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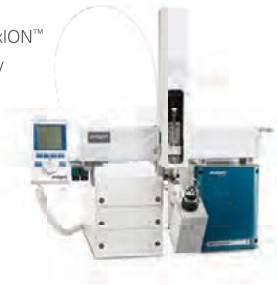

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FOREWORD

The Bioanalysis Glossary

An essential new resource for bioanalysts!

The Future Science editorial team is delighted to bring you the first edition of The Bioanalysis Glossary, which we hope will be regarded as an essential resource for everyone who works in bioanalysis or related fields. Over 20 leading bioanalytical experts from industry and academia have been working closely with the Future Science editorial team over several months to develop this definitive glossary.

This guide will be particularly useful for those moving into the field or working with bioanalytical laboratories for the first time, and as a reference for experienced bioanalysts writing reports, research papers or presentations. Importantly, this glossary will aid in harmonization of the terminology used in the bioanalytical community within and between companies, universities and individuals. With increased globalization in drug development, it is now more important than ever before that scientists speak the same bioanalytical language.

For this glossary, bioanalysis is defined as the quantitative or qualitative measurement of analytes in biological matrices, including tissue, blood, serum, urine or other body fluids (and not the broader term used by biochemists for biochemical characterization).

We have included core bioanalytical terminology to ensure that it can be used consistently and – in recognition of the important role that bioanalysis plays in drug development and other related fields such as metabolomics, antidoping testing and therapeutic drug monitoring – important terminology relevant to bioanalysis has also been included. This reinforces the fact that bioanalysis involves much more than just providing data – bioanalysts should be actively engaged in discussions relating to all stages of drug development, and a better understanding of related areas such as pharmacokinetics and how the data will be used leads to more insightful and useful bioanalyses.

Therefore, this glossary includes core established bioanalytical terminology, as well as definitions from related fields (e.g., pharmacokinetics and metabolomics) and pertaining to technology used in bioanalysis. Terms related to regulated bioanalysis are included, and recently introduced language that has now become commonplace is concisely defined. Some key examples of these include incurred sample reanalysis, dried blood spots and matrix effects.

It is our intention that this glossary will be updated when required to allow for the inclusion of new terms and to incorporate any changes to definitions. In this vane, we welcome your feedback and suggestions for future editions.

Laura Dormer
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SCOPE

In this glossary, bioanalysis is defined as the quantitative or qualitative measurement of analytes in biological matrices, including tissue, blood, serum, urine or other body fluids. The broader use of the term used by biochemists for biochemical characterization is excluded.

This glossary lists terms and definitions:

- Directly associated with the field of bioanalysis;
- That describe closely related techniques, technologies and applications of bioanalysis, which are important or useful for bioanalysts to understand.

It covers:

- General bioanalytical terms;
- (Bio)analytical techniques and equipment;
- Pharmacokinetics;
- Clinical trials;
- Metabolomics;
- Antidoping testing;
- Therapeutic drug monitoring;
- Regulatory and validation terminology;
- Drug development;
- Statistical terminology.

TERMS & DEFINITIONS

1 2D chromatography

Use of two **high-performance liquid chromatography (HPLC)** columns, typically in the heart-cut format, to resolve complicated bioanalytical issues such as **interference** peaks or **matrix effects**.

2 absolute bioavailability

Extent of drug absorbed upon extravascular administration in comparison to the dose size administered (i.e., percentage absorbed).

3 absorption

The process of uptake of a drug from the site of administration.

4 accelerator mass spectrometry

A form of mass spectrometry that accelerates ions to very high kinetic energies before analysis, allowing separation of a rare isotope from an abundant neighboring isotope. It is used to study **drug metabolism** and in microdosing studies (i.e., **absolute bioavailability** and Phase 0 studies).

5 acceptance criteria

Predefined criteria, such as for **accuracy** or **precision**, to be used for accepting or rejecting an experimental outcome.

6 accuracy

The degree of closeness of the determined value to the nominal or known true value. Percentage **accuracy** is calculated as (determined value/true value) × 100.

7 accurate mass

In mass spectrometry, determination of the mass of an **analyte** with sufficient **accuracy** to enable the elemental composition to be found.

8 acid dissociation

Sample pretreatment step (often a decrease in pH) used to dissociate an **analyte** from a protein (e.g., drug–**antidrug antibody [ADA]** complexes), often used in conjunction with various **immunoassay**/immunoextraction **method** formats.

9 affinity-based biosensor

Device able to detect the concentration of **analytes** by their specific binding with several biotransducers, such as receptors, aptamers or antibodies.

10 alignment

The data processing step where one corrects for artifacts created by the analytical instrumentation, for example, **retention time (RT)** variations or shifts along the *m/z* axis between **samples**. **Alignment** is critical for all mass spectrometry (MS)-based detection methods and separation approaches as well as nuclear magnetic resonance (NMR) data from complex samples, because there must be one-to-one correspondence between the variables being compared in order to accurately ascertain the differences in the chemical compositions between samples.

11 analyte

A specific chemical moiety being determined, which can be intact drug, biomolecule or its derivative, **metabolite** and/or degradation product in a biologic **matrix**.

12 analyte fortification

Addition of the compound of interest to the **biological matrix** for preparation of **calibration standard** or **quality control samples (QCs)**. A common informal term is 'spiking'.

13 analytical procedure

The sequence of steps necessary to perform a complete analysis described in adequate detail to permit the procedure to be reliably and reproducibly performed by someone knowledgeable in the field. See also "**method**".

14 analytical range

The range of concentration or other quantity values in the specimen over which the **method** is applicable without modification.

15 analytical run

A complete set of analytical and study **samples** with an appropriate number of standards and **quality control samples (QCs)**.

16 anchor calibrator

Standard point outside of the range of quantification, used to assist in fitting the nonlinear regression (e.g., 4-parameter or 5-parameter logistic) of the **standard curve** in **ligand-binding assays (LBA)**.

17 antibody

A protein molecule elicited in response to treatment with an **antigen** that is capable of binding to a specific determinant on the antigen. Also used as biotherapeutics.

18 antibody–drug conjugate (ADC)

Biologically active small molecule (payload) chemically linked with a monoclonal antibody (mAb).

19 anticoagulant

A substance added to the blood during sample collection to prevent blood clotting (coagulation).

20 antidrug antibody (ADA)

Also known as 'antitherapeutic antibody', a pre-existing or treatment-induced antibody that is capable of binding to the drug. Opiates, sulfa drugs and other small molecules can induce ADAs.

21 antigen

A substance eliciting the formation of antibodies in a suitable host.

22 aptamer

Nucleic acid molecule engineered to bind to various molecular targets. The mode of action of an aptamer is dependent upon its shape but not its sequence.

