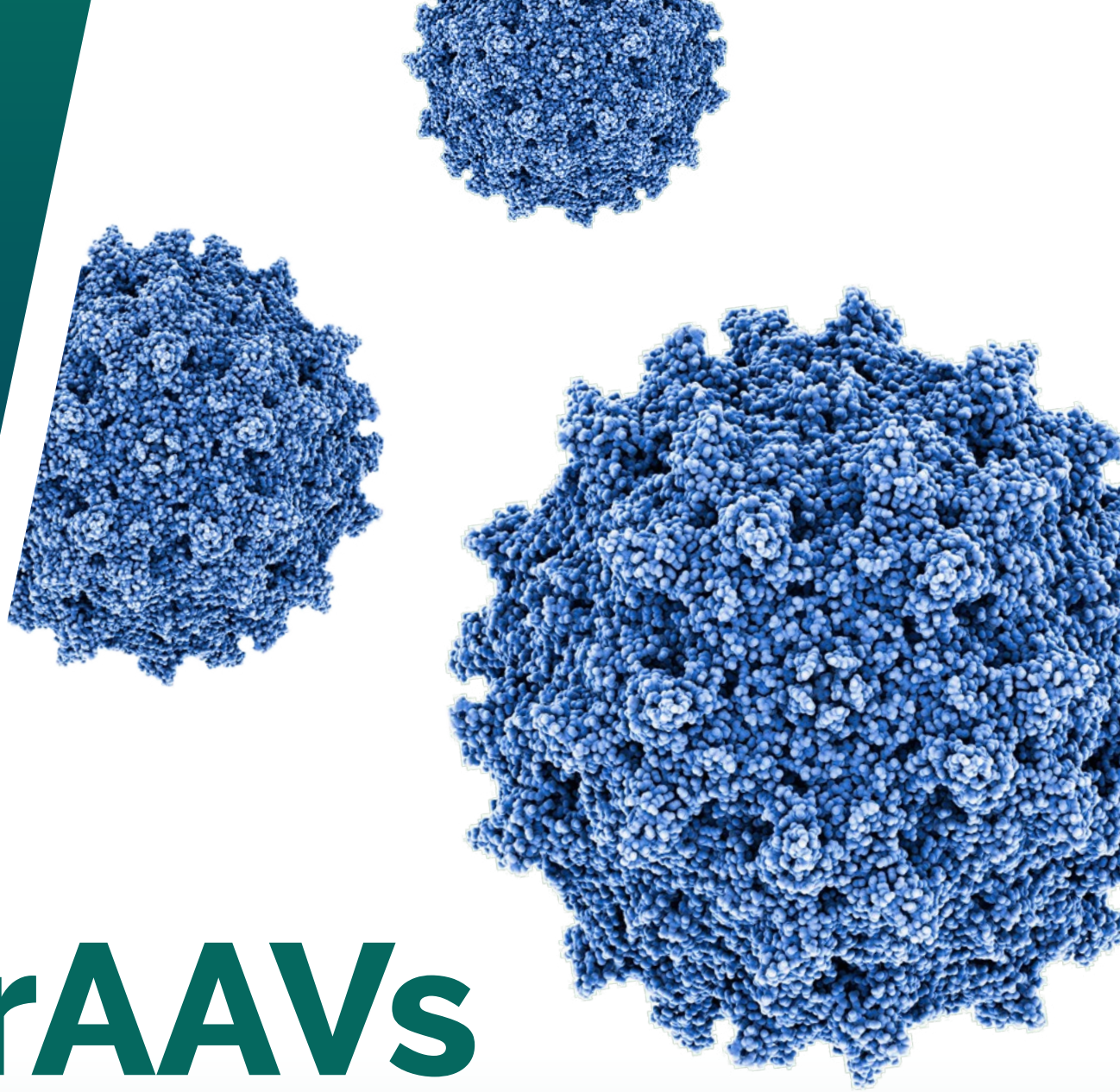
QUALITY ASSISTANCE
Contract Research Organisation

Analytical services



rAAVs

Recombinant Adeno-Associated Viral Vectors

Recombinant Adeno-Associated Viral Vectors

Due to their complex structure and size, as well as a constantly evolving regulatory landscape, the physico-chemical and biological characterisation of viral vector-based products is challenging.

