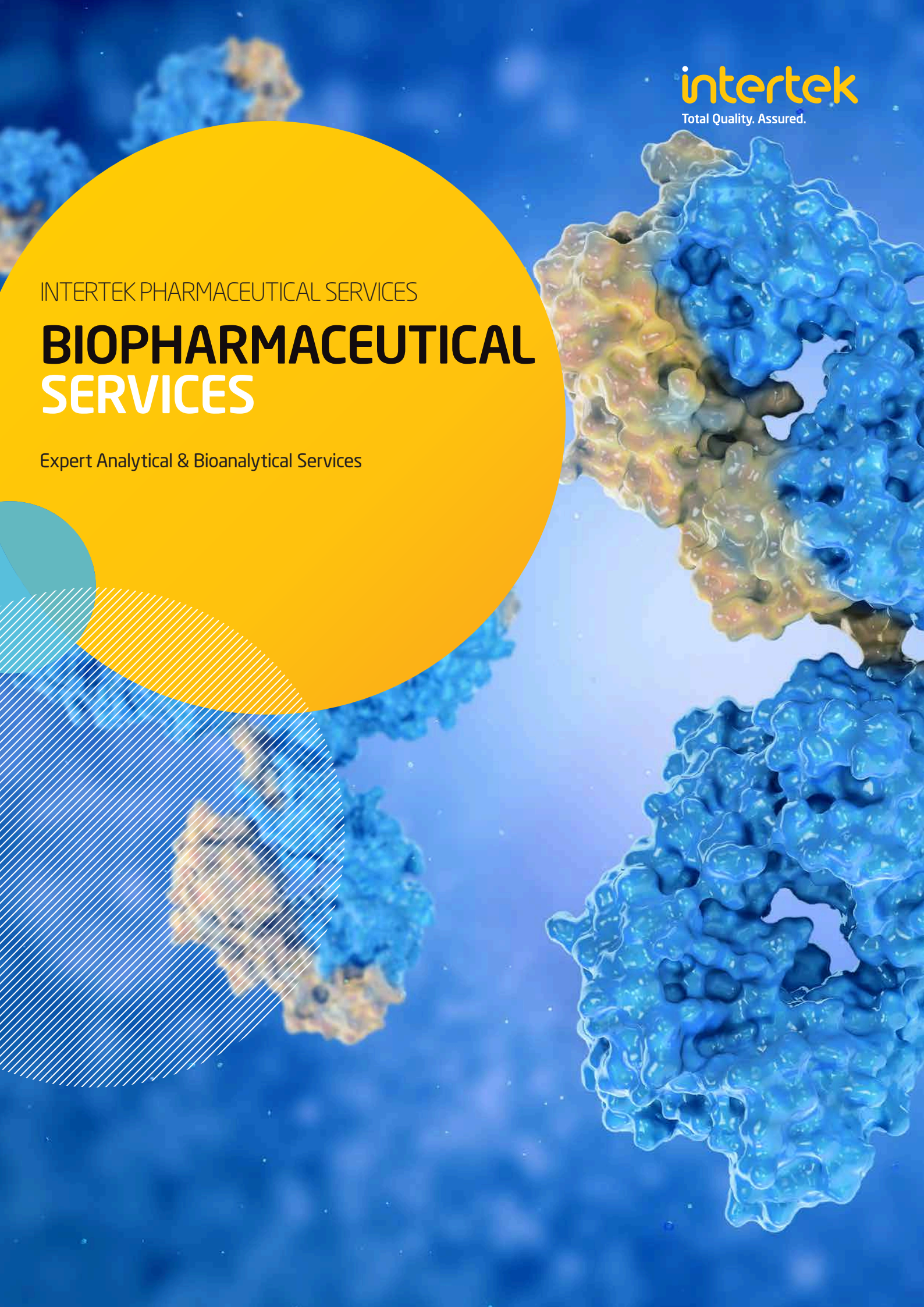


intertek
Total Quality. Assured.

INTERTEK PHARMACEUTICAL SERVICES

BIOPHARMACEUTICAL SERVICES

Expert Analytical & Bioanalytical Services

Our Biopharmaceutical Expertise

To meet your development milestones and comply with regulatory requirements, you will need high quality bioanalytical and analytical data to aid informed decision-making and identify sources of risk. Safety assessment is key, as slight changes in the structure, physicochemical properties, stability and impurity profile of a biologic can provoke an adverse immune response.

Our thought-leaders have over 25 years of experience in biopharmaceutical development support across a wide range of product types. We provide regulatory-led, phase-appropriate, tailored analytical program design with GLP / GCP / GMP compliant laboratory services which help you to navigate the challenges of development, regulatory submission, and manufacturing.