23 aqueous normal-phase (ANP) liquid chromatography (LC)

A variant of normal-phase **liquid chromatography** (in which the **stationary phase** is more polar than the **mobile phase**) for which the mobile phase components and additives are water-miscible. **Hydrophilic interaction liquid chromatography (HILIC)** and chromatography on silica hydride-based phases are popular examples of ANC LC.

24 area under the curve (AUC)

The area under the plot of **matrix** (e.g., **plasma**) concentration of drug against time after drug administration.

25 assay-appropriate scientific validation

One process of scientific validation where, irrespective of the stage of development in which the study is supported, assay criteria for scientific validation are defined to allow valid and documented decisions to be made from the reported concentrations.

26 atmospheric pressure chemical ionization (APCI)

A soft ionization technique for the production of gas-phase ions typically most efficiently with nonpolar small molecules involving nebulization of a liquid flow, application of a sheath gas and a corona discharge tip to place a charge on vaporized molecules. The produced ions are transferred into the vacuum interface region of a mass spectrometer for subsequent analysis.

27 audit

A systematic and independent examination of study- or trial-related activities and documents to determine whether the activities were conducted, and the data were recorded, analyzed, and accurately reported according to the **protocol**, **standard operating procedures (SOPs)**, **good laboratory practices (GLP)** or **good clinical practices (GCP)**, and other applicable regulatory requirement(s).

28 audit trail

An essential documented record, often automatically acquired, for an instrument, computer system or process that allows reconstruction of events in a chronological manner. Typically includes the date and time of an action, the user name and the action taken.

29 automation

The use of automated device(s) to perform part or all of a bioanalytical procedure.

30 autosampler

Part of an instrument (often a high-performance [or pressure] liquid chromatography [**HPLC**]) allowing the injection of **samples** in a reproducible and unattended manner.

31 back-calculation

Process of calculating the concentrations of calibration standards or **unknown samples** using their instrumental responses, according to the best-fitted line through the calibration points.

32 balance

A device used in a bioanalytical laboratory to weigh out solid and liquid materials, such as reference and **internal standards** or buffer components.

33 basal value

Measured value; such as, for a **biomarker**, before the administration of a drug.

34 baseline

The chromatographic signal of a system in the absence of an **analyte**.

35 batch

A number of study **samples** of unknown concentration along with the appropriate standards and **quality control samples (QCs)** that are processed at one time. See also "**analytical run**".

36 bias

The difference between an experimental value and a nominal value expressed as a percentage, sometimes used as a measure of **accuracy** or trueness. Bias (%) = [(Experimental value - Nominal Value)/Nominal Value] × 100%.

37 bioanalysis

The quantitative or qualitative measurement of analytes in biological matrices, including tissue, blood, serum, urine or other body fluids.

38 bioavailability

The fraction of a drug that reaches the systemic circulation unchanged.

39 bioequivalence

Equivalence in the **plasma area under the curve (AUC)** of test and reference products.

40 biolayer interferometry

An analytical methodology based on a shift in the **interference** pattern of the light reflected through a **biosensor** resulting from biomolecular bindings on the biosensor surface.

41 biologic/biotherapeutic/biopharmaceutical

One of a diverse group of macromolecules with therapeutic potential that are usually derived from living organisms or systems and include monoclonal antibodies, proteins and peptides.

42 biological matrix

A material of biological origin that can be sampled for the measurement of analytes, including blood, serum, **plasma**, urine, feces, cerebrospinal fluid, saliva, sputum and various tissues.

43 biomarker

Protein or small molecule indicative of homeostasis or a disease state that can indicate disease progression or a response to a therapeutic intervention.

44 biosensor

Protein-based receptor that is linked to a detection system and allows for the measurement of an exogenously added ligand, often a protein.

45 biosimilar

Also known as 'follow-on biologic'. Subsequent version of an innovator biopharmaceutical product.

46 biotransformation

Metabolic or catabolic changes to an administered drug in a biological system.

47 blank sample

A sample of a **biological matrix** to which no analytes and no **internal standard** have been added, which is used to assess the specificity of a bioanalytical **method** and to confirm absence of **contamination**.

48 blood:plasma distribution ratio

The extent to which a drug is distributed between **plasma** and the red blood cell fraction of blood, often expressed in the blood-to-plasma concentration ratio of the drug.

49 bridging immunoassay

Immunoassay method for detection of **antidrug antibodies (ADA)** that is enabled by the formation of a ternary complex or 'bridge' where one arm of the ADA binds to the capture reagent (e.g., solid phase adsorbed or biotin-labeled drug) and the second arm binds to the detection reagent (e.g., hapten-, **enzyme**- or ruthenium-labeled drug). Often the detection reagent is a labeled version of the capture reagent.

50 calibration curve

A set of calibration standards at various known concentrations whose measured instrument responses are used to construct a regression curve to measure concentrations of **incurred samples** and **quality control samples (QCs)**.

• 51 calibration range

The interval between the upper and lower concentration (amounts) of **analyte** in the sample (including these concentrations) for which it has been demonstrated that the **analytical procedure** meets the requirements for **precision** and **accuracy**. See also "**analytical range**".

• 52 calibration standard

A **biological matrix** to which a known amount of **analyte** has been added.

• 53 capacity factor

Also known as 'retention factor', k (previously k′); applies to isocratic column chromatography. A measure of chromatographic retention, for which the calculation involves both the **retention time** and the column void time.

54 capillary zone electrophoresis

Method in which analytes are separated on a gel in a narrow-bore capillary, based on their differential migration due to their charge-to-size ratio. Separation is performed in a narrow-bore capillary generally filled with a buffer solution across which an electric potential is applied.

55 carryover

The inadvertent transfer of an **analyte** to a **blank sample** or other **samples** in a **batch**. Typically, this occurs following analysis of samples with a high **analyte** concentration.

56 cell-based neutralizing antibody assays

Method for the detection or quantitation of neutralizing **antidrug antibodies (ADA)** that block the functional properties of the drug. These assays utilize a cell line that is responsive to the drug either by directly responding to it or by responding to a ligand that shows altered activity in the presence of drug.

57 centrifugation

A process that involves the use of centrifugal force for the sedimentation of heterogeneous mixtures with a centrifuge. In **bioanalysis**, it is often used to separate blood from **plasma**, to separate protein precipitates from the liquid fraction, pellet suspended cells or to separate two immiscible solvents during **liquid–liquid extraction**.

58 certificate of analysis (CoA)

A document that shows the characterization of a **reference standard** and suitability to be used to support **good laboratory practice (GLP)**, **good clinical practice (GCP)** or **good manufacturing practice (GMP)** studies.

59 chiral chromatography

Chromatographic technique that is capable of separating enantiomers via diastereomeric complex formation with differential partitioning into the **mobile phase**.

60 chiral compound

A compound that contains an asymmetric center.

61 chromatogram

In chromatographic analyses, a graphic display of chromatographic output, typically showing the response as the y-axis and time as the x-axis.