With extensive experience in the analysis of innovative products and thanks to a continuous investment in new technologies and machinery, *Quality Assistance* can assist you in the development of your recombinant Adeno-Associated Viral Vectors (rAAVs) products from early phases to commercialisation.

	NON-CLINICAL		CLINICAL		POST-REGISTRATION
DEVELOPMENT, VALIDATION & APPLICATION OF ANALYTICAL METHODS					
GMP	DS/DP characterisation				
GMP	Preliminary stability studies	Forced degradation studies		Photostability	(In-use) Stability studies
GMP	DS/DP batch analysis (release testing)				
GLP	PK/TK sample analysis Formulation/buffer analysis		GCLP	PK sample analysis Biomarker analysis	
G(C)LP	Immunogenicity				

GENERAL PROPERTIES	Appearance	
	pH, osmolarity	
	Water content / residual moisture (if lyophilised)	KF titration (volumetric, coulometric, oven)
	Particulate matter	Optical microscopy / Light obscuration / Imaging Particle Analysis
	Microbiology	Bioburden / Sterility (filtration, direct inoculation)
	Bacterial endotoxins and Pyrogens	LAL / MAT / rFC
	Extractable volume	
MANU-FACTURING RESIDUALS	Residual solvents	HS-GC (FID, MS)
	Elemental impurities	ICP (OES, MS)
	Residual salts	HPAEC (conductimetry) / ICP (OES, MS)
	Residual HCP	Immunoassays (ELISA, Gyrolab, Octet (BLI), Biacore (SPR)) / UPLC (MS-MS) / 2D-Gel / 2D-DIGE
	Residual DNA	qPCR / ddPCR / PicoGreen / Electrophoresis (agarose)
	Residual RNA	RiboGreen / Electrophoresis (agarose)
	Residual benzonase	Immunoassays (ELISA, Gyrolab, Octet (BLI), Biacore (SPR))
	Process contaminants (CsCl, iodixanol, antifoam, Triton X100, Tween, PEI,etc.)	GC (FID, MS) / ICP (OES, MS) / (U)HPLC (UV, CAD, MS, ELSD)
PACKAGING	Container Closure System Integrity	Bubbling / Dye ingress / Microbial ingress
	Leachables	GC (FID, ECD, MS) / ICP (OES, MS) / (U)HPLC (UV, ELSD, CAD, MS)
	Cytotoxicity / Biological reactivity	Cell-based assays / USP <87>
POTENCY	Cell based assay	Different readouts

IDENTITY	Genome sequencing	NGS
	Genome identity	PCR / restriction enzyme mapping
	Viral vector	(U)HPLC (MS) / Immunoassays (ELISA, Gyrolab, Octet (BLI), Biacore (SPR)) / SDS-PAGE
PURITY / INTEGRITY	Viral vector aggregates	SEC-(U)HPLC(UV, RI, MALS) / AF4 (UV, RI, MALS) / DLS / Imaging Particle Analysis
	Replication competent viral vectors	Infectivity assay (qPCR)
	Full / Empty capsids	CGE / Anion Exchange Chromatography (UV) / SEC-(U)HPLC (UV, RI, MALS) / SoloVPE
	Genome integrity	NGS, CGE, (U)HPLC/UV, ddPCR, qPCR
	Protein degradation products / modifications	(U)HPLC-MS
QUANTITY	Infectious vector titre	qPCR / ddPCR
	Vector particle concentration	qPCR / ddPCR / AEX / UV spectroscopy
	Total protein	BCA / Lowry / Bradford / UV / (U)HPLC (UV)
	Capsid concentration	Immunoassays (ELISA, Gyrolab, Octet (BLI), Biacore (SPR)) / MA-DLS
EXCIPIENTS	Assay / impurities	GC (FID, ECD, MS) / ICP (OES, MS) / (U)HPLC (UV, ELSD, CAD, MS)

Analytical services

Analytical development and robustness assessment

- **Method development**
  from scratch or optimisation of existing methods according to analytical Quality by Design (AQbD)
- **Method qualification**
  in accordance with protocols adapted to the development stage
- **Method validation**
  according to protocols compliant with ICH, FDA and EMA requirements
- **Method transfer**
  from or to your laboratory, in accordance with customised protocols including analyst training if needed
- **SOPs and development, transfer, qualification, and validation reports**
  adapted to your needs
- **Statistical analysis of validation results**
  including total error concept

