BIOSIMILARS

A COMPLETE DEVELOPMENT PLATFORM

FROM ORIGINATOR THROUGH COMPARABILITY TO MARKET

SGS

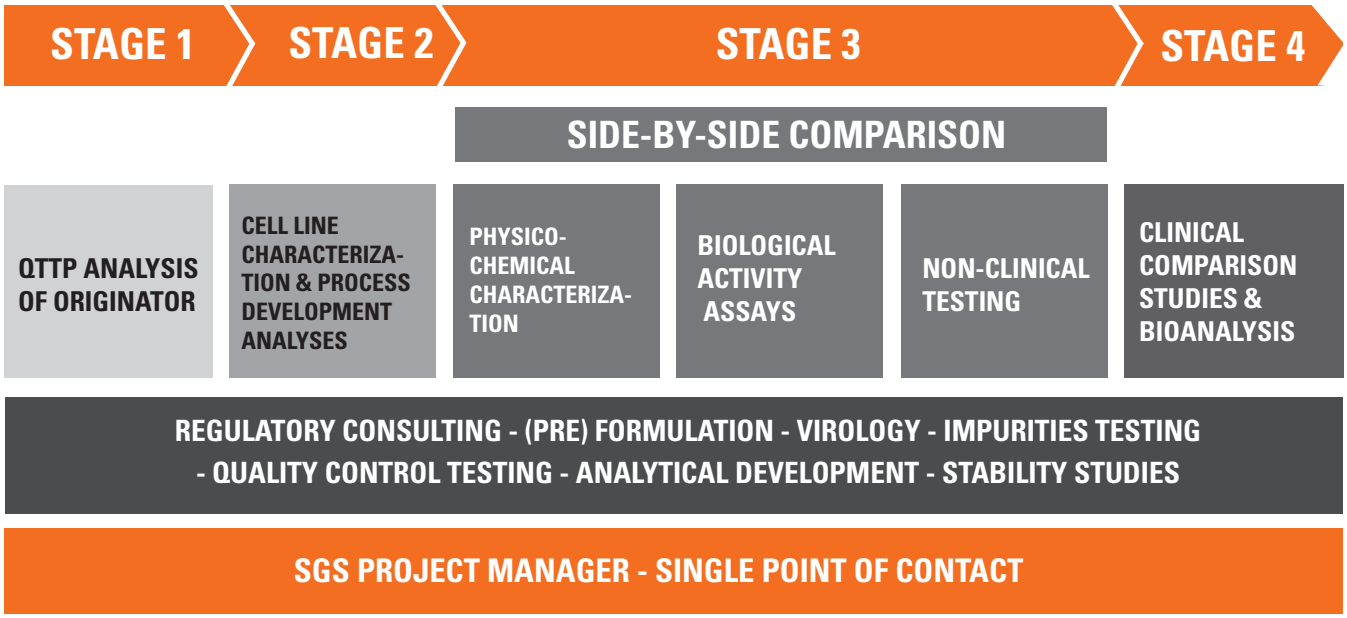
STREAMLINE YOUR R&D, REGULATORY, ANALYTICAL, AND CLINICAL NEEDS WITH ONE PROVIDER

The development pathway of a biosimilar is unlike that of a novel biotherapeutic. While there is an increased requirement for analytics throughout a biosimilar development project, and a Phase II clinical trial is generally omitted, careful consideration must be given to the planning of the other phases of development. Many regulatory authorities reference a "step-by-step" approach to establishing biosimilarity.

Based on many global Health Authorities' requirements/guidelines, SGS's broad service portfolio delivers an integrated Biosimilar Development solution. Clients can move seamlessly through the critical stages of their biosimilar development from product characterization and biosafety testing, to full comparability studies and clinical trials.

SGS is your single source, experienced partner for all of your biosimilar testing requirements.

BIOSIMILAR DEVELOPMENT SOLUTION



OVER 30 YEARS EXPERIENCE IN BIOLOGICS COMPARABILITY ANALYSIS

To meet the growing technical needs of our clients for biopharmaceutical development, SGS has invested in a laboratory network focusing on Centers of Excellence in Biopharmaceutical Services. Clients benefit from these unique SGS locations (in North America, Europe and Asia) which have accumulated specific knowledge and expertise in the biopharmaceutical arena.

Across the network, SGS has experience with originator and biosimilar versions of products including:

- Filgrastim
- Insulin
- Somatropin
- FSH
- Interferons
- FVIII
- EPO
- Fusion proteins
- Antibodies (MAbs)
- Antibody related products such as antibody drug conjugates (ADC)

A key regulatory concept is the "totality-of-the-evidence". SGS can assess information from physicochemical and biological characterization together with non-clinical and clinical pharmacological data to establish biosimilarity. As a result, clients receive expert consultancy to navigate regulatory pathways around the world.