62 chromatographic column

Essential component of a liquid or gas chromatographic system, containing the **stationary phase** and through which flows the **mobile phase**. Separation is typically effected through partitioning, adsorptive, electrostatic or affinity-based interactions between the **analyte** in the mobile phase and the stationary phase.

63 chromatography

A system using a **stationary phase** (see "**chromatographic column**") and a **mobile phase** to effect separation of molecules in a given sample.

64 clinical laboratory improvement amendments (CLIA)

Regulates clinical laboratory diagnostic testing in the USA and requires clinical laboratories to be certificated.

65 clinical sample

A sample received from a patient or healthy volunteer (e.g., from a **clinical trial**) for **bioanalysis**.

66 clinical trial

Study to evaluate a new drug or treatment in healthy or diseased human subjects.

67 coadministered medicines

Two or more drugs administered concurrently to a subject.

68 coefficient of variation (CV)

A statistical term used for the measurement of **precision**. It is equivalent to **relative standard deviation (RSD)** and is calculated as (standard deviation/mean) × 100%.

69 competitive ligand-binding assay

An analytical methodology based on the competition of an **analyte** with an **endogenous compound** for a receptor or antibody ligand, which is linked to a detector system.

70 compliance

The adherence to **standard operating procedures (SOPs)**, **good laboratory practices (GLPs)**, **good clinical practices (GCPs)** or other regulatory standards. It is typically demonstrated through the accurate and complete record keeping of activities (e.g., sample custody and analysis) allowing for poststudy reconstruction and examination of the **raw data** and events.

71 computer software validation

A process of using predefined protocols and procedures to test the suitability and integrity of computer software for its intended use.

72 contamination

A phenomenon whereby **analyte** material from a known or unknown source (e.g., from another sample) accidentally enters a sample or analytical component that then enters the analytical system, and results in erroneous measurements.

73 contract research organization (CRO)

An organization that provides fee-based services to pharmaceutical and biopharmaceutical companies.

74 core run

A set of calibration standards and **quality control samples (QCs)** analyzed during assay validation to assess the **precision** and **accuracy** of the assay.

75 counter ion

A general term used to describe the ion with opposite charge to the **analyte**. May represent the ion used to form a salt or to improve chromatographic performance.

76 critical reagent

Essential component of an assay (particularly **ligand-binding assays [LBAs]**) whose characteristics are crucial to assay performance. These reagents, such as antibodies, peptides and conjugates, require thorough characterization and documentation, and may require significant amounts of time to acquire and/or to determine if suitable for use. They are usually **analyte**-specific, difficult to replace, and have a direct impact on the results of an assay.

77 cross-reactivity

In immunology, cross-reactivity refers to the reaction between an antibody and an **antigen** that differs from the antigen (**analyte**) of interest. It arises when a molecule (particularly a protein or peptide) has an **epitope** sufficiently similar to one on the analyte of interest to cause that molecule to bind to the antibody in a **ligand-binding assay (LBA)** in a similar way to the analyte of interest. Specificity is related to the concept of cross-reactivity. If an antibody is highly specific it has low cross-reactivity with analytes other than that of interest.

78 cross-validation

Comparison of performance of a (developed) **method** with a bioanalytical method through the analysis of the same set of **samples**. Cross-validation may include statistical comparisons of **quality control** and **incurred sample** results.

79 cumulative urinary excretion curve

Plot of the actual cumulative amount of drug excreted into urine versus time upon administration of a drug.

80 curvature

Within **linear regression**, the manifestation of a nonlinear (i.e., curvilinear) response versus concentration profile within a given concentration range for a quantitative bioanalytical **method**. From a statistical approach, curvature is the rate at which the slope changes. It is the second derivative of any function; for a straight line, the second derivative is '0', for a quadratic regression model (also a linear function), the rate is positive or negative.

81 cut point

The value at, or above, which instrument response is considered positive and below which response is considered negative.

82 cytochrome P450

A superfamily of heme-containing enzymes that can metabolize a variety of compounds via multiple pathways.

83 daughter ion

An electrically charged product of the reaction of a particular **parent ion** in mass spectrometry. Typically, occurs in mass spectrometric analysis in the reaction quadrupole as the result of high-energy interactions between the **analyte** and carrier gas. Also known as "**product ion**".

84 derivatization

The chemical modification of functional groups to change the characteristics of compounds to be more favorable for analysis (e.g., more sensitive, differentiated from other molecules in the **matrix**, more specific, more volatile, fluorescent).

85 diagnostic assay

An assay appropriate to use in clinical decision-making for an individual patient. Such assays generally fall into one of six categories:

- Assays that screen for disease in an apparently healthy population;
- Assays used to aid in the diagnosis of a particular disease;
- Assays that monitor a disease or the efficacy of its treatment;
- Assays that stratify risk;
- Assays that prognose the natural course of a disease or condition;
- Assays that predict response to a therapeutic intervention.

86 diastereoisomer

Stereoisomers of a compound, with multiple chiral centers, that have different absolute configurations at one or more, but not all, chiral centers. Such compounds have different physicochemical properties, and, in theory, can be resolved under conventional methods of chromatography.

87 digestion

The enzymatic digestion of a macromolecule (usually protein) into smaller fragments (peptides) prior to analysis by mass spectrometry.

88 dilution

The procedure of adding control **matrix** to **incurred samples**. This process is used to bring incurred samples with concentrations above the **upper limit of quantification (ULOQ)** into the curve range for analysis.

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89 dilution QC sample

Samples of control **matrix** spiked with **analyte** to which additional control matrix is added prior to analysis. Used to evaluate the acceptability of **incurred samples** analyzed after **dilution**.

90 discriminative metabolomics

The process of comparing the metabolites present in multiple **samples** collected under different conditions (e.g., disease states, drug treatment, among others) conducted to identify which metabolites are associated with the different conditions under which the samples are collected.

91 diversion of LC flow

Typically used to direct mobile eluent containing contaminants at a time point before the **elution** of the **analyte** of interest away from the LC-MS source. Usually a make-up mobile phase is directed to the LC-MS source while the eluent is diverted away in order to maintain instrument stability (e.g., avoid drying the curtain plate).

92 doping analysis

Laboratory procedures aimed at ascertaining the use of banned performance-enhancing substances and methods in sport by the analysis of biological fluids.

93 dosage regimen

The systematized schedule under which compounds are administered for therapy; that is, the proper compound mass and proper time interval between compound administration required to produce clinical effectiveness or to maintain a therapeutic concentration in the body.

94 dose–response curve

The graphical presentation of pharmacological response versus amount of compound administered (e.g., dose).

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95 dosing interval

The time period between multiple administrations of a compound.

96 dosing vehicle

Substance used to facilitate the **absorption** or administration of the drug.

