BIOANALYSIS COMPETENCE SHEET
(LC)-ICP-MS in Drug Development

(LC)-ICP-MS for elemental analysis in drug development studies. Fully GLP compliant laboratory. Assay validation according to FDA, EMA and ICH guidelines.

(LC)-ICP-MS at QPS

▶ ICP-MS detects elements instead of molecules. With the exception of a few elements (such as C, H, N, O and the noble gasses), all 'pharmaceutical-important' elements can be detected. A specific element serves as a tag for the molecule of interest, thus enabling quantitation of the drug molecule in a particular matrix. The technique is highly linear and can be used quantitatively for a broad concentration range. Sample processing is relatively straightforward and high throughput, resulting in fast turnaround times (Fig. 1).

▶ ICP-MS measure total and free concentration. Typical applications are pharmacokinetic, pharmacodynamic, toxicology, mass balance, imagining, and metabolite profiling. Furthermore, ICP-MS is frequently used for limit testing of elements, trace elemental analysis, and formulation analysis (Fig. 2 and Fig. 5).

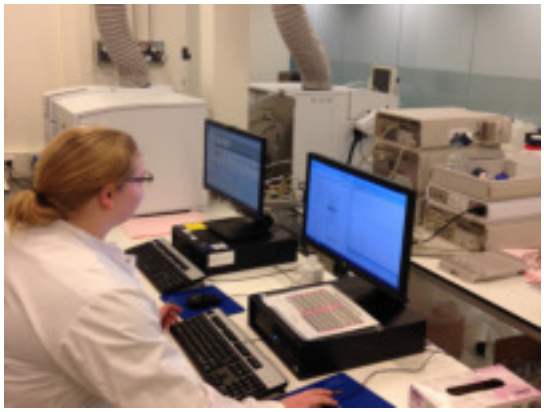

Fig. 1. Two of the three LC-ICP-MS Agilent systems at the QPS lab

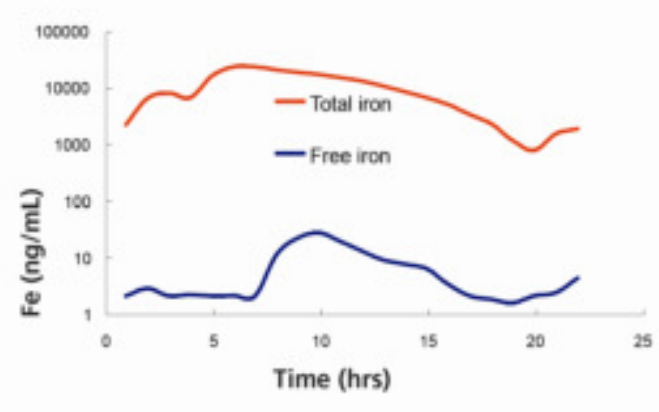

Fig. 2. Human serum PK curves of total (protein bound + free) and free iron concentrations after dosage of an iron sucrose compound for screening purposes. Free iron was obtained using ultra-filtration (10 kDa) prior to quantitation by ICP-MS.

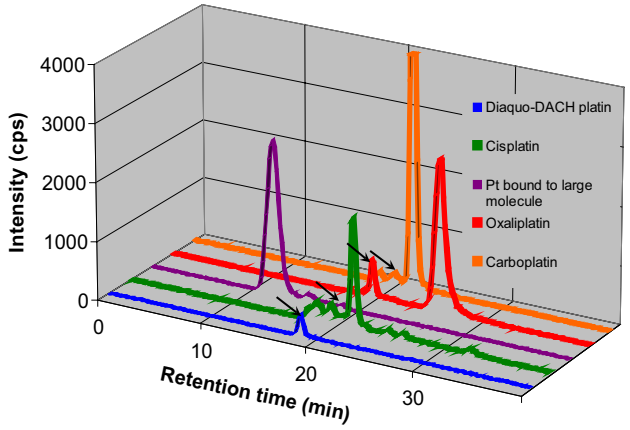

Fig. 3. Chromatographic separation of platinum compounds, both free and bound to large molecules in a single run. Arrows indicate the Diaquo-DACH platin present as degradation product in different platinum compounds.

▶ LC-ICP-MS measures molecule specific concentration. ICP-MS coupled with HPLC measures the element concentration of all compounds in the matrix that contains the element of interest that are chromatographically separated. This combination enables metabolite profiling and determination of biotransformation and/or degradation products, and different valances or species of the element (Fig. 3).

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Sample preparation

- Acidic dilution (e.g., plasma, blood, serum, urine, formulation).
- Digestion (e.g., feces, tissue, bone) by two DigiPREP MS systems (Fig. 4).
- Ultrafiltration and equilibrium dialysis for determination of free (unbound) drug concentrations.
- Solid-phase and liquid extraction if required.

Fig. 4. 2x DigiPREP for digestion of 216 samples (tissue, feces or bone) per run using nitric acid, hydrogen peroxide and controlled heating.

Analytical possibilities

- HPLC separation for quantitation of parent compound and metabolites.
- Serial detection using ICP-MS and UV (diode array).
- Parallel detection using ICP-MS and LC-MS/MS.
- ELISA-ICP-MS.

