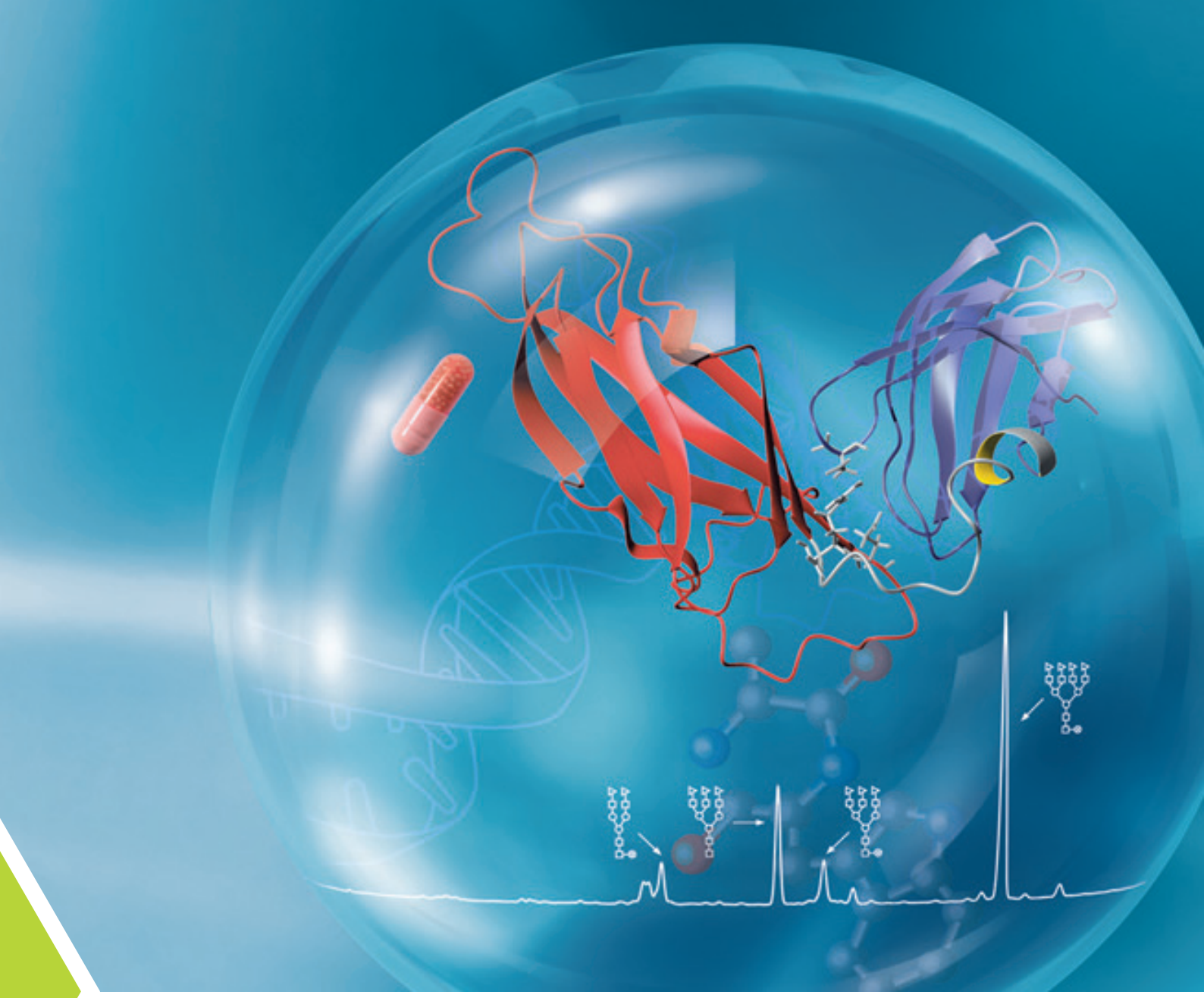


Analysis of Protein Biopharmaceuticals

Solvias provides comprehensive cGMP services for protein-based drugs, to biotechnology and pharmaceutical companies, **at every stage of drug development**

solvias

At Solvias, we work closely with you...

…to design customized programs

Solvias can help you to solve your most complex analytical challenges by providing expert guidance and by designing flexible and customized programs. **Complex projects are coordinated by dedicated professional customer project managers.**

…that meet your needs

Methods destined for use in pharmaceutical release testing are developed with a focus on robustness and reproducibility. The goal of the method development program is to establish a reliable method and carefully describe it in a standard operating procedure (SOP) that can readily be executed at Solvias or transferred to your laboratory of choice. Within the framework of the method development program, critical parameters such as the linearity, reproducibility, and LOQ will be checked to ensure reliable analytical results. A written SOP that includes product specifications is a prerequisite for beginning a method validation program. The method validation program is performed under cGMP according to ICH guidelines and typically includes the following parameters: specificity and selectivity, accuracy and precision, limit of detection (LOD) / limit of quantification (LOQ), linearity and measurement range, robustness, and solution stability.