With facilities located in India, Europe (UK, France, Switzerland) and the USA, our strong scientific and technical leadership coupled with project management and regulatory support, deliver a responsive, flexible (bio)analytical resource, to drive your development and manufacturing programs forward.

Our biopharmaceutical services

- GLP Clinical & Preclinical Bioanalysis (PK, ADA, Nab)
- Immunogenicity Studies
- Analytical Programme Design
- Structural Characterisation (ICH Q6B)
- Physicochemical Properties (ICH Q6B)
- Biophysical Characterisation
- Comparability Studies
- Biosimilar Programmes
- Process Residuals Determination
- Product Related Impurities Determination
- Purity and Impurity Assessment
- GMP Potency / Cell Based Assays
- Method Development & Validation
- Extractables / Leachables
- GMP Quality Control Testing
- GMP Batch & Final Product Release Testing
- ICH Stability Studies
- Forced Degradation Studies
- Drug Delivery / OINDP Expertise

Our experience

- Recombinant Proteins & Glycoproteins
- Monoclonal Antibodies
- Antibody-Drug Conjugates
- Biosimilars / Biobetters
- Peptides
- Growth Factors
- Interferons
- Interleukins
- Vaccines
- Viral Vectors
- Oligonucleotide Therapeutics

Protein Characterisation

To achieve a well-characterised biologic, we apply a strategic analytical program that is tailored to your molecule.

Protein therapeutics can present significant analytical challenges. Our characterisation packages are tailored to your biomolecule and reflect the requirements of ICH Guidelines to meet the analytical challenges of a 'well characterized' or 'specified' biological product.

Programs encompass many different analytical techniques and provide information ranging from evaluation of physicochemical properties and structural features including primary, secondary and higher order structure and assessment of post-translational modifications. Programs also include determination of biological potency and assessment of purity /impurity profiles. We continually invest in advanced analytical instrumentation which allows us to deliver data with the highest sensitivity, accuracy and resolution.

Structural Characterisation	
Amino Acid Sequencing/ Peptide Mapping:	Sequencing studies and peptide mapping using a broad range of enzymatic or chemical digestion followed by Mass Spectrometry (LC-MS/MS or MALDI-TOF MS).
Amino acid composition:	Pharmacopeia methods.
Terminal amino acid sequence:	Confirmation of N- and C-terminal sequences and evaluation of modifications and / or heterogeneity.
Disulphide bridge mapping:	Assessment of the degree and positions of both expected and mis-matched disulphide bridges by extended LC-MS/MS study and colorimetric test for free sulfhydryl groups.
Carbohydrate structure:	Glycosylation studies typically including levels of monosaccharides and sialic acid, N/O linked glycan profiling (NPLC, HILIC, IEX or CE-LIF), enzymatic digest and MALDI –TOF or LC-MS/MS.
Physico-chemical Properties	
Molecular weight:	Molecular weight of intact proteins by MALDI-MS, ESI-MS and LC-MS supported by orthogonal techniques such as MALLS and SDS-PAGE.
Isoform pattern:	Isoform and impurity studies using PAGE, SDS-PAGE, IEF, CE, HPLC.
Extinction coefficient:	Determination and Validated Extinction Coefficient studies.
LC patterns:	For ID, homogeneity, purity – HPLC, UPLC, SEC, RP HPLC, IEX, AEX.
Spectroscopic patterns:	CD, FTIR, 1D & 2D NMR, Fluorescence, UV-Visible.
Electrophoretic patterns:	CE(CZE), cIEF, CGE, SDS and NATIVE PAGE, Western Blot.
Concentration:	Lowry, BCA, Total AA, Total Nitrogen, Bradford.
Aggregation studies:	SEC (MALLS), DLS, Western Blot, CE, Gel Electrophoresis, SEM/TEM.
Process Impurities:	Residual host cell DNA by qPCR, Residuals (such as antibiotics, antifoaming agents).
Potency Assays	
Cell-based Assays:	To support characterisation, stability, comparability testing and product release, for example, Complement-dependent cytotoxicity (CDC), Antibody–dependent cell cytotoxicity (ADCC) and Neutralisation and Proliferation Assays.

We apply our bioanalytical expertise and industry insight to design strategic and efficient bioanalytical programs

Bioanalytical Expertise

Large molecule bioanalysis

We have extensive experience in the development, validation, and sample analysis of quantitative and qualitative Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) immunochemistry and LC-MSMS expertise in support of pre-clinical and clinical development programs in full regulatory compliance (FDA, EMA and OECD GLP regulatory standards).

Our bioanalytical experts are highly experienced in developing and validating assays for pharmacokinetic (PK), toxicokinetic (TK), pharmacodynamic (PD), immunogenicity, efficacy and safety biomarker studies with diverse immunochemistry technologies, radioimmunochemistry (RIA) and functional assay platforms.