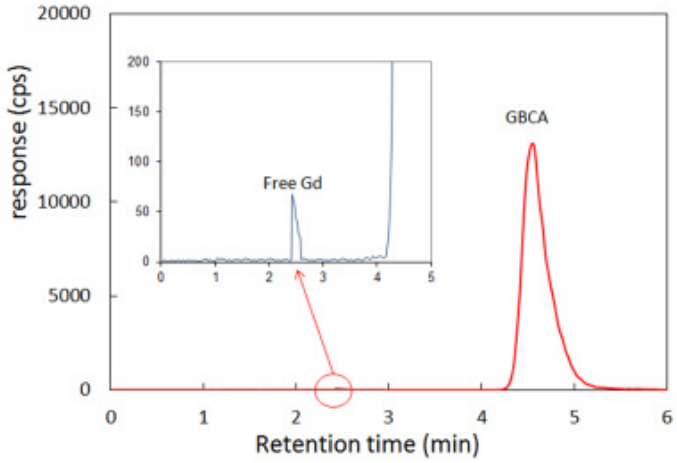

Fig. 5. Example of an LC-ICP-MS chromatogram showing the peaks of free Gd, as originated from the degradation of the chelated Gd molecule, (see insert) and the intact chelated Gadolinium, depicted by GBCA analyzed from a human plasma sample. LC-ICP-MS assays were developed to determine free Gd3+ and chelated for Dotarem, Primovist and several potential new Gadolinium based contrast agents (GBCA's). A ratio of free to chelated up to 1 : 20,000 could be obtained with an LLOQ of 10 ng/ml. The LLOQ can vary and depends on the matrix. Beside an LC-ICP-MS assay an ICP-MS assay was developed for determination of total Gd in human plasma with both precision and accuracy within 5%.

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Examples of different elements of interest for ICP-MS related to various applications:

METALLOPEPTIDES		METALLODRUGS		MISCELLANEOUS	
Metalloenzymes:	Cu, Fe, Mg, Mn, Mo, Ni, Se, Zn	Indazolium, imidazolium:	Ru	DNA restriction fragments:	Fe, Mn, Co, Pb, Cd
Metallothioneins		Chemotherapeutica:	Pt, Ru, Rh, Ti, Ga, As, Au	Metalloporphyrines:	As(III)/As(V), Ge, Sb,
Physiological:	Zn, Cu, Se	Bone resorption:	La, Eu, Gd, Tb, Yb		Se, Co(II)/Co(III)
Xenobiotic:	Cd, Hg, Ag, ...	Anti-arthritic therapeutica:	Au	Ferrocene derivatives:	Fe
Phytochelatins:	Cd, Ag, Cu, Pb, Zn	Anti-diabetes therapeutica:	V, Cr, Cu, Zn, Mn, Mo	Cobalamines, cobanamids:	Co
Transport proteins		Gastrointestinal disorders,		Imaging agents:	Tc, Fe, Gd, Mn, I, Ba
Albumin:	Cu, Al; Transferrin: Fe, Al	stomach ulcer:	Bi, Al	Amino acid-complexed	
CorA:	Mg, Co, Fe, Ni			metals:	Zn, Cu, Mn, Ni

Some examples of (LC)-ICP-MS assays developed at QPS

- Determination of free and total platinum in urine, whole blood, red blood cells or plasma from new or existing platinum drug formulations used in oncolytic studies, e.g., oxaliplatin, cisplatin and carbopltin.
- An assay had been developed to analyze micelle and/or protein bound and free platinum in one analytical run using LC-ICP-MS and size exclusion chromatography.
- Simultaneous determination of free and chelated Gd (up to 1 : 20,000) in MRI Gadolinium Based Contrast Agents (GBCA) which are in development for having lower free Gd concentration (Fig. 6).
- Determination of platinum in mouse plasma and mouse organs by LC-ICP-MS.
- Determination of total and non-ceruloplasmin bound copper in human serum and copper in human urine for Wilson disease.
- Determination of copper, zinc, aluminum, and iron in human blood. These elements play a role in Alzheimer and Parkinson disease and are considered as biomarker.
- Determination of total and free iron in iron sucrose studies (Fig. 4), and transferrin bound copper in human serum by LC-ICP-MS (Fig. 6).

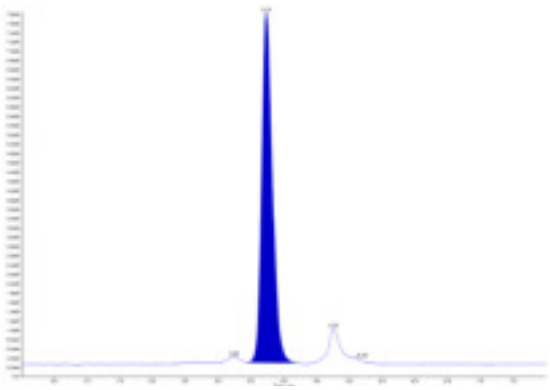

Fig. 6. Chromatogram of iron in human serum determined as Transferrin bound iron (TBI) by LC-ICP-MS after dosing of iron sucrose. The TBI is chromatographically separated from other iron sources in human serum. This method to determine TBI by LC-ICP-MS and total iron by ICP-MS is much more reliable than the classical spectrophotometric method.

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Why QPS?

- We have built up vast ICP-MS experience since 2004 in method development, validation and quantitation of many elements in various animal species and matrices, from R&D to preclinical and manufacturing origin.
- We have 3 LC-ICP-MS systems and thus sufficient capacity for your studies.
- We have extensive equipment for sample preparation.
- We are very flexible, cooperative and have a broad experience in (bio)analytical chemistry, including regulatory aspects.
- We are used to conducting complex studies.
- We value face-to-face meetings. You are welcome to visit us and view our laboratory.

Whether your focus is:

- Small molecules
- Protein biotherapeutics
- Vaccines
- Gene therapy



QPS provides a full range of bioanalytical solutions to support drug development from discovery through clinical development and filing.

QPS is a Global CRO

with locations around the world to serve the evolving needs of the Pharmaceutical and Biotech industries

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