97 dried blood spot (DBS) sampling

A **matrix** sampling methodology based on applying whole blood (e.g., obtained from a heel-, tail- or finger-prick) onto a (paper) substrate which is subsequently dried and sealed in bags with desiccant for possible storage and shipping prior to extraction and analysis.

98 drug metabolism

See "**biotransformation**".

99 drug–drug interaction

The effect of other drugs on the **pharmacokinetics (PK)** and **pharmacodynamics (PD)** of the coadministered drug.

100 dry-down

The evaporation of solvents, typically organic, during the sample preparation process.

101 electrochemiluminescence

An analytical methodology based on the detection of light generated during electrically stimulated chemical reactions of compounds in solution.

102 electrospray ionization (ESI)

A soft ionization technique useful for dealing with nonvolatile or thermally labile molecules. Instead of fragmenting the molecule into many smaller charged particles making subsequent interpretation difficult, it ionizes the molecule through the generation of small droplets, which are then analyzed in the gas phase by mass spectrometry.

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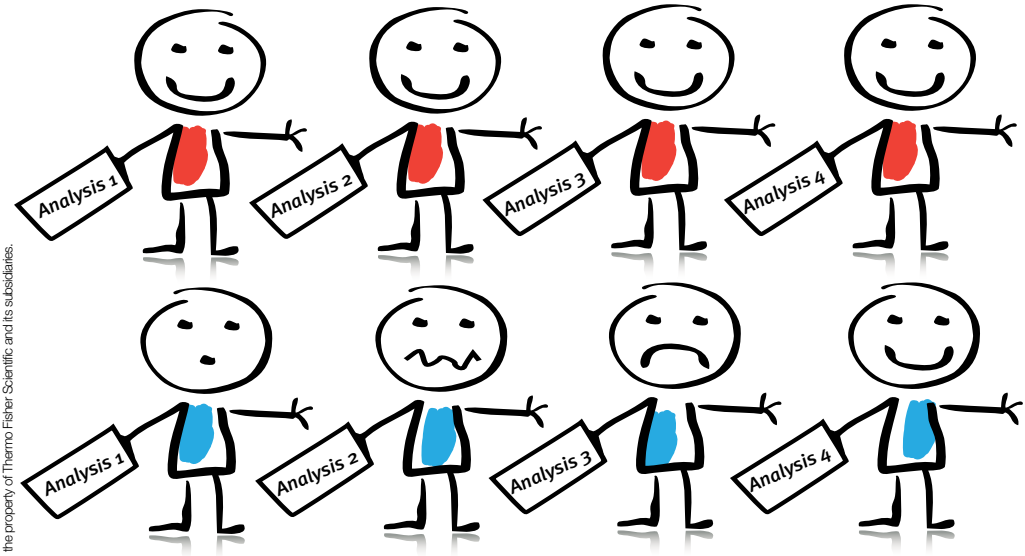

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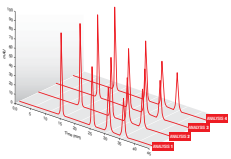

Providing confidence in your analytical results

103 elimination half-life

After equilibrium is reached, the time necessary to reduce the drug concentration in the **plasma** to one-half.

104 elution

The process of desorbing an **analyte** from a **stationary phase** with a **mobile phase**.

105 enantiomer

One of two stereoisomers that are mirror images of each other (i.e., nonsuperimposable/not identical).

106 endogenous compound

Components naturally present in biological fluids obtained from animals or humans.

107 enzyme

Proteins that speeds up the rate of a chemical reaction in a living organism.

108 enzyme induction

The increase in the rate of enzymatic processes resulting in faster metabolism of a compound. If a drug stimulates its own metabolism, it is called autoinduction.

109 enzyme inhibition

The decrease in the rate of metabolism of a compound usually by competition for an **enzyme** system.

110 enzyme-linked immunosorbent assay (ELISA)

A form of **immunoassay**.

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111 epimer

Stereoisomer with more than one chiral center that differs in the configuration at only one center.

112 epitope

The part of an **antigen** that is recognized by the immune system (i.e., antibodies, B or T cells).

113 error

The difference between an estimate of a quantity and its true value. This difference (positive or negative) may be expressed either in the units in which the quantity is measured or as a percentage of the true value.

114 European Medicines Agency (EMA)

Regulatory body responsible for the protection of public and animal health in the European Union through the scientific evaluation and supervision of medicines.

115 excretion

The final elimination of a compound and its metabolites from the body's systemic circulation via the kidney into urine and via bile into feces.

116 extractability

The extent to which an **analyte** can be recovered from a **biological matrix**.

117 extrapolation

The estimation of the concentration of an **unknown** sample outside the established **calibration range**, on the basis of the observed relationship between the **nominal concentration** of the calibrators and the instrumental response and under the assumption that this relationship will also be applicable outside the calibration range.

118 false negative

A false-negative result for a sample indicates that the sample gives a test result of 'negative' for an **analyte** of interest although the analyte is actually present in the sample or is present in a concentration above the **cut point** of the assay.

119 false positive

A false-positive result for a sample indicates that the sample gives a test result of 'positive' for an **analyte** of interest although it is not actually present in the sample or is present in a concentration below the **cut point** of the assay.

120 FDA Form 483

A form used by the **US FDA** to document and communicate concerns discovered during their inspections.

121 fingerprinting

A multivariate pattern expressed in the data that can be applied for sorting datasets into categories so that conclusions can be drawn about classification of individual samples.

122 first-in-human (FIH)

Clinical trial where a medical procedure, previously developed and assessed through ***in vitro*** or animal testing, or through mathematical modeling is tested on human subjects for the first time.

123 first-pass effect

The phenomenon where drugs may be metabolized following **absorption** from the GI tract but before reaching systemic circulation.

124 fit-for-purpose

Qualification of a bioanalytical **method** with scientific rigor for the intended purpose where all applicable parameters may not be evaluated as per regulatory guidance. See also "**tiered approach**".

