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Quotient Sciences

Molecule to cure. Fast.™

# Bioanalytical services to accelerate drug development

## Introduction

Delivering rapid bioanalytical data is critical to drug development. From drug discovery, through to preclinical and clinical studies, understanding drug exposure and behavior are imperative to dose selection, and accelerating drugs to clinic and commercialization. Through the use of robust bioanalytical techniques, biological samples can be processed and analyzed to identify and quantify compounds of interest, such as small molecules and their metabolites, as well as peptides, proteins, nucleic acids and other analytes.

At Quotient, we are experts in the development, validation, and application of bioanalytical assays. Our dedicated team of bioanalytical chemists are globally recognized and have more than 40 years' experience in supporting all stages of drug development, from early preclinical through to First-in-Human (FIH), and onwards to Phase II and III patient studies. We help our customers gain a clear understanding of the fate of their drug in the body, whether it is in a preclinical model, healthy volunteer, or patient.

Combining our development and validation experience of over 400 bioanalytical assays, along with our integrated service lines, we can ensure that critical decision-making data are rapidly processed, robust and reliable.

**Developing methods for your molecules: Sensitivity, specificity, and speed**

When developing and validating bioanalytical methods, a number of aspects should be considered, including:

- Selecting the right biological medium to analyze, e.g. whole blood or plasma;
- Appropriate method(s) of detection, e.g. LC-MS, GC-MS, ICP-MS etc., to detect the molecule(s) of interest;
- Optimization of the extraction process and parameters to ensure that the bioanalytical data provides an accurate representation of the amount of drug or metabolite in the sample;
- Determining a suitable reference standard (similar to the analyte in terms of structure and properties) which can be used to produce calibration and quality control standards, ensuring the quality and accuracy of the results;
- Limits of detection and quantification (LOD and LOQ), and the dynamic range;
- Precision, sensitivity and specificity.

Typically, bioanalytical methods are developed to support the first preclinical pharmacokinetic studies and optimized for maximum tolerated dose (MTD) and dose range finding (DRF) studies. All bioanalytical assay methods must be fully validated according to EMA and/or FDA guidelines[1,2] before GLP tox studies commence. Prior to this, Scientific Validation (SV), which has wider acceptance criteria, can be used to give an indication of exposure.

At Quotient, we can develop and validate bioanalytical methods for multiple types of biological media including blood, plasma, serum, urine and a broad range of tissues. Our highly sensitive mass spectrometry (MS) based instruments allow us to measure drug levels at very low concentrations (typically a LLOQ of 1 ng/mL, or less), thus enabling us to measure the fate in the body over a longer elimination phase. In addition, our range of UPLC equipment allows high throughput sample analysis and rapid data generation.

Our goal is to develop bioanalytical methods using very small volumes of biological medium (ideally 50 µl aliquot, or less). This allows us to support the '3Rs' (Replace, Reduce, Refine) initiative.

## Bioanalysis throughout drug development

Measuring drug exposure in biological systems is fundamental to drug development, to determine pharmacokinetics (PK) and pharmacodynamics (PD), and to understand ADME (Absorption, Distribution, Metabolism and Excretion), toxicity and efficacy. The resulting bioanalytical data are required to not only support clinical trial applications but, ultimately, drug approval.

In drug development, time is always of the essence, so we have streamlined our method development lead times to 4-6 weeks. In our GLP and GCP accredited facilities, we provide comprehensive bioanalytical support to studies throughout drug development including preclinical PK, toxicokinetic (TK), dose escalation and selection studies, as well as clinical bioavailability, bioequivalence, pharmacodynamics and multi-centre Phase II and III studies. Table 1 summarizes the studies supported by Quotient's bioanalytical services throughout drug development.