A milestone-based program can easily be designed and adapted to best fit the needs of your drug development program. All product-specific intellectual property (IP) for methods developed by Solvias is assigned to the customer.

…and are tailored to your drug

The selection of the techniques to be used is based upon the properties of the drug. For example, to establish a stability indicating method, techniques such as CE and HPLC are applied to samples that have been stressed (e.g. temperature). As both are orthogonal methods with different separation processes, they reveal a complementary picture of product-related degradation forms. The optimal method can then be further developed. We preferentially apply quantitative methods, if quantification is desired (e.g. capillary electrophoresis instead of flat bed electrophoresis).

Technology base

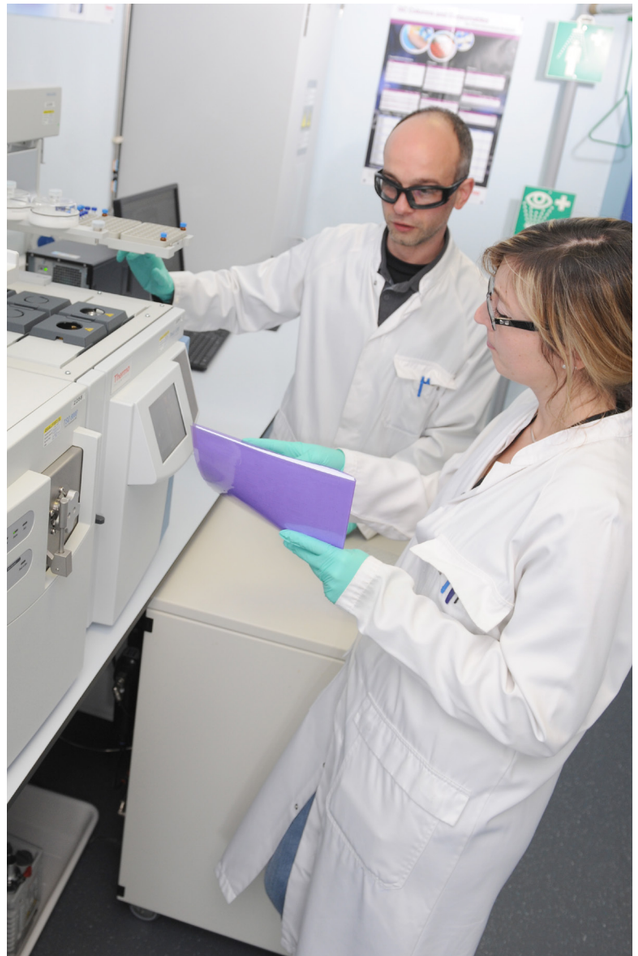
A broad range of capabilities allows Solvias to apply the best solution to your problem

- Capillary electrophoresis (CZE, CE-IEF, CE-SDS; UV and LIF detection)
- Chromatography (HPLC, GC, DC, SEC, IEC; many special detectors)
- Electrophoresis (IEF, SDS-PAGE, native gel; standardized and ready gels)
- Amino acid analysis
- Mass spectrometry (ESI, MALDI-TOF/TOF-MS)
- Western blotting
- ELISA
- Hyphenated techniques (LC-MS)
- Quantitative PCR, threshold system
- Spectroscopy (UV/VIS, CD, fluorescence)
- Analytical ultracentrifugation
- Light scattering (MALS, DLS)
- DNA sequencing (cGMP)

Services

Bioanalytical programs individually tailored to meet your needs

Primary activities
Characterization (for regulatory submission)
Method development and validation (ICH)
QC Release testing (cGMP)
Stability studies (cGMP)
Comparability
Additional services include
Certification, storage and supply of customer-specific reference substances
Analytical support in process validation
Analytical support in formulation development
Extractables and leachables
Analytical troubleshooting
Quality
FDA-inspected
cGMP contract laboratory approved by Swissmedic
ISO 9001-certified QM system



Applications

Complete characterization programs according to ICH Guideline Q6B: comprehensiveness is our strength

Structural characterization
Amino acid sequence
Amino acid composition
Terminal amino acid sequence
Peptide map
Sulfhydryl groups and disulfide bridges
Monosaccharide analysis
Carbohydrate structure
Spectroscopy
Purity
Determination of molecular entities composing the drug substance
Quantity
A_{280}
Quantitative amino acid analysis
Nitrogen determination
Proteinassay (Lowry)
Immunoassay (ELISA)