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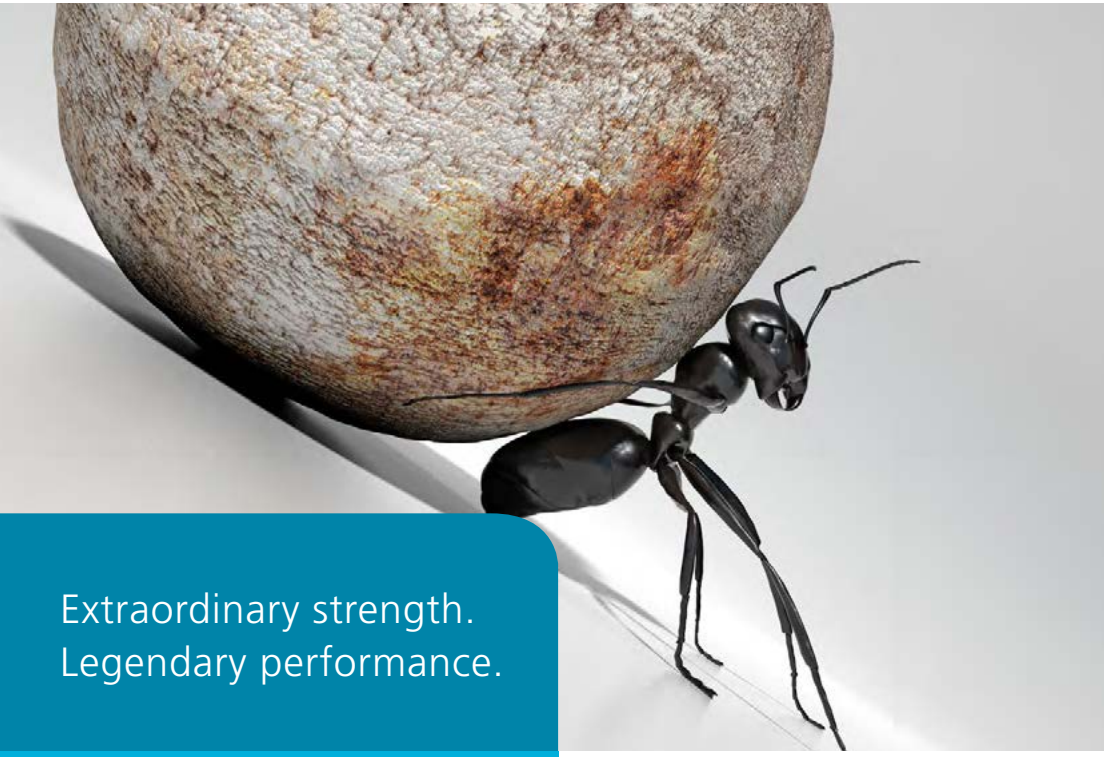

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125 flow cytometry

Laser-based analytical technique used for cell counting, cell sorting and **biomarker** detection.

126 free drug

Drug in the body that is not bound to a protein (e.g., albumin), target or antibody.

127 full validation

Establishment of all validation parameters for a particular **analyte**(s) in accordance with health authority regulations.

128 functional neutralizing antibody assay

A **neutralizing antibody** binds to distinct functional domains of a therapeutic protein and blocks its activity or function. A functional neutralizing antibody assay detects if the **antidrug antibody** neutralizes the drug activity.

129 gas chromatography (GC)

Chromatographic technique using a carrier gas, typically helium or hydrogen, as **mobile phase**, where the injected liquid sample is typically immediately vaporized in the injection port. The walls of the column are coated with a thin viscous liquid layer, the **stationary phase**, on an inert solid support.

130 good clinical practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

131 good laboratory practice (GLP)

A set of regulations that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived.

132 good manufacturing practice (GMP)

A set of regulations that provides a framework within which manufacturing of drugs, food and active pharmaceutical ingredients is planned, performed, monitored, recorded, reported and archived.

133 gradient elution

Increase of the **elution** strength by either linearly or step-wise changing the **mobile phase** composition (e.g., increasing acetonitrile percentage for a mobile phase used for reversed-phase elution).

134 hematocrit

The volumetric proportion of red blood cells in blood.

135 hemolysis

Lysis (rupture) of red blood cells resulting in release of hemoglobin and other cellular matter into the plasma.

136 hepatic clearance

The hypothetical volume of distribution in milliliters of unchanged drug cleared in 1 min via the liver.

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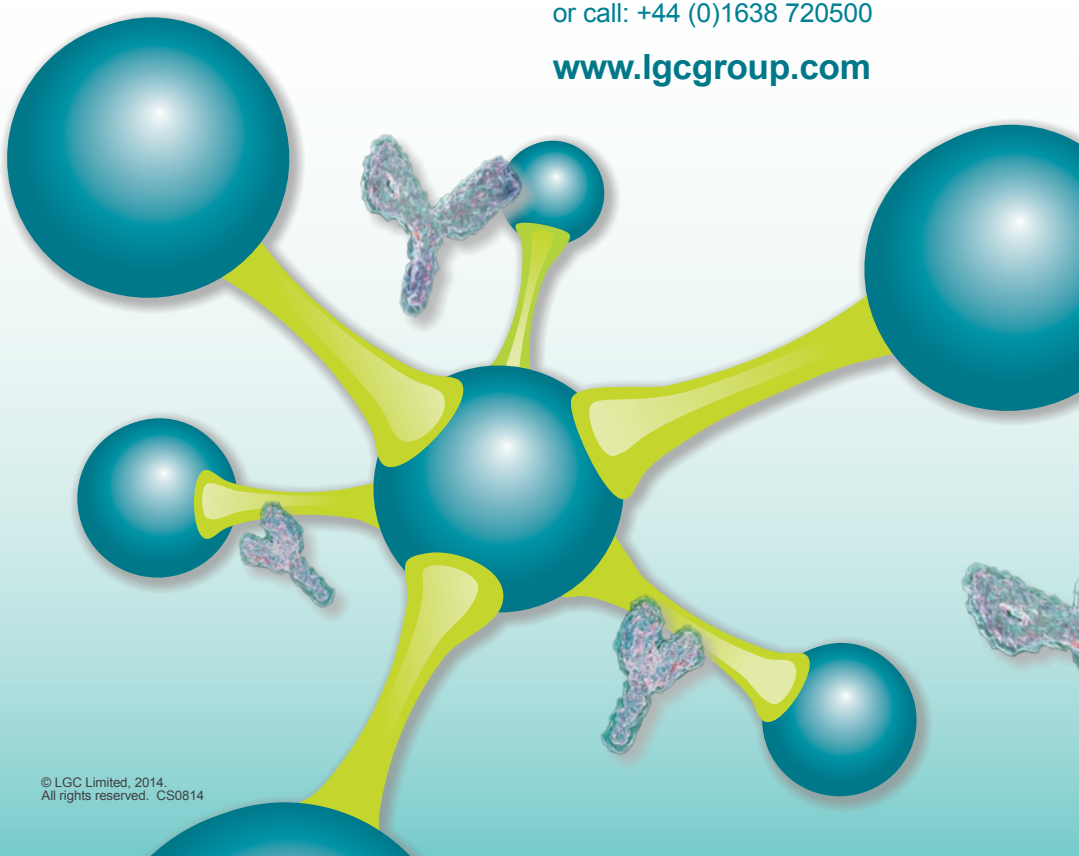

137 high-performance (or pressure) liquid chromatography (HPLC)

Chromatographic technique where the sample is injected onto a liquid **mobile phase**, which is pumped at high pressure through a column, packed with adsorbent material (**stationary phase**).

138 high-resolution mass spectrometry (HR-MS)

Mass spectral analysis with resolution >10,000 full-width at half-maximum where resolution = m/δ m, with m being mass and δ m the full width of the peak at half its maximum height (FWHM).