**Table 1:** Summary of the studies supported by Quotient's bioanalytical services throughout drug development.

| Development phase | Studies supported |
|---|---|
| Preclinical | › Drug metabolism and pharmacokinetics (DMPK)<br>› Preclinical pharmacology<br>› Toxicokinetics, including GLP tox studies<br>› Dose escalation and selection |
| Phase I | › First-in-human (single and multiple ascending dose)<br>› Relative bioavailability and pharmacokinetics<br>› Clinical pharmacology<br>› Drug-Drug-Interaction (DDI)<br>› Bioequivalence<br>› 14C ADME and mass balance<br>› Pharmacodynamics, metabolites and biomarkers analysis |
| Phases II & III | › Multi-center global trials<br>› Relative bioavailability and pharmacokinetics<br>› Pharmacodynamics, metabolites and biomarker analysis |

### Integrated Toxicokinetics (TK) and Pharmacokinetics (PK)

Toxicokinetic and pharmacokinetic analysis helps to provide a dose related assessment of the absorption and distribution of a molecule, how it is metabolized in the body, and excreted. Our industry leading experts offer PK and TK data analysis and reporting, supporting both preclinical and clinical studies. By integrating bioanalysis with TK and PK analysis, we accelerate the delivery of data and improve decision making, reducing the risk of downstream delays.

### Dose selection and prediction

It is imperative to be able to accurately predict the behavior of your drug in vivo before it enters clinical trials to mitigate against any unexpected outcomes.

Prediction of a drug's exposure in humans is made using information obtained from in vitro experiments (e.g. metabolic stability, permeability, protein binding, blood plasma ratio and other physicochemical properties) along with PK information from preclinical studies (e.g. bioavailability, clearance, volume of distribution and routes of excretion).

Typically, a model or correlation is built which demonstrates that in vivo performance in the preclinical species is understood and predictable. Learnings from these preclinical species' predictions are applied to a human model, which can then be used to predict human performance with greater confidence.

At Quotient, we have extensive experience with FIH predictions using physiologically-based »

pharmacokinetic (PBPK) modelling, and can also perform predictions using traditional empirical methodology such as compartmental PK modelling, allometry and in vitro to in vivo extrapolations. PBPK has the advantage of being able to make predictions in more complex scenarios, for example food effects on drug exposure, changes in formulation, or where patients have raised gastric pH, potentially as a result of medications such as proton pump inhibitors.

Using these predictions, our pharmacokineticists routinely help customers to select the appropriate dose for a successful clinical study.

**Modifying methods through development**

Drug exposure in vivo can differ from predictions and may change in preclinical and clinical studies. Where exposure is higher, bioanalytical samples can be diluted into the validated dynamic range. However, if the dynamic range is no longer appropriate, the method must be revalidated. Timelines are highly dependent on the magnitude of revalidation required, as well as the type of molecule, and can take between 2 days to 4 weeks.

**Bioanalysis kit and capabilities**

There is a wide range of methods and technologies that can be used for sample extraction and detection, depending on the type, size and concentration range of the analyte of interest. Highly sensitive and sophisticated techniques, such as liquid chromatography (LC) combined with tandem mass spectrometry (MS/MS), are typically the methods of choice. Hybrid technologies using LC and gas chromatography (GC) or time of flight (TOF) applications can also be used for the detection and quantification of volatile analytes, or for structural identification.

Table 2 below gives an overview of the breadth and depth of Quotient's bioanalytical instrumentation capabilities and their applications. Our high-resolution instruments can improve the validity and quantity of the data that drug developers require. With our cutting-edge mass spectrometry platforms, we can identify and quantify analytes to determine if, and how, your drug is metabolized in the body.

**Table 2:** Overview of Quotient's bioanalytical instrumentation and applications

| Instrumentation | Applications |
|---|---|
| ICP-MS and ICP-MS/MS | Elemental analysis |
| Xevo UPLC-MS/MS | › Small molecule NCE analysis<br>› Peptide, small protein and NBE analysis<br>› Highly sensitive, LLOQ <1ng/mL<br>› High throughput |
| Quantum and Vantage UPLC-MS/MS | › Small molecule NCE analysis<br>› Sensitive, LLOQ ~1 ng/mL<br>› High throughput |
| GC-MS and GC-MS/MS | Detection and analysis of volatile analytes for NCEs and biomarkers |
| QTOF | › Structural identification for NCEs<br>› Peptide and protein identification<br>› NBE analysis |
| LC-ICP-MS | Elemental speciation |
| LC-HR-MS | High resolution structural identification |
| LC-TRAP-MS and LC-TOF-MS | High resolution molecule analysis, quantification and structural identification |

**Streamlining study analysis**
Developing, validating and implementing robust bioanalytical processes can be resource and data intensive. It is important to ensure that the specialist knowledge and expertise are readily available to troubleshoot all the complexities and demands of a bioanalytical program, ensuring project continuity and timely delivery of high-quality output.