- Over 30 years experience
- Complete service portfolio from Originator sequencing to clinical comparison testing
- Analysis conducted at SGS Centers of Excellence for biopharmaceutical services
- GGLP / cGMP compliant, adhering to ICH Topics Q6B and Q5
- Dedicated project manager
- Experience across all product types
- Clinical Pharmacology Unit located in a favorable regulatory environment (Belgium)

PHYSICOCHEMICAL CHARACTERIZATION AND PRODUCT QUALITY ATTRIBUTES

TO FULFILL REGULATORY REQUIREMENTS

STAGE 1	STAGE 2
ORIGINATOR	**CELL LINE & PROCESS DEVELOPMENT**
• Determination of exact sequence & structure • MS/MS *de-novo* sequencing • Protein/glycoprotein sequencing • Determination of PTMs • Quality target product profile defined	• Chemistry testing of raw materials • Purity, identity & stability – Virus & microbial detection – Pre-MCB screening – MCB, WCB, bulk characterization – EPC – Genetic stability

As the leading pioneer in biosimilar comparability testing, SGS has in-depth expertise in biopharmaceutical characterization using high-end mass spectrometry and cutting edge ancillary biochemical and biophysical techniques such as DSC, CD, DLS, etc.

The first step in development involves the determination of the exact sequence/structure of the originator product. This involves *de novo* MS/MS sequencing with careful interpretation and assignment of levels of post-translational modifications in multiple batches.

Physicochemical and biophysical techniques are also employed to provide an assessment of the higher order structure. At this stage, the Quality Target Product Profile (QTPP) is defined representing the desired specifications for the final product.

Screening continues during cell-line development to select appropriate clones.

These techniques are required again later in the development process, for the head-to-head comparison of the biosimilar against batches of originator. A full analysis package for physicochemical characterization (including aggregate analysis) to GLP/cGMP is available, adhering to ICH Topic Q6B "Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products":

- Structural characterization and confirmation
- Physicochemical properties

Clients benefit from a complete analytical package or individual analyses depending on specific needs including:

- Full mass spectrometry characterization services
- Higher order structure analysis services

STAGE 3
PHYSICOCHEMICAL CHARACTERIZATION
• Primary and higher order structure • ICH Q6B analytical regime • Qualitative and quantitative assessment of quality attributes of multiple batches

Biological molecules are inherently complex and heterogeneous. Demonstrating the comparability of such molecules, while maintaining strict compliance to an ever changing regulatory environment, is a challenge that SGS has successfully met on behalf of its clients for over 30 years.

CELL BANK & BULK HARVEST CHARACTERIZATION

Cell substrates used in the production of biopharmaceuticals may contain endogenous viruses or may become contaminated with adventitious viruses or other agents, including bacteria and mycoplasma, during the manufacturing process.

SGS provides a complete package for characterization of the cGMP manufacturing process for biosimilars including cell banks, raw materials of animal origin, unprocessed/processed bulk harvests, and batches of clinical product.

An extensive array of safety tests are available to demonstrate identity, stability, and purity at each stage of the production process. Complete packages are available for CHO, mouse, human, avian, simian, and insect cell substrate bio-production systems. Master cell bank (MCB), working cell bank (WCB), cells at the limit (CAL) or end of production (EPC), non-purified harvest (BH), purified harvest (PB), E. coli banks, and clinical lot (CL) are tested in accordance with ICH, FDA, EMA, USP/EP guidelines:

- Cell bank identity and genetic stability
- Microbial contaminants
- Adventitious virus detection
- Retrovirus detection
- Impurities and other safety tests

STAGE 2 → **STAGE 3**

CELL LINE & PROCESS DEVELOPMENT	BIOLOGICAL ACTIVITY	PRE-CLINICAL
• Chemistry testing of raw materials • Purity, identity & stability (ICH Q5) – Virus & microbial detection – Pre-MCB screening – MCB, WCB, bulk characterization – EPC – Genetic stability	• Functional/potency: – *In-vitro* assays – Bioassays, ADCC – Cell-based assays – Immunogenicity and biomarkers	• Safety - Immunology - Virology

SGS has developed and validated methods for biosimilar products to comply with current international regulatory requirements.

FROM SCREENING TO PROOF - BIOANALYSIS

Our bioanalytical services for biosimilar development start at Stage 2 for early clone selection, and continue throughout Stage 3 for characterization of biological activity and immunological properties (Q6B). SGS's services are specifically tailored, enabling non-clinical *in vitro* comparability testing, pharmacokinetic (PK) and pharmacodynamic (PD) assessments in animal and human samples, PK/PD modeling studies and immunogenicity screening during clinical studies.

