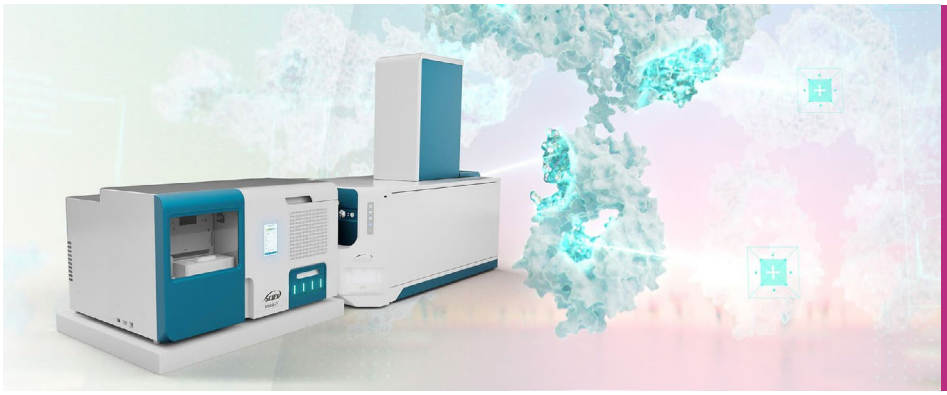
With over 50 years of experience, SCIEX provides innovative and reliable analytical solutions that support every stage of the drug development pipeline. By leveraging SCIEX expertise, researchers can enhance their workflows, reduce risks, and bring life-changing therapeutics to market more efficiently.

Key Resources:

Webinar: Access a summary of key takeaways and expert insights from the webinar, focusing on how innovative technologies, like the Intabio ZT system, can ensure the production of gh-quality and stable biotherapeutic products.

Research Insights: Recent studies and findings that explore the challenges and solutions in protein therapeutics.

Technological Innovations: Learn more about the Intabio ZT system and its capabilities in transforming drug development processes.



For details on the Intabio ZT system, visit:

How to Intabio ZT >

Intabio ZT system >