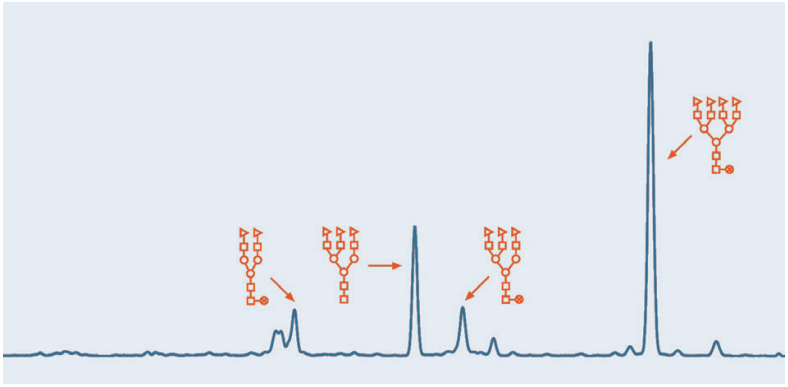
Process-related impurities
Residual solvents
Leachables (e.g. ligands for affinity chromatography)
Cell media components (e.g. growth hormones)
Residual DNA
Residual host cell protein
Detergents
Physicochemical properties
Molecular weight
Molecular size
Isoform pattern
Isoelectric point
Extinction coefficient
Electrophoretic patterns
Liquid chromatographic patterns
Spectral properties
Glycan analysis
PEG analysis

Process-related impurities
Degradation
Aggregation (dimers, higher oligomers and aggregates)
Protein oxidation
Protein deamidation
Disulfide scrambling
Buffer/matrix composition (anion, cation, Tween®)
Residual water (Karl Fischer)
Excipients
All classes of molecules
Contaminants
Microbial contamination
Endotoxin
Virus contamination
Heavy metals

Practical solutions to complex problems

Solvias brings years of pharmaceutical experience to solve the most complex analytical and regulatory challenges

- Peptide mapping by LC-MS
- Disulfide bridging by LC-MS
- Determination of oxidative forms by e.g. LC-MS and LC-UV
- Isoelectric focusing by capillary electrophoresis
- PEG substitution by capillary electrophoresis and mass spectrometry
- Carbohydrate analysis by e.g. HPLC and capillary electrophoresis HPAEC-Dionex, MALDI-TOF/TOF mass spectrometry
- Content determination by amino acid analysis
- Determination of extinction coefficient by amino acid analysis and UV/VIS absorbance
- Quantification of Tween®
- Conformational Analysis by FTIR



We focus on reliable and efficient methods for pharmaceutical release testing

Disulfide Bridging

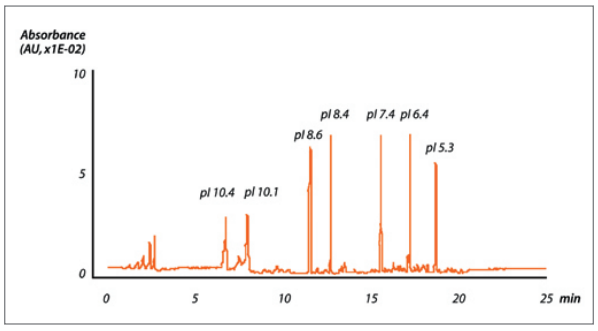
- Enzymatic cleavage of the native protein LC-MS separation and identification of peptide fragments
- Proof of proper folding by presence of species with proper disulfide bridging and absence of improperly bridged fragments
- Reductive alkylation to induce shift of bridged peptides in the chromatogram as a control step

Carbohydrate Analysis in Release Testing

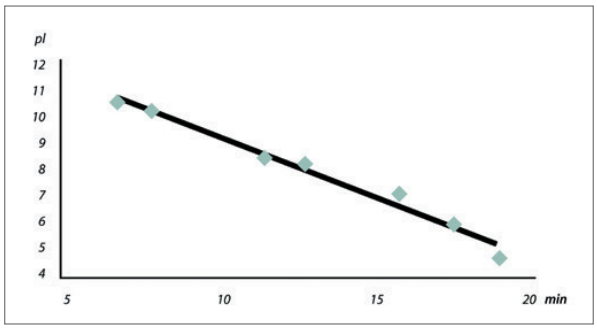
- Sialic acid by HPLC
- Neutral sugars by HPLC
- Glycosylation with and without sialic acid by capillary electrophoresis
- HPAEC-PAD

Biosimilar/Follow-On Biologics

- Comprehensive choice of state-of-the-art methodology
- Experience to ensure successful registration
- Dedicated project management



Separation of protein pI markers by CE-IEF



Plot of the isoelectric point versus migration time obtained by CE-IEF

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Cf. our publication: Application of capillary zone electrophoresis and reversed-phase high-performance liquid chromatography in the biopharmaceutical industry for the quantitative analysis of the monosaccharides released from a highly glycosylated therapeutic protein, K. Racaityté, S. Kiessig and F. Kálmán (Solvias AG): **Journal of Chromatography A, Volume 1079, Issues 1–2, 24 June 2005, pages 354–365.**