139 homogenate

Suspension of tissue cellular fragments and constituents obtained after the tissue is homogenized, lysed, sonicated and/or digested.

140 homegenization

Technique used to homogenize tissues, which can be mechanical, sonication, bead beating and/or enzymatic.

141 hydrophilic interaction liquid chromatography (HILIC)

A variant of normal-phase chromatography that uses hydrophilic (polar) **stationary phase** and hydrophobic (mostly organic) **mobile phase**. Retention increases with hydrophilicity of analytes and the order of **elution** is opposite to that obtained with **reversed-phase chromatography**.

142 hydrophobic interaction liquid chromatography (HIC)

A form of chromatography whereby a **matrix** containing hydrophobic groups binds proteins from aqueous solutions to different extents depending on the protein structures and a range of controllable factors including concentrations of salts, pH, temperature and organic solvents.

143 hyperlipidemia (lipemia)

Abnormally high levels of lipids and/or lipoproteins in blood, often associated with genetic factors and diabetes. **Bioanalysis** of hyperlipidemic **samples** may be compromised due to the lipid content and **method** performance is typically checked using a spiked blank hyperlipidemic **matrix**.

144 immunoaffinity chromatography

Combines **liquid chromatography** with the specific binding of antibodies or related agents. The **method** can be used in assays for a particular target or for purification and concentration of analytes prior to further examination by another technique.

145 immunoassay

Assay using antibodies to detect or quantify an **analyte**.

146 immunocapture

Direct capture of a molecule onto a surface coated with an antibody to the molecule.

147 immunogenicity

The ability of a molecule (e.g., protein, nucleic acid, carbohydrate, lipid or small drug molecule) to provoke an immune response in the body of a human or animal.

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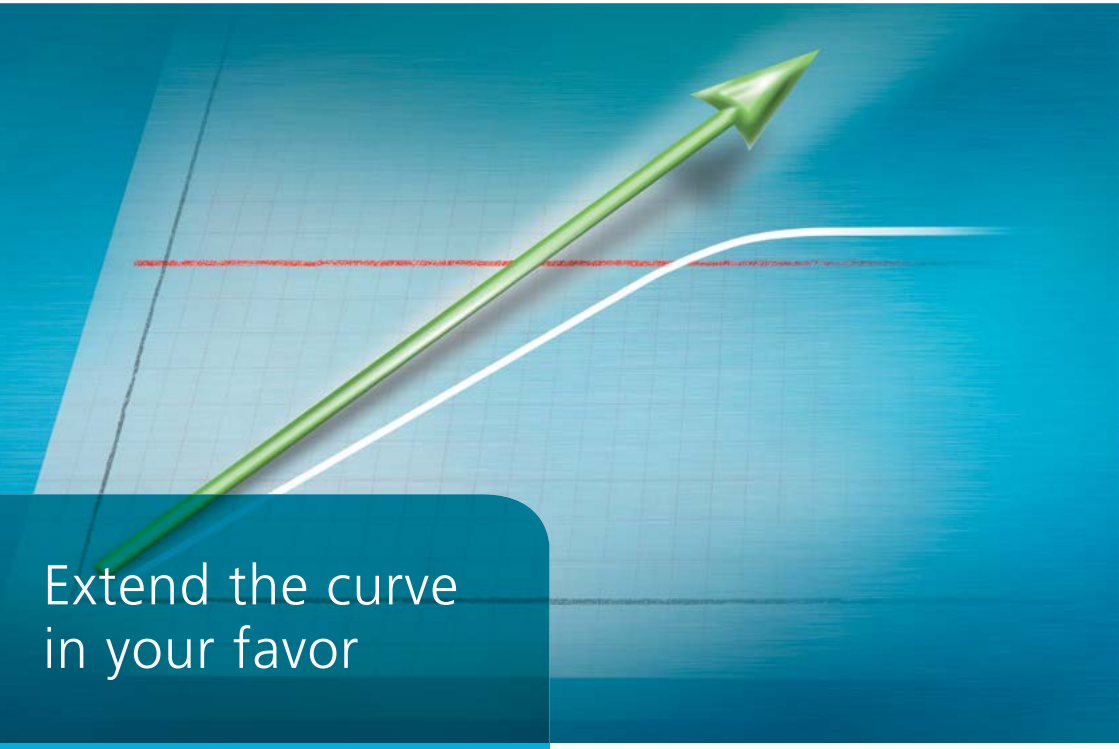

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148 immunogenicity assay

Method to detect an immune response to an administered therapeutic drug (usually a protein) in biological fluids (usually serum or **plasma**).

149 imprecision

Equivalent meaning to **precision**, the standard deviation or **coefficient of variation** of the results in a set of replicate measurements.

150 *in vitro*

Experiments performed outside of living bodies by using cells or artificial culture medium.

151 *in vivo*

Experiments conducted using living bodies.

152 inaccuracy

Numerical difference (positive or negative) between the mean of a set of replicate measurements and the true value.

153 incurred sample

Study sample from subjects or animals.

154 incurred sample reanalysis

Repeated measurement of **analyte** concentration from a portion of the incurred study **samples** from dosed subjects to determine whether the original analytical results are reproducible.

155 in-source fragmentation

Fragmentation of the molecule in the LC-MS interface. Typical examples of in-source fragmentation include loss of a glucuronide or loss of water.

156 instrument qualification (IQ/OQ/PQ)

A process that tests the suitability of the given instrument(s) and associated software/hardware for their intended usage by following a predefined **protocol**.

157 interassay precision

Precision of the measurement of an **analyte** between separate assay occasions, analysts or equipment.

158 interference

The effect of components present in the **samples** on the **accuracy** of measurement of another component.

159 interim data

A report of results and their evaluation based on analyses performed during the course of a trial or experiment prior to their completion.

160 intermediate precision

A measure of **precision** that reflects within-laboratory variations: different days, different analysts, different equipment, among others.

161 internal standard

Test compound(s) (e.g., a structurally similar analogue, or stable isotope-labeled compound) added to calibration standards, **quality control samples (QCs)** and study **samples** at a known and constant concentration to correct for experimental variability during sample preparation and analysis.

162 interpolation

The means of calculating the concentrations of incurred and **quality control samples (QCs)**, through the established back-calculated line of regression of **nominal concentration** against instrumental response.

163 intra-assay precision

Precision of the replicate measurement of an **analyte** within a single assay occasion.

164 intravascular administration

All routes of administration where the drug is directly introduced into the blood stream.

165 intrinsic clearance

Theoretical unrestricted maximum clearance of unbound drug by an elimination organ.

166 Investigational New Drug (IND)

The means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The **US FDA** reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk.

167 Investigator's Brochure (IB)

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

168 ion-exchange chromatography

Chromatographic separation based on the charge of the analytes.

