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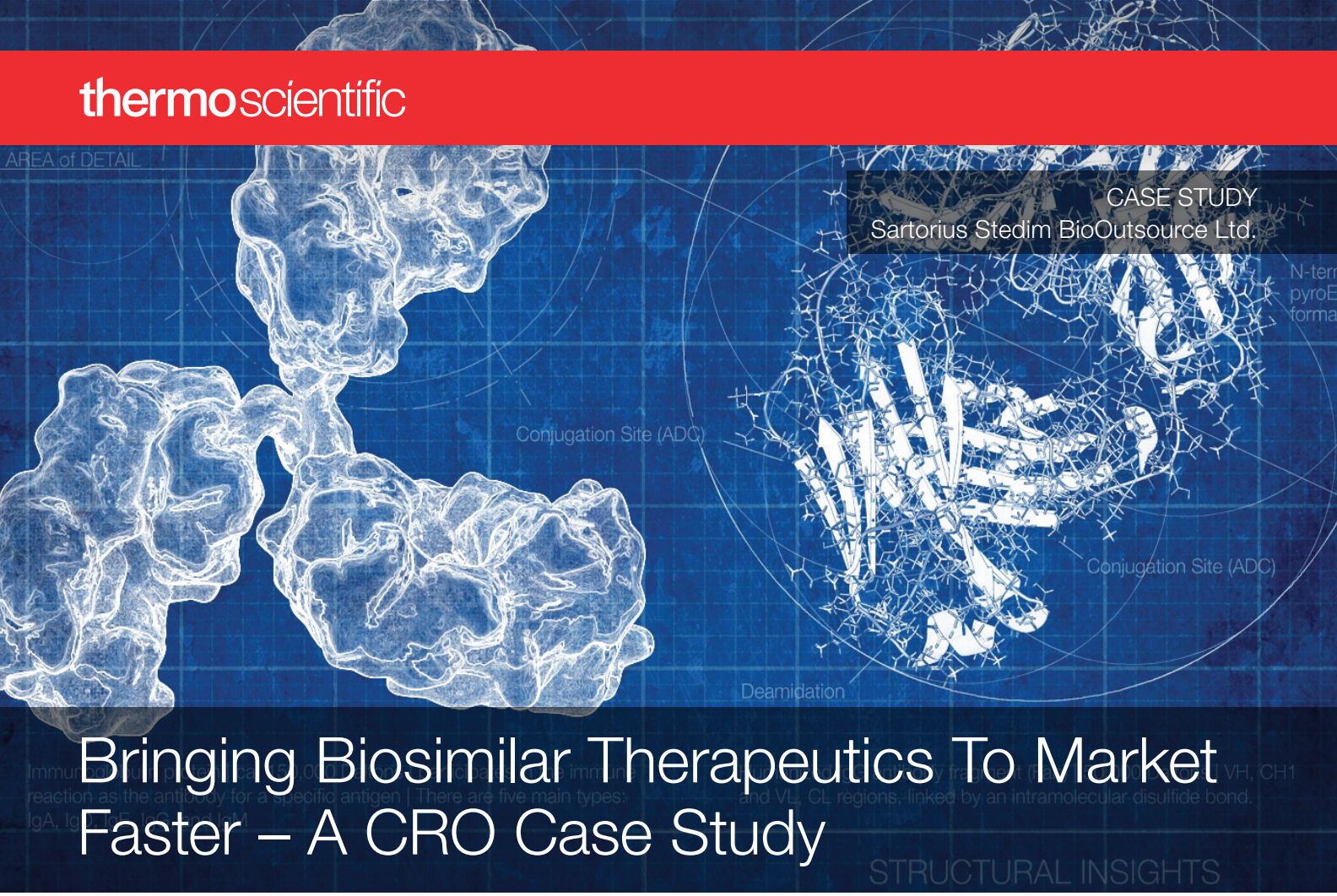

Bringing Biosimilar Therapeutics To Market Faster – A CRO Case Study

Delivering fast and confident answers

Sartorius Stedim BioOutsource Ltd. is an industry leader in the characterization and comparability of biosimilar to originator biologics, providing comprehensive testing services to the biopharmaceutical industry.

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Sartorius Stedim BioOutsource have created a niche within the industry, dedicated to rapid and confident biological and structural evaluation of biosimilar monoclonal antibodies (mAbs). Offering a comprehensive range of physicochemical and biological testing to support biosimilar development, working with over a dozen biosimilar molecules and around forty biosimilar developers.