Stability studies

Protocol design and optimisation

Identification of degradation products and unknown impurities

Stability studies

- Preliminary assessment and short-term studies
- Following ICH guidelines
- Forced degradation studies
- Photostability (under controlled conditions)

Storage

- Climatic chambers (including 7 walk-in models), refrigerators, freezers including ultra-low temperature, liquid nitrogen vapour phase
- All ICH conditions available
- Customised conditions for specific requests

ICH CONDITIONS
- 20°C ± 5°C
5°C ± 3°C
25°C ± 2°C/40±5% RH
25°C ± 2°C/60±5% RH
30°C ± 2°C/35±5% RH
30°C ± 2°C/65±5% RH
30°C ± 2°C/75±5% RH
40°C ± 2°C/≤ 25% RH
40°C ± 2°C/75±5% RH

OTHER CONDITIONS
- 30°C ± 5°C
- 5° C ± 2° C
15°C ± 2°C
20°C ± 2°C
22.5±2.5°C/1000 lux ±400 lux
30°C/<40% RH
50°C/<40% RH
60°C/<40% RH

ULTRA-LOW CONDITIONS
Vapour phase nitrogen (-135°C)
- 70°C ± 10°C
≤ - 70°C
- 60°C ± 10°C

References:
- *ICH Q1A(R2): Stability Testing of New Drug Substances and Products*
- *ICH Q1B: Stability Testing : Photostability Testing of New Drug Substances and Products*
- *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology*
- *ICH Q5C: Stability Testing of Biotechnological/Biological Products*
- *ICH Q6B: Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

Batch testing (release testing)

Customised testing following methods transferred to our laboratories or developed and validated by *Quality Assistance*

Compendial testing in accordance with Ph. Eur., USP-NF and JP

Bioassays expertise (cell-based and binding assays)

Retained samples

- Back-up storage facilities for your retained samples, an integral part of your disaster recovery programme

OOS-OOT procedure compliant with FDA requirements (Full scale investigation)

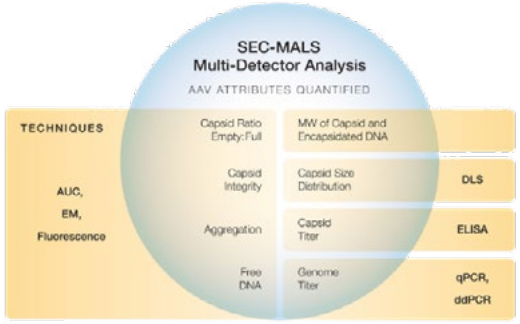
Certificate of analysis approved by a Qualified Person

Bioanalytical services

Thanks to a complete analytical platform and sound experience, *Quality Assistance* can provide you with all the requested methods to characterise the PK and immunogenicity of the product.

Characterisation studies

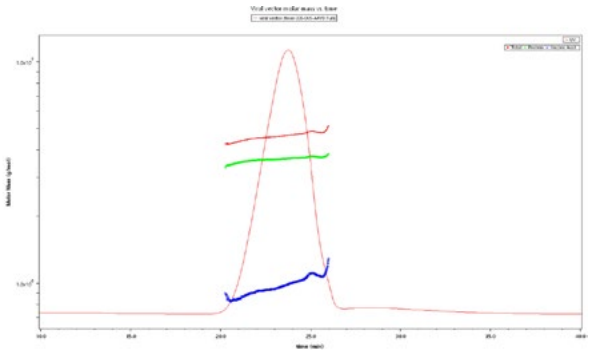
A full characterisation of a rAAV-based products usually requires the use of several analytical techniques and consequently a large amount of sample. Due to the cost of sample, clients often ask to reduce as much as possible the quantity used for quality control purposes. Therefore, **the use of Multi-Attribute Monitoring (MAM) analytical methods is a solution that can help to spare expensive samples.**



Quality Assistance has implemented a SEC-UV/RI/MALS analytical workflow on our **Wyatt Technology system (Dawn®, Optilab®)** that can measure the following **critical quality attributes in a single run using a reduced volume of sample:**