We offer comprehensive bioanalytical services to support complex products including proteins, synthetic peptides, humanized monoclonal antibodies, antibody drug conjugates, conjugated drugs, growth factors, hormones and cytokines. Additionally, we offer industry unique capabilities, for example, quantitative, high resolution NMR which is an ideal tool for bioanalysis of PEGylated moieties.

Biomarker assays

We deliver discovery and clinical biomarker solutions to support your precision medicine strategy enabling you to better predict the long-term safety and efficacy of your products. Our dedicated biomarker team has expertise in the qualification and validation of biomarkers using ELISA, and ECL platforms (including multiplexing, prototypes and custom multiplexing and Luminex) in multiple matrices and anticoagulants.

- Quantitative Ligand Binding Assay Capabilities
- Quantitative ELISAs for Proprietary Compounds
- Immunogenicity Studies
- Neutralization Cell-based Assay Development, Validation and Sample Analysis
- Radioimmunoassays (RIA), Enzymatic Assays
- Fluorometric Assays, Luminescence Assays
- Biotinylations & Ruthenium Labeling
- Mode of Action Studies
- Bioanalytical LC-MS/MS for Biologics
- Affinity Interactions by SPR
- NMR approaches for PEGylated Biomolecules
- Biomarker Assays

CASE STUDY

Novel Approaches for An Enzyme Activity Assay

A client desired an activity assay for a PEGylated enzyme for which a commercial colorimetric assay was available. The colorimetric assay did not meet the performance criteria for regulated work. An immunoassay was then developed but was subject to significant matrix effects.

Our Solution

Development of a replacement assay was complicated by endogenous substrate and enzymatic product. To overcome this, the specificity of LC-MS/MS was employed and an activity assay developed using a stable labeled substrate which produced a labeled product, which could be differentiated from the endogenous analyte.

Benefit Delivered to our Client

A enzymatic activity LC-MS/MS assay was developed and successfully validated to regulatory standards. The method was used in multiple pharmacokinetic studies and enabled the client to move forward with their drug development program.

Specialist Expertise

Biosimilar services

Our biosimilar thought leaders apply a strategic approach to developing biosimilarity data with programs that provide highly relevant early stage characterisation and late stage comparative data. These programs begin with extensive structural and functional characterization of both the proposed biosimilar product and the reference product and evaluate and compare all pertinent features of the biosimilar product and are based on the criteria outlined in ICH Q6B. This analytical characterization serves as the foundation of a biosimilar development program. Programs encompass many different analytical techniques and provide information ranging from evaluation of physiochemical properties and structural features including primary, secondary and higher order structure and assessment of post-translational modifications and cell-based assays to determination of biological potency with the goal to show that the molecule is structurally and functionally highly similar to a reference product and so is anticipated to behave like the reference product.

Monoclonal antibodies

Our experience spans recombinant monoclonal antibodies and related products such as biosimilars, fusion proteins, Fab-fragments and Fc fragments and antibody drug conjugates (ADCs) throughout the product lifecycle with a focus on monitoring relevant critical quality attributes (CQAs), assessment of the impact of process changes on physicochemical properties and structure, the presence of product-related impurities or process-related impurities.

- Characterisation (Q6B)
- Primary Sequence Confirmation (Peptide Map)
- N/C terminal Sequence, Disulphide Bridge Mapping and PTMs
- Carbohydrate Structure
- Aggregation Studies
- Higher Order Structural Studies
- Aggregation Studies
- Heterogeneity, Purity and Variants
- Potency

Protein Analytics

Post Translational Modifications (PTM)

We apply our knowledge of anticipated PTM and potential PTMs based on your product's specific structural characteristics to design strategic analytical programs that meet the requirements of regulatory expectations and industry guidance such as ICH Q6B. Using enzyme or chemical digestion coupled with highly sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) and a range of chromatographic techniques we can detect and identify a range of PTMs.

- Deamidation
- Glycosylation
- Phosphorylation
- Acetylation
- Alkylation
- Sulfation
- Glycylation
- Methylation
- Oxidation
- Mis-matched S-S bridges
- Truncation
- N/C-terminal Modifications

Biophysical characterisation

Our biophysical characterisation team applies a wide range of techniques such as to interrogate the biophysical behavior of your molecule. We examine product's higher-order structure (HOS), including secondary and tertiary structure using Circular Dichroism (CD), FTIR, Fluorescence, 1D / 2D High field 600MHz NMR studies (NOESY & TOCSY), aggregation (using SEC-MALS, DLS, SV-AUC), oligomerization and degradation of the drug substance. To support formulation development we study proteins in the buffer and in the presence of additives / excipients of interest. To support IND or NDA submissions we assess spectroscopic, thermodynamic and hydrodynamic properties.