169 ion-mobility spectrometry

Technique used to separate ions based on relative mobilities in a drift cell with electric field and carrier buffer gas. The mobility of an ion depends on cross-sectional area, shape and charge.

170 ion-pairing chromatography

The use of strongly ionic additives, typically in a **mobile phase**, that undergo electrostatic binding to oppositely charged analytes. A frequent goal of ion pairing in chromatography is to reduce or eliminate adverse peak shape, particularly tailing, caused by a positively charged **analyte** interacting with secondary silanols on a silica-based column.

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171 ion-pairing reagent

A reagent used in ion-pairing chromatography to selectively modify and increase the retention of charged analytes. Typically includes a hydrophobic tail with an ionizable head group whose charge is opposite that of the **analyte** that when complexed produces a neutral complex of improved chromatographic properties.

172 ion suppression

Reduced detector response in mass spectrometry as a result of competition for ionization between the **analyte** of interest and **matrix** components.

173 ion trap mass spectrometer

A mass spectrometer with an analyzer that traps ions in a cell and scans appropriate ranges to eject according to *m/z*.

174 isobaric isomers

Compounds with identical molecular weights but different spatial configurations.

175 isocratic elution

A chromatographic **elution** using a single and consistent **mobile phase** composition.

176 isotope dilution

An isotopically enriched substance is added to an analytical sample. The ratio of the **dilution** of the isotope can then be used to determine the amount of **analyte** in the sample.

177 isotopologue

An isotopically labeled analogue of a given compound.

178 lab-on-a-chip

See "**microfluidics**".

179 laboratory information management system (LIMS)

Software package utilized in bioanalytical laboratories as a central database for sample management and analysis.

180 ligand-binding assay (LBA)

Quantitative **method** based on the binding of ligand molecules to antibodies or receptors, typically used for biomolecules where the reliance is on highly specific **epitope**–**paratope** interactions between **antigen** and antibody.

181 limit of detection (LOD)

The lowest concentration of an **analyte** that a bioanalytical procedure can reliably differentiate from background noise. Commonly defined by a signal-to-noise ratio of 3.

182 linear regression

An approach for modeling the linear relationship between concentration and instrument response (typically the ratio between **analyte** and **internal standard**).

183 liquid chromatography (LC)

Chromatographic technique that employs a liquid mobile phase, a liquid sample injected, and a packed column **stationary phase** of appropriate chemistry for the required selectivity. This technique can be coupled to a variety of detectors, most notably mass spectrometry for **bioanalysis**.

184 liquid–liquid extraction

Means of sample extraction that relies on the partitioning of an **analyte** between an aqueous component and a water-immiscible organic component.

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185 locked nucleic acid (LNA)

Oligonucleotide containing one or more of the 2′-O,4′-C-methylene-β-D-ribofuranosyl nucleosides called LNA monomers. The major feature of LNAs is the high-affinity hybridization to complementary nucleic acids because of high thermo-stability, resulting in enhanced selectivity and assay sensitivity.

186 lower limit of quantification (LLOQ)

The lowest amount of **analyte** in a sample that can be quantitatively determined with predefined **precision** and **accuracy**.

187 mass spectrometer transition

The representation of the **parent ion** nominal mass to the measured fragment ion in a triple quadrupole or time-of-flight (TOF) mass spectrometer (e.g., 842→456).

188 mass-to-charge (*m/z*)

The characteristic of a molecule or molecular fragment that represents its nominal mass divided by the number of charges the molecule carries. This value is typically used to represent the parent and **product ions** in mass spectrometry assays and is used to define the nominal mass settings for the filtering of the **analyte** out of the mixture of all present ions.

189 master schedule

A GLP requirement for all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, the identity of the sponsor and name of the **Study Director**.

190 matching matrix

Blank **biological matrix** or **matrix** surrogate prepared from a recipe, used for the preparation of **calibration standard** and **quality control samples QCs)**, intentionally similar to the matrix of **incurred samples** requiring analysis. Matrix matching is often used in tissue analysis where blank tissue is unavailable or limited to best compensate for **matrix effects**.

191 matrix

Whole blood, **plasma**, serum, urine, or other **biological matrix** selected for analysis. A **matrix** not containing exogenous chemicals (except **anticoagulant**) and their metabolites is called blank matrix.

192 matrix effect

The direct or indirect alteration or **interference** in instrumental response due to the presence of **matrix** constituents in extracted **samples** or unextracted samples for LBAs), which the overall **method** selectivity is inadequate to address.

193 matrix factor (MF)

The ratio of the **analyte** response in the presence of **matrix** to the response in the absence of matrix. MF = analyte response in the presence of matrix/analyte response in the absence of matrix.

194 metabolite

An intermediate and product of metabolism; in **bioanalysis**, this usually refers to a product of the metabolism of an administered therapeutic, but metabolites can also be products of metabolism of other exogenous or endogenous substances.

195 metabolite features

Peaks with a unique mass-to-charge ratio or deconvoluted as a cluster of different mass spectrometry (MS) species (adducts, neutral losses) corresponding to a unique mass-to-charge ratio, a unique **retention time** and with an intensity value (or area under the peak).

196 metabolite profiling

The measurement of all low-molecular-weight metabolites and their intermediates in a biological system. See also "**metabolomics**".

197 metabolites in safety testing (MIST)

The detection, confirmation and comparison of the exposure of drug metabolites observed in human clinical trials with those observed in animal studies. Used to establish the safety of the human metabolites through demonstrating adequate exposure in animal species.

198 metabolome coverage

The ability of an analytical technique to detect all metabolites (endogenous or exogenous) in complex biological **samples**. No technology can currently provide analysis of all analytes in such samples, and as a result, a combination of techniques is required to increase metabolome coverage.

199 metabolomic biomarker

An endogenous **metabolite** whose concentration changes in response to disease or treatment thereof. Such metabolites can be used for the purpose of diagnosis, disease subcategorization, prognostication and prediction of therapeutic sensitivity to treatments.

200 metabolomics

Often used interchangeably with the term 'metabonomics', is an analytical strategy that entails the comprehensive analysis of the low-molecular-weight compounds (<1000 Da) involved in the metabolic networks of living organisms and their response to pathophysiological or other stimuli. This methodology involves the use of advanced **metabolite profiling** techniques, such as **nuclear magnetic resonance (NMR) spectroscopy** and/or mass spectrometry hyphenated or not with a separation technique such as GC, LC or capillary electrophoresis (CE), combined with multivariate statistical analysis.

201 meta-metabolomics

Quantitative analysis of **metabolite** patterns in a complex host–microbiome system (including multiple partners); for example, used to identify metabolic networks related to health or disease issues.

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202 method

A comprehensive description of all procedures used in sample analysis.