- Total particle concentration
- Genome titre
- Aggregates content
- Empty / Full ration
- Capsid molar mass (Mw)
- Genome molar mass (Mw)
- Capsid size and distribution
- Capsid integrity
- Impurities

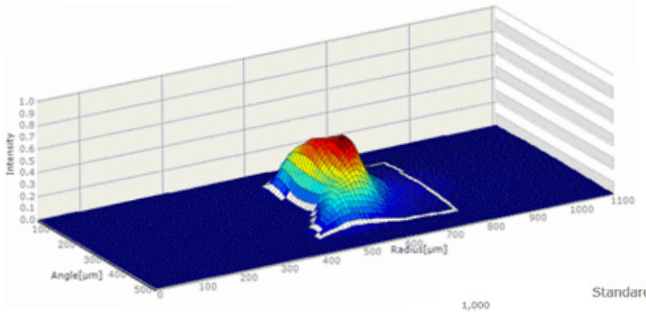
In case of larger aggregates, the AF4 **(ECLIPSE® from Wyatt Technology)** can be used instead of SEC to monitor the same critical quality attributes.

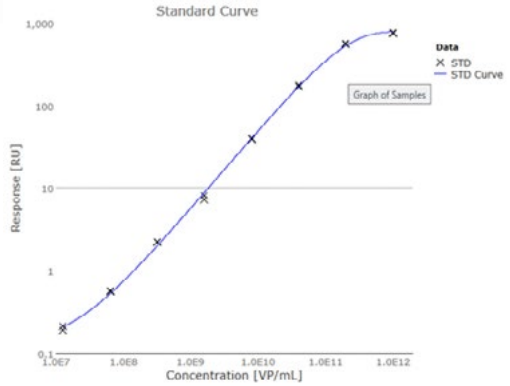


Immunoassays

Analysis of viral vectors requires **the use of immunoassays, either for the determination of residual host cell proteins or for identification and quantification of the viral capsid itself.**

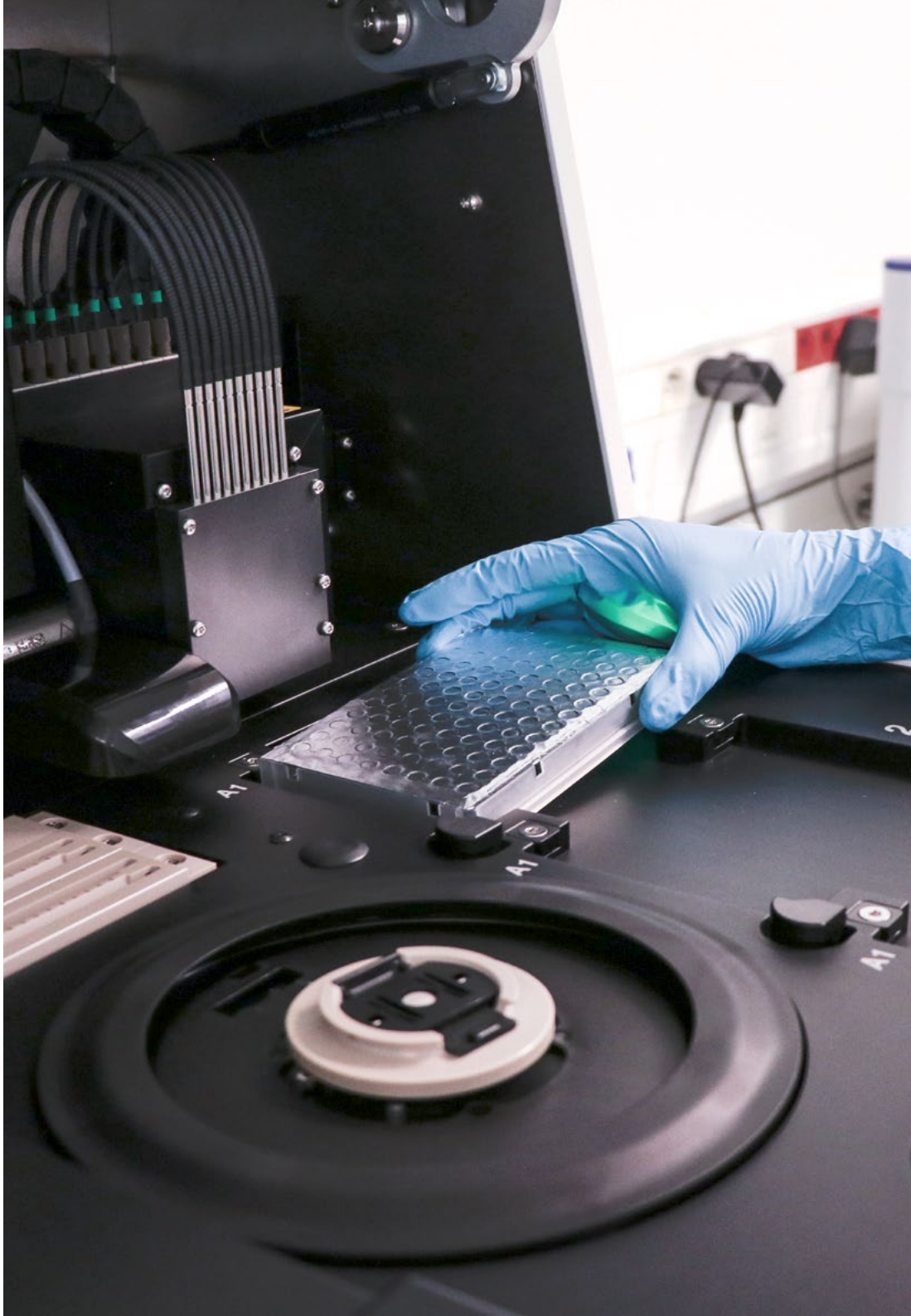
Quality Assistance recently installed the **Gyrolab xPlore™ (Gyros Protein Technologies)**, an automated immunoassay solution that provides increased data quality and reduced hands-on time. Thanks to this technology, methods are implemented for AAV capsid quantification and for residual HEK293 determination.