Implementing a single project manager for each customer study allows us to efficiently align bioanalysis with the corresponding preclinical or clinical study and accelerate the availability of data, meaning that we can turn around bioanalytical data in as little as 3 days. We generate interim and final bioanalysis reports to meet the timelines of our customers and in a format that is compliant with regulatory filing documentation.

As well as supporting preclinical and clinical studies performed at third party vendors, we provide integrated bioanalysis for FIH studies conducted at Quotient, further streamlining clinical evaluation timelines.

**Secure sample and data management**
The use of highly sophisticated bioanalytical techniques generates large amounts of data which are critical for development and regulatory approval. It is, therefore, vital to ensure that secure systems are in place to store, organize and manage bioanalytical samples and corresponding data, while continuously safeguarding quality and integrity.

At Quotient, we ensure the chain of integrity is maintained from bedside to bench. Our fully integrated chain of custody uses 1D and 2D barcode accession to enable sample security and traceability. We have full Data Sciences capabilities in-house and provide data in CDISC formats, SEND for non-clinical datasets and SDTM for clinical bioanalytical data, to meet the needs of our customers and align with regulatory requirements.

Case study

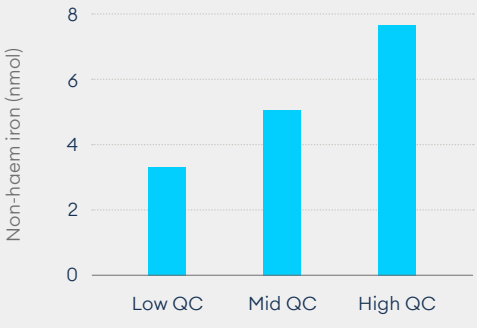
## Biochemical assay optimisation, validation & application

**Background**
A UK specialty-pharma company required a bioanalytical assay for its regulatory non-clinical safety study.

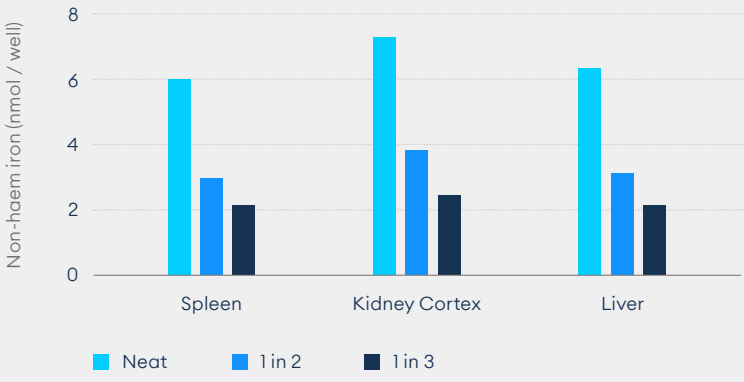
**Project scope**
The customer required the development and validation of a bioanalytical assay to measure non-haem iron in tissues. This would subsequently support one of the pivotal objectives for a regulatory non-clinical safety study.

**Output and impact**
Procedures for tissue extraction of non-haem iron were optimized and partnered with a colorimetric assay. Following validation, the assay was used to support a non-clinical study: non-haem iron was detected and quantified in all tissues (liver, kidney and spleen) and exhibited a dose-response. The data supported the aims of the study and proved the utility of a non-haem iron assay in a GLP setting.