Potency assays

Potency bioassays are an integral part of release and stability testing. Intertek's experienced specialists perform cell based potency and ligand binding assays which can be performed to GMP for regulatory submissions or as a non-regulatory study under high quality standards.

Glycosylation

Glycosylation studies are designed to be product specific, however, these typically include determination of the levels of neutral and amino monosaccharides as well as sialic acids, assessment of glycoform distribution and glycan structure elucidation. Multiple technologies are applied to the determination including selective enzymatic cleavage and MALDI-TOF Mass spectrometry HPLC, HILIC, IEX or CE-LIF, to provide the level of structural information required.

Product related impurities determination

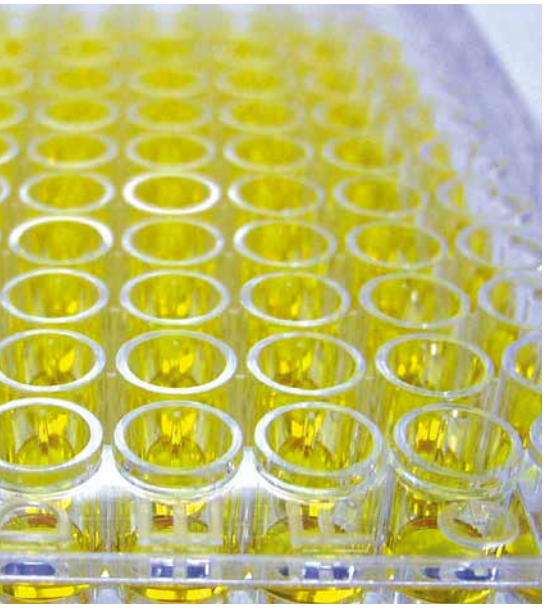
Our scientists perform detailed characterization using a diverse range of technologies which include chromatographic, electrophoretic, mass spectrometry (MALDI-MS, LC-MSMS) and spectroscopic (IR, NMR and fluorescence approaches) to determine truncated forms and other modified forms such as deamidated, isomerised, mismatched S-S linked, oxidised or altered conjugated forms (e.g., glycosylation, phosphorylation). For truncated forms, we use an enzyme or chemical cleavage of peptide followed by characterisation by chromatography (e.g. HPLC) or SDS-PAGE approaches. We also perform peptide mapping to yield useful information about the variant.

Process residuals determination

Our process residual analysis services apply a range of highly specific and sensitive techniques to residual cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or chromatographic media used in purification, solvents and buffer components to offer robust quantification supporting process validation, monitor the batch to batch variation and support GMP lot release. For trace antibiotics such as Kanamycin, Tobramycin, Gentamycin, Amoxicillin, Chloramphenicol, we apply highly selective approaches such as tandem mass spectrometry (LC-MS/MS) with Multiple Reaction Monitoring (MRM). We also apply MS techniques to the determination of surfactants and antifoams agents which typically include Triton-X, Tween 20, Tween 80, Pluronics and polyglycol P2000.

- Kanamycin
- Tobramycin
- Gentamycin
- Amoxicillin
- Chloramphenicol
- Methotrexate
- Glutathione
- Dithiothreitol
- IPTG
- Triton-X
- Tween
- Pluronics
- Polyglycol P2000
- Trace metals
- Downstream-derived impurities
- Leachables from process equipment
- Particulates

Development Support



ICH stability testing

With dedicated ICH storage stability facilities that are integrated with advanced analytical capabilities, we can offer stability-indicating method development and validation alongside efficient stability programs that focus on the critical quality attributes OF your molecule.

Comparability studies

The FDA and EMEA require demonstration of comparability compliant with ICH Q6B and Q5E guidelines. Intertek has undertaken many detailed comparability studies since 1999. There is a regulatory expectation that "orthogonal" approaches are applied such that conclusions for key quality attributes are based on multiple approaches.

QC release testing

Important for both bulk lots and finished products, our suite of release tests includes assays for concentration, purity and quality testing. Release tests can be developed and validated in-house, transferred from clients or include Pharmacopeia Monograph testing.

Formulation development

Formulation of biopharmaceuticals for inhaled or nasal delivery allows for a more convenient method of administering compounds systemically, and also allows direct targeting of the respiratory system, however, this brings new challenges. Our experts integrate formulation with tailored analytics that focuses on the impact of formulation on the safety and efficacy of the drug whilst monitoring aggregation, fragmentation, deamidation, hydrolysis, oxidation, isomerisation, succinimidation, deglycosylation, disulphide bond formation/ breakage and other crosslinking reactions.

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