Sartorius Stedim BioOutsource has expertise in the binding activity and subsequent functional consequences of biosimilar monoclonal antibodies. Their holistic approach combines functional assays with structural analyses to answer why there are changes in drug

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candidate activity. Sartorius Stedim BioOutsource focus on structural and physicochemical analyses following **ICH Q6B** guidelines, while supporting clients through clone selection, process development and assessment of product stability. All analyses are performed following the principles of Good Manufacturing Practice (GMP); giving clients' confidence in the quality and traceability of their data.

Therapeutic proteins are complex, requiring a multitude of physicochemical tests to elucidate structure. Sartorius Stedim BioOutsource focuses on high quality, high resolution data to support biosimilar clients in the endeavor to prove 'fingerprint-like' structural similarity, including:

- **Charge variant profiling**
- **Aggregate analysis**
- **Glycan analysis**
- **Intact mass analysis**
- **Peptide mapping**

A key mantra that drives productivity at Sartorius Stedim BioOutsource is their ability to offer clients cost-effective 'Speed to Market'; enabled through a comprehensive range of cutting edge, off-the-shelf assays for biosimilar characterization and comparability.

"In the biosimilar field, speed to market is crucial. When we decided to expand our service portfolio we recognized the need for state-of-the-art, cutting edge technology that could rapidly and confidently resolve small differences in the structure of a molecule."

—Dr Martin De Cecco, Biochemistry R&D,
Sartorius Stedim BioOutsource

"Providing a total solution for biosimilar characterization and comparability reduces the need for the client to work with multiple subcontracting partners, which makes their process more efficient and cost effective."

—Dr Terry Gray, Field Marketing,
Sartorius Stedim BioOutsource

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"Where possible, we wanted to run short, high-throughput methods without loss of resolution. The speed, reproducibility and robustness of the workflow was very attractive."

—Dr Martin De Cecco, Biochemistry R&D, Sartorius Stedim BioOutsource

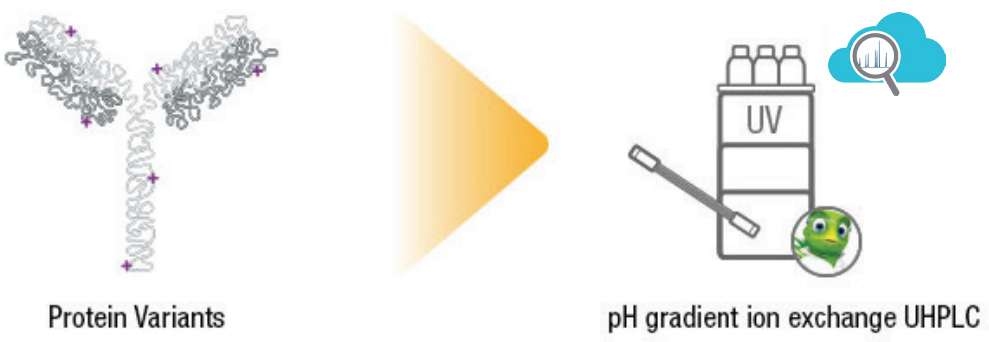
This strategy is clearly manifested in the recent investment by Sartorius Stedim BioOutsource of an innovative, fast and robust charge variant workflow. The Thermo Scientific™ Charge Variant Workflow comprises:

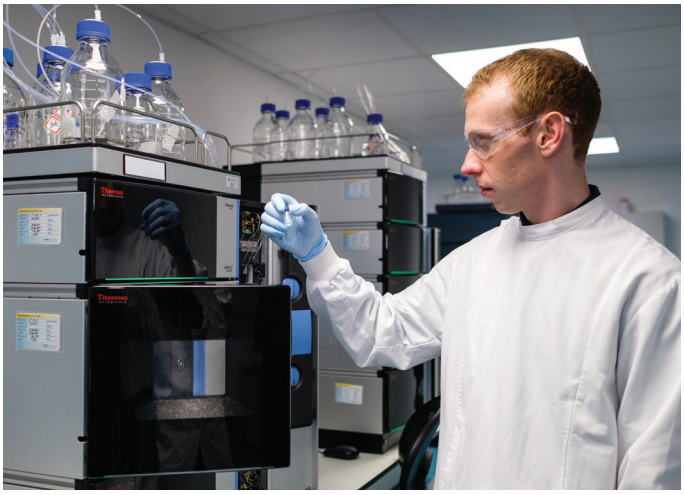
- **Thermo Scientific™ CX-1 pH Gradient Buffer Kits**
- **Thermo Scientific™ MAbPac™ SCX-10 columns**
- **Thermo Scientific™ Vanquish™ Flex UHPLC systems**
- **Thermo Scientific™ Chromeleon™ CDS software**