In addition to Gyrolab xPlore™, depending on application and client request, *Quality Assistance* can **offer several other technologies:**

- ELISA using Spectramax M5e or i3 from Molecular Device
- AlphaLISA using Envision from Perkin Elmer
- SPR using Biacore T200 from Cytiva
- BLI using Octet from Sartorius




FORTÉBIO
octet RED96e

Droplet Digital PCR (ddPCR)

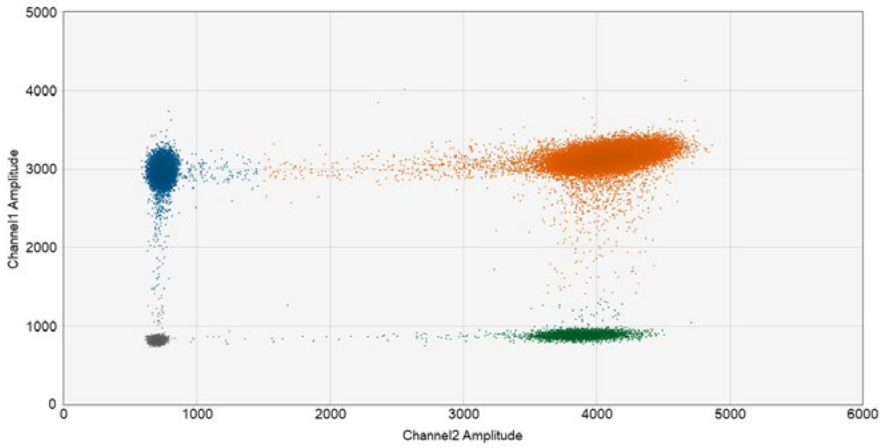
Another important aspect of the control of viral vectors is linked to the **genomic part of the vector.**

For this purpose, we offer ddPCR analysis using the **QX200™ droplet digital PCR system (Bio-Rad). ddPCR provides absolute quantification of the target genome without the use of standard curves.**

Compared to standard qPCR, also available at *Quality Assistance*, this equipment provides a more precise and sensitive solution for a **wider range of applications**, such as:

- Detection of residual DNA,
- Determination of the viral vector genome integrity
- Quantification of viral vector particles
- Quantification of viral load
- Distinction of genomic variations
- Gene expression studies