**Non-haem iron inter-assay precision and accuracy**




**Non-haem iron in tissue**



Case study

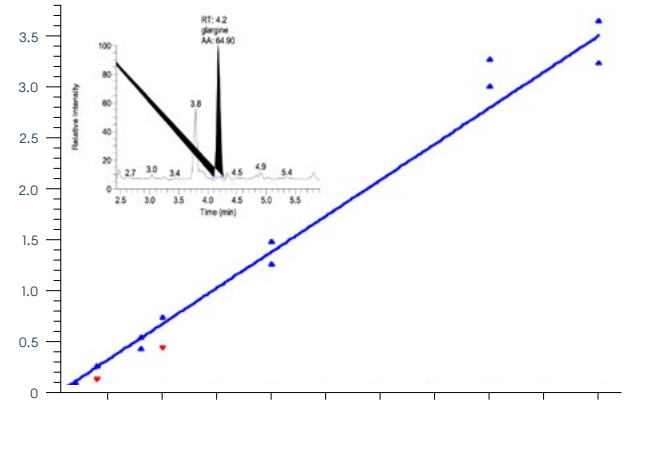
# Analysis of insulin analogues

**Background**
A European biotech company, developing an NCE to fulfill an unmet patient need, required insulin analogue analysis to gain regulatory approval.

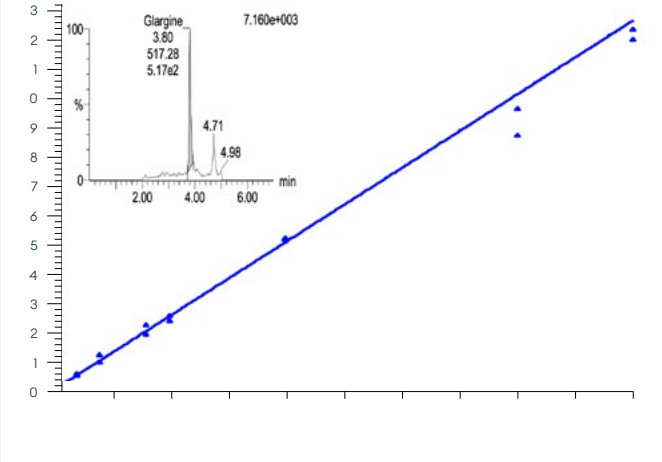
**Project scope**
Pivotal clinical studies require precise measurement of multiple insulin analogues from a small volume of plasma. The existing methodologies enabled successful proof of concept and non-regulated PK studies to be completed, but did not meet the precision necessary for regulatory acceptance.

**Output and impact**
A new mass spectrometer was purchased, installed and verified for insulin analogue analysis within 4 months, meeting the customer's timeline for a key clinical trial. All clinical samples were analyzed and provided key endpoint data for the study.

**Old system: 2 points excluded $r^2 = 0.98$**




**New system: 0 points excluded $r^2 = 0.99$**




## Summary

Highly sensitive bioanalytical techniques enable the identification and quantification of analytes such as small molecules, peptides, proteins, nucleic acids and metabolites, all from very small volumes of biological samples.

Delivering rapid bioanalytical data is critical to meeting milestones in drug development. From drug discovery through to preclinical and clinical studies, understanding drug exposure, safety and metabolism are essential in accelerating drugs to clinic and commercialization.

At Quotient, we are experts in the development, validation, and application of bioanalytical assays. Our industry-leading bioanalytical team has more than 40 years' experience in supporting all stages of drug development, from early preclinical through to FIH, and onwards to Phase II and III patient studies.

We pride ourselves on our relationships with customers, and the speed with which we report our bioanalytical data. Over the past 5 years, we have supported bioanalysis projects for almost 100 customers globally, ranging from virtual companies and biotech to mid-sized and large Pharma. To date, we have developed and validated more than 400 bioanalytical methods.

Contact us to discuss how we can help you gain a clear understanding of the biological fate of your molecules and accelerate your development programs.


**References**

1. Bioanalytical Method Validation. Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration. May 2018. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

2. Guideline on bioanalytical method validation. European Medicines Agency. 21 July 2011. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf

## About Quotient Sciences

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, molecules need to become cures, fast. Because humanity needs solutions, fast.

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