Charge variants can occur in therapeutic protein products for a number of reasons, including sequence variation, post-translational modification and chemical degradation; for example asparagine and/or glutamine deamidation or C-terminal lysine truncation. Depending on the nature of the modification, the resultant species can be more acidic or more basic than the main peak. As these changes can influence the stability and biological activity of the product, the charge heterogeneity represents a challenge to demonstrating comparability.

For a candidate biosimilar, any differences need to be identified quickly and minimized as early as possible. This would involve further optimization of the cell culture process, or, when related to stability of the drug product, further formulation optimization.

A fast and confident charge variant profiling routine can significantly accelerate candidate development time.





"The CX-1 pH Buffer Kits are really popular with the team in the lab because they are easy to prepare. In a few minutes you are ready to go. Plus we have full traceability from the certified kits."

—Dr Martin De Cecco, Biochemistry R&D, Sartorius Stedim BioOutsource

How does the charge variants workflow save time?

This workflow offered Sartorius Stedim BioOutsource advantages in a several key areas:

1. ***Simple reagent preparation***

- A simple 1 minute CX-1 pH gradient buffer preparation workflow – Saving daily laboratory time.
- Complex preparation routines are eliminated - Saving development time and reducing training.
- Data quality is improved through the use of certified reagent kits – Improving confidence in results.

2. ***Advanced pH gradients & column chemistries***

- Unlike traditional cation exchange chromatography using salt gradients, it is possible to predict the pH and the expected retention of the charge variants and use a narrow pH range to achieve higher resolution separations.
- pH gradient platform methods are applicable to a range of biologics - Saving method development time.
- pH gradients can improve variant separations - Simplifying data evaluation and saving reporting time.
- Unique, patented CX-1 pH Gradient Buffer Kits enable fast and linear pH gradients, giving separation of some commercial biosimilar mAb variants in <5 minutes - Reducing instrument acquisition time and increasing throughput.
- CX-1 pH gradients are robust – Simplifying transfer of methods from R&D into operations for routine use.
- MAbPac SCX-10 provides exceptional resolving power, permitting the separation of monoclonal antibody variants that differ by as little as a single charge – Delivering confident results.

3. ***UHPLC built for biopharma***

- Robust chemistries are paired with Vanquish Flex UHPLC and SmartInject - giving a system with stability and reproducibility over thousands of runs - Saving maintenance and qualification time.
- Vanquish Flex UHPLC has twice the sample capacity of many UHPLC systems – allowing for high throughput workflows.
- Short <5 minute run times allow increased throughput – rapidly delivering return on investment.
- Vanquish Flex UHPLC has a fully biocompatible flow path, for extremely low carryover and SmartInject to provide the ultimate retention time stability and sharper peaks – giving confidence in results and supporting greater throughput.

4. ***Easy access to proven methods***

- Thermo Scientific™ AppsLab Library of Analytical Applications is an on-line method repository stocked with ready to go applications that can be downloaded direct to the instrument as one-click eWorkflows for Chromeleon - Significantly reducing method development time.

5. ***Simple path from sample to knowledge***

- Powerful, intelligent peak detection algorithms for complex chromatograms increase the speed of data (re)processing – Saving manpower and reducing manual intervention.
- Advanced compliance features essential for data integrity – Ensure confidence in results and adhere to the principles of GMP.