Determination of genome concentration (AAV x eGFP) by ddPCR



European leader in analytical sciences

Quality Assistance is a leading European **Contract Research Organisation** providing the pharmaceutical industry with **all the analytical services** required by **EMA and FDA** regulations for the development and marketing of **innovative human medicinal products.**

- **Biotherapeutics, monoclonal antibodies, antibody-drug conjugates**
- **New Chemical Entities, peptides, oligonucleotides**
- **mRNA**
- **Viral vectors**
- **Vaccines**
- **Cell-Based Medicinal Products**
- **Nanomedicines**

Located in Belgium, *Quality Assistance* has all of its laboratories centralised on one site, counts 250 highly qualified employees and more than 40 years' expertise at the forefront of analytical sciences.

Using our state-of-the-art, product-dedicated expertise in analytical sciences, we assist our clients from candidate selection, through non-clinical and clinical studies, to marketing authorisation.

In order to evaluate the Quality, Safety and Efficacy of the given drugs for each client project, we design customised solutions, define analytical protocols, as well as develop and validate specific new analytical methods.

In addition, we perform characterisation, stability, pharmacokinetic, biomarker and immunogenicity studies, and batch release testing.

Our environment is GMP, GLP, GCLP/GCP compliant.

Your one-stop shop on one site

All laboratories on one site

All services compliant with EMA and FDA regulations

Product-dedicated expertise

Extensive experience in developing and validating analytical methods

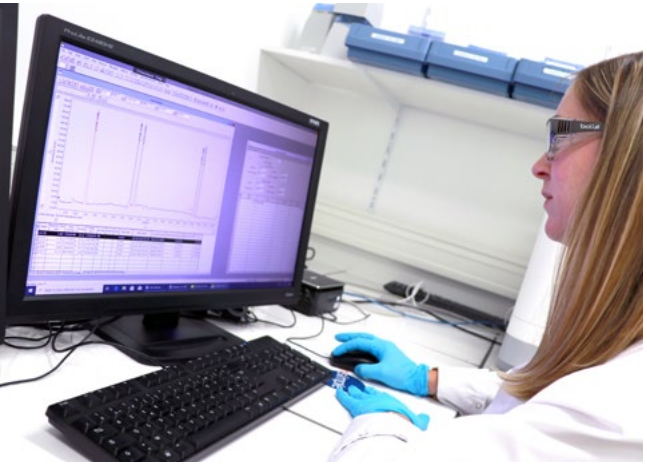
GMP, GLP and GCLP/GCP compliance: reliable and quality partner

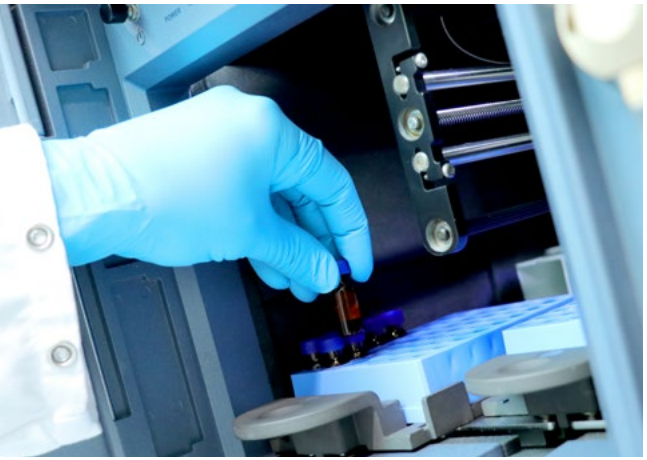
One step ahead with full command of the regulatory landscape (e.g. EMA, FDA, ICH, OECD, GAMP) and scientific and technical monitoring

A LIMS developed in-house to ensure a complete traceability of your project

A unique Point of Contact for your project management

Strong financial health and long-term viability





Key Account Manager

Administrative & commercial questions

- Request receipt
- Budget evaluation
- Proposal transmission
- Invoicing
- Satisfaction survey
- Client follow-up

Technical Point of Contact

Scientific & technical questions

- Scientific discussion and writing of Technical Agreement
- Protocol and description of analytical work
- Planning and respect of deadlines
- Technical supervision and follow-up
- Regular client communication
- Reporting

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