Our regulatory and integrated project management support ensures timely results for strategic decision-making. With our regulatory knowledge and OECD-GLP compliant study management approach, our expertise is available for developing new assays, impleenting/optimizing existing assays, and validation of methods for both innovator and biosimilars according to global regulatory guidelines (e.g., EMA Draft Guideline on Validation of Bioanalytical Methods, FDA Guidance for Industry — Bioanalytical Method Validation) and published recommendations.

STAGE 2-4

BIOANALYSIS
• Method development & validation • PK and PD assessments in animal and human samples • *In vitro* comparability testing • Immunogenicity testing (safety & efficacy applications)

PLATFORMS AND READOUTS

- ELISA, EIA, RIA
- Multiplexing analysis
- Absorbance
- Fluorescence
- Time-resolved fluorescence
- Luminescence
- FACS analysis
- Cell-based assays
- HT chemistry, Immunology & biomarker testing (e.g. Roche Cobas 6000)

POTENCY ASSAYS

Bioassays are used to determine the potency of a biosimilar by comparing the biological response related to its mode of action with that of the comparator product. Our expertise covers a range of biosimilar classes and products such as monoclonal antibodies, anti-viral compounds (interferons), cytokines, growth factors and hormones. Typical assays we support are:

- Antibody-dependent cell cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)
- Apoptosis/programmed cell death (PCD)
- Proliferation testing
- Receptor phosphorylation
- Metabolic activities (e.g. lipogenesis, glucose uptake)
- Receptor binding assays (e.g. Fc receptor assays for mAbs)
- Granulocyte activation

With a proven track record in supporting the development of biological and biomarker testing, our Center of Excellence leads the bioanalytical analysis and assay development within the Life Science Services network, offering a complete suite of bioanalytical services for biosimilars.

FROM SCREENING TO PROOF - CLINICAL TRIALS

- Full service CRO capabilities
- Regulatory expertise
- Fast approval from Health Authorities for clinical trial submissions (2 weeks)
- Large CPU facilities with eSource system for online safety data
- Easy access to patients (multisite trials)
- Global network of clinical monitors
- Comprehensive experience in biologics clinical trials
- GMP pharmacy

SGS's clinical research facilities include eight trial management offices across Europe and the US, as well as a clinical unit located in Antwerp, Belgium with a total of 92 hospitalization beds, which has successfully passed several recent US FDA inspections.

For optimized early phase clinical trials, SGS features sample tracking for safety lab data interfaced with Oracle for PK samples, Full eSource clinic automation (EDC), GMP pharmacy for on-site formulation and a Biosafety Level 2 quarantine facility.

SGS has specific experience performing clinical trials in biosimilars and works to educate principal investigators on the value of conducting biosimilar trials. SGS is able to conduct the complete range of studies required to demonstrate biosimilarity of your molecule, including:

- Comparative PK/PD studies in healthy and target population: dose-response trials, distribution, density, avidity and other characteristics of the indication receptors
- Clinical efficacy in randomized parallel group clinical trials in sensitive populations
- Safety data and risk management program

STAGE 4

CLINICAL COMPARISON

- Early & Late Phase Clinical Trials
- Comparative PK/PD studies in healthy and target populations
- Clinical efficacy in randomized parallel trials in sensitive populations
- Regulatory affairs services

QUALITY CONTROL
FROM DEVELOPMENT TO BATCH RELEASE

STAGE 1 > **STAGE 2** > **STAGE 3** > **STAGE 4**

SGS has been offering high quality analytical testing services to the biotech industry for decades. To support biosimilar manufacturers throughout all stages of development we offer a wide range of quality control testing services, including:

- Method development & validation
- ICH stability storage and studies – accelerated and forced-degradation
- Analytical chemistry, impurities analysis, purification and characterization of degradants
- Microbiology
- Virology
- Raw materials testing
- Evaluation and control of the expression system
- Container testing (extractables & leachables)
- (Pre) Formulation

SGS's cGMP facilities are located in many of our network laboratories in the US, Canada, Belgium, France, Germany, Switzerland, the UK, India, China, and Singapore.

ABOUT SGS

SGS Life Science Services is a leading, global contract service organization providing analytical development, biologics characterization, biosafety and quality control testing, as well as clinical research services. With 19 laboratories across Europe, North America and Asia, SGS represents the broadest global network of contract analytical and bioanalytical laboratories. In addition to laboratory testing services for the bio/pharmaceutical market, SGS also provides Phase I-IV clinical trial management services encompassing clinical pharmacology studies, data management, PK/PD modeling & simulation services, pharmacovigilance and regulatory consultancy.

VISIT SGS.COM/BIOSIMILARS

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WHEN YOU NEED TO BE SURE

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