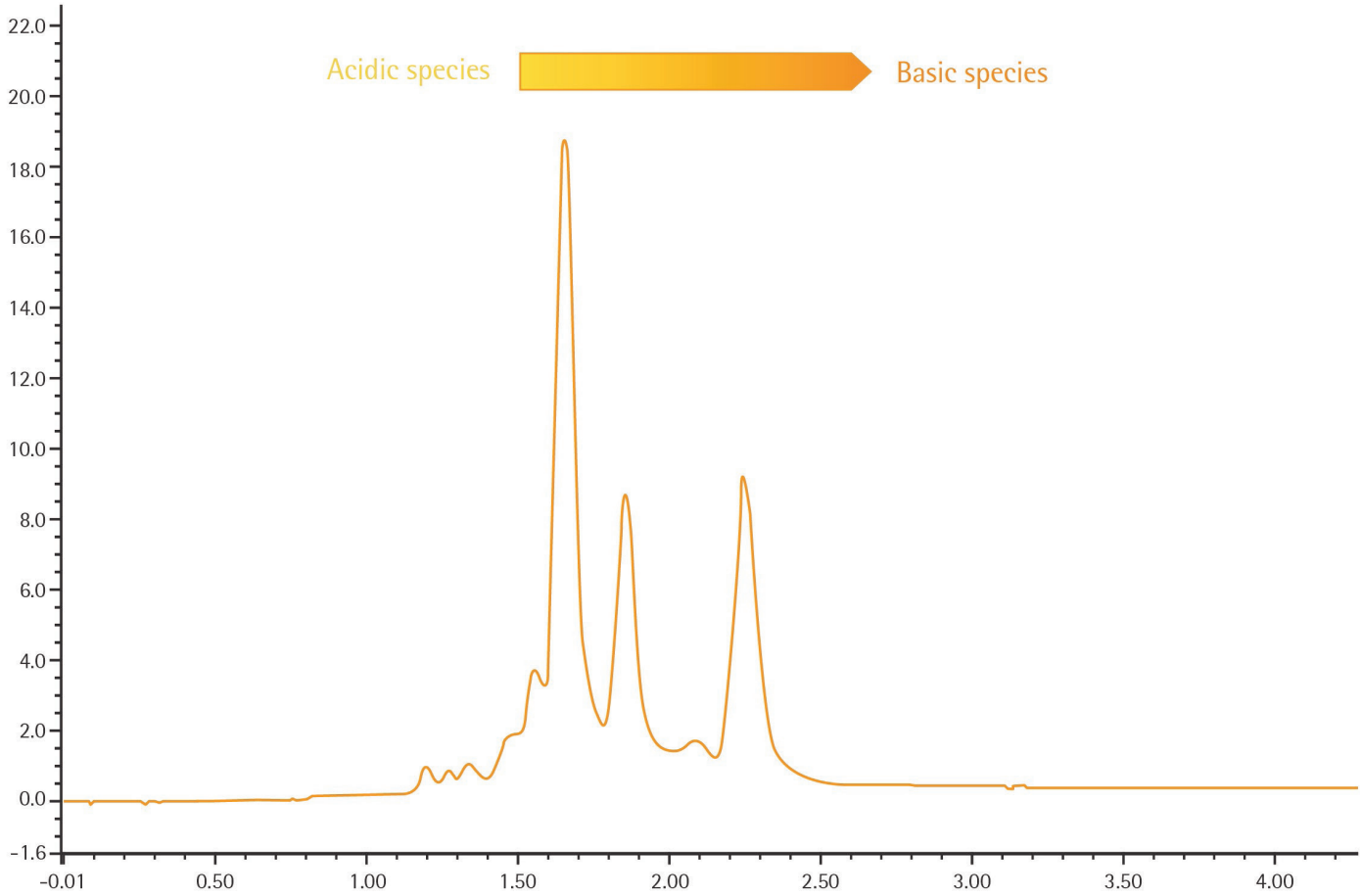


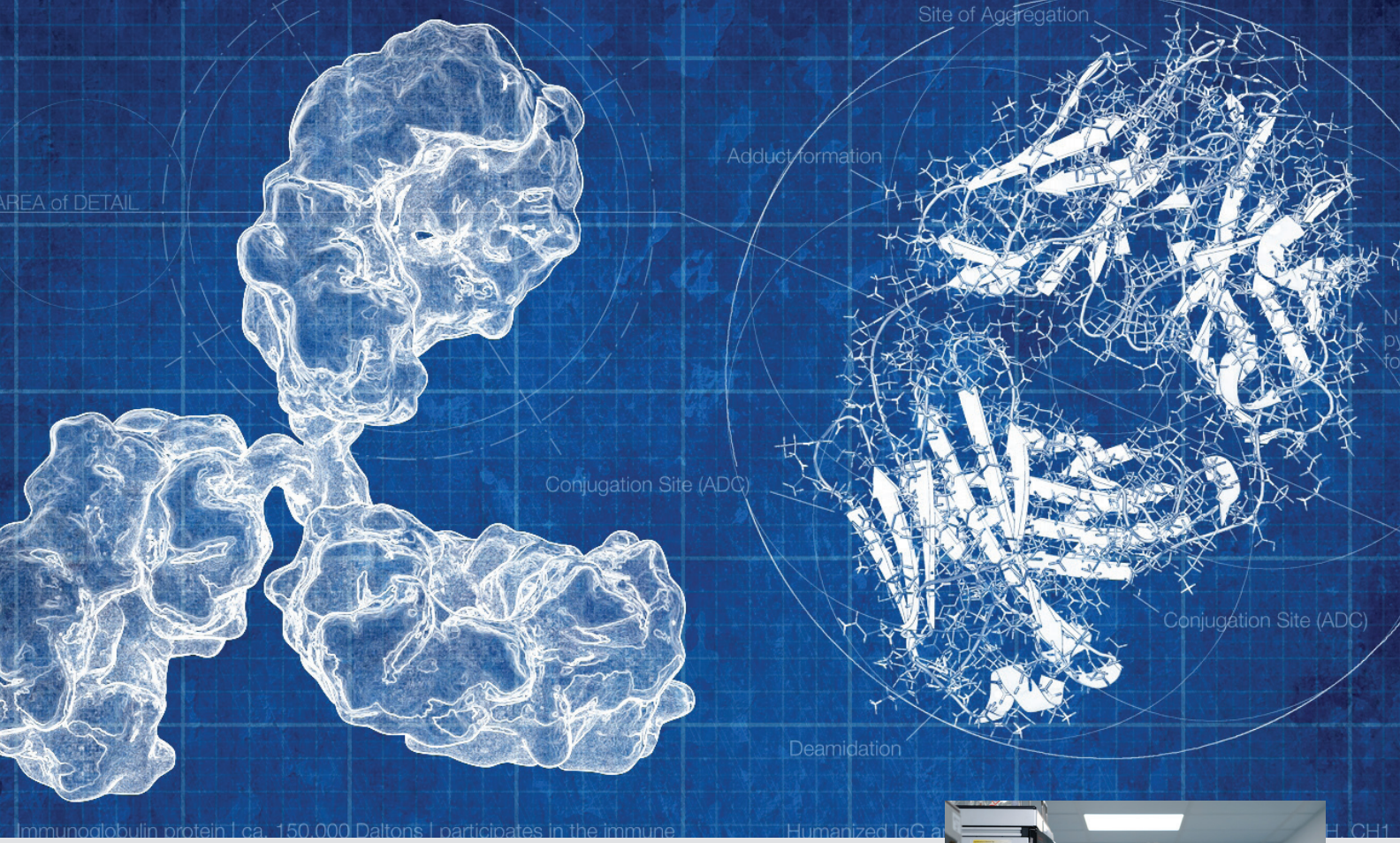
Figure 1 Ultra-fast charge variant profiling of a monoclonal antibody at Sartorius Stedim BioOutsource using the complete Thermo Scientific Charge Variant Workflow

Fast to implement, fast to deliver

The ultra-fast charge variant separations achieved at Sartorius Stedim BioOutsource, Figure 1, are because of several advances in chromatographic techniques. The mechanism of pH gradient chromatography lends itself to the use of shorter, faster columns; the availability of high pressure rated small particle size ion exchange columns are a perfect match to pH gradient methodology; patented buffer formulations form a linear pH gradient which allows intelligent optimization of the platform methods applicable to a range of mAbs; finally, the Vanquish UHPLC system has SmartInject technology, extremely low delay volumes, high precision gradient formation and a fully biocompatible flow path. The entire workflow delivers confidence and speed, from sample to knowledge.

The workflow has enabled Sartorius Stedim BioOutsource to qualify and achieve productivity within a very short timeframe. Moreover, they are able to achieve their exacting strategy of providing fast, confident protein characterization services to their clients.

For more information on services from Sartorius Stedim BioOutsource Ltd. please visit www.biooutsource.com



"The system was installed and qualified in three days, we had training and we were ready to run samples within a week."

—Dr Martin De Cecco, Biochemistry R&D,
Sartorius Stedim BioOutsource

Find out more at **www.thermofisher.com/ChargeVariants**

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