203 method qualification

Subset of the validation processes that verifies **method** performance to demonstrate that an analytical method is working according to predefined **acceptance criteria**.

204 method validation

A comprehensive set of experiments to investigate whether an analytical **method** is functioning according to predefined **acceptance criteria**. For **regulated bioanalysis** criteria should be in **compliance** with guidelines published by regulatory authorities.

205 micellar electrokinetic chromatography

Electrodriven separation technique where an ionic surfactant, generally sodium dodecyl sulfate (SDS), is added to the separation buffer at a higher concentration than its critical micelle concentration and micelles act as a pseudo-stationary phase allowing solute partition simultaneously to electrophoretic separation.

206 microbore column

A **chromatographic column** with a small inner diameter (≤1 mm), which is operated at lower **mobile phase** flow rates than a conventional column and provides increased detection sensitivity. It is attractive for the analysis of small volume (or low concentration) **samples**.

207 microflow

Microliter flow rates (usually ≤50 µl/min) employed in chromatographic separations with **microbore columns**.

208 microfluidics

A field of technology using systems in which very small volumes of fluids are handled. For **bioanalysis**, this term usually refers to miniaturized devices that contain small flow channels and that combine one or multiple analytical functions in a single device. Also known as "**lab-on-a-chip**".

209 microsample

Sample of blood or any other **biological matrix** in the low µl/µg range utilized for certain preclinical or clinical studies, particularly with small animals or children.

210 mixed-mode

The use of multiple retentive modes to effect a separation, pertaining to a chromatographic or solid-phase extraction process. For example, ion-exchange can be performed in conjunction with reversed-phase partitioning.

211 mobile phase

In chromatography, the liquid or gas that moves through or along the **stationary phase** of a column. Separation of a mixture of analytes is achieved by differences in their partitioning between the mobile and stationary phases.

212 molecularly imprinted polymer (MIP)

An artificial affinity material consisting of a synthetic polymer, which is formed in the presence of a compound (the template), that is later removed and thus leaves specific binding sites for the template and structurally related molecules.

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213 monolith

A solid support that consists of a single piece of porous material characterized by a bimodal pore size distribution (macroporous and mesoporous), which confers favorable mass transfer properties, a large surface area and low pressure drops suitable for use in analytical or purification methods.

214 multi ascending dose (MAD; also known as 'multiple ascending dose')

A drug is given repeatedly at intervals shorter than those required to completely eliminate the drug from the previously given dose. This dosing is used to study the **pharmacokinetics (PK)**/**pharmacodynamics (PD)** of multiple doses for safety and tolerability. The dose is increased over time to a predetermined maximal level.

215 multiple reaction monitoring (MRM)

A quantification strategy used in **tandem mass spectrometry** in which an **analyte** ion with a particular mass-to-charge ratio (the **precursor ion**) is selected by a first quadrupole (Q1) in the mass spectrometer, and more than one product of a collision-induced dissociation reaction, each with a particular mass-to-charge ratio (the **product ion**), are selected in another quadrupole (Q3) and detected.

216 multiplexing

The ability of an analytical technique or device to process or analyze multiple **samples** simultaneously. This term also refers to the determination of multiple analytes using the same assay or run, such as a panel of biomarkers.

217 multi-site study

Any study that has phases conducted at more than one site.

218 nanoflow

Nanoliter per minute flow rates employed in chromatographic separations with very narrow-bore capillary columns (≤500 nm i.d.).

219 nanofluid liquid chromatography

A liquid chromatographic **method** employing **mobile phase** flow at very low flow rates (nl/min).

220 neutralizing antibody (NAb)

An antibody that is formed ***in vivo*** in response to treatment with an **antigen** and that binds to a drug and blocks its function. For an **enzyme** drug, a neutralizing antibody would block its action on the substrate. For an agonist or antagonist drug, an antibody that blocks the drug binding to its ligand would neutralize the drug. Antibodies that bind to epitopes on a drug that do not affect the function of the drug are non-neutralizing antidrug antibodies.

221 New Drug Application (NDA)

A process in the USA through which drug sponsors formally apply for approval by the **US FDA** for the sale and marketing of a new pharmaceutical.

222 nominal concentration

Theoretical or true concentration.

223 non-cell-based neutralizing antibody (NAb) assay

Analytical technique to assess the presence of neutralizing antidrug antibodies in a sample without using intact cells for analysis. Typically, such an assay uses the isolated drug target coated onto a plate and generates an analytical response upon binding of the drug to its target. The presence of a neutralizing **antidrug antibody** will interfere with the ability of the drug to bind to its target, resulting in a measurable change in assay signal.

224 nonspecific adsorption/binding

Undesirable phenomenon of the chemical adsorption of analytes to the interior surfaces of the vessels. Typically addressed by the use of a solvent composition within which the given **analyte** has increased or free solubility at the appropriate concentrations, the use of vessels of different material or surface chemistry, or the addition of compounds that block or compete for the binding of the **analyte** to the surface.

225 nontargeted analysis

Analysis of the composition of a complex sample without applying predefined selection criteria, with the aim to identify previously **unknown** sample components. The opposite of selective (targeted) analysis in which specific data are generated.

226 normal-phase chromatography

A type of chromatography employing a polar **stationary phase** and a nonpolar **mobile phase**. Hydrophobic analytes have limited affinity for the stationary phase and are eluted first, while hydrophilic analytes tend to adsorb to the stationary phase and are eluted by increasing the polarity of the mobile phase.

227 nuclear magnetic resonance (NMR) spectroscopy

Analytical technique that exploits the magnetic properties of some atomic nuclei to determine the physical and chemical properties of the atoms or molecules that contain them. Can provide highly detailed structural information and can be used both quantitatively and qualitatively.

228 online extraction

A bioanalytical methodology that integrates sample extraction, typically in the solid-phase extraction format, and chromatography after injecting biological **samples** such as **plasma** with no or minimal pretreatment.

229 optimization

The process of varying the conditions of an analytical **method** to determine the optimal **method** conditions.

230 oral administration

Route of administration where a substance is taken through the mouth. This includes buccal, sublingual and prelingual administration routes.

231 Organisation for Economic Cooperation and Development (OECD)

An international economic organization of 34 countries founded in 1961 to stimulate economic progress and world trade. It has issued a set of **good laboratory practice (GLP)** guidelines that are followed in multiple (e.g., European) countries.

232 orthogonal

Within a quantitative **method**, refers to at least two separation modes that demonstrate different selectivities, the optimized combination of which is favorable. The separation modes can be extractive, chromatographic or mass spectrometric.

233 out of specification (OOS) investigation

An initial laboratory finding that is outside of predefined limits requires a documented investigation of the cause, assessment of the potential impact, corrective action and preventive action.

234 outlier

A result that differs unreasonably from the others in a set of data, and is therefore a suspect measurement. Outliers may be verified as such using statistical methods.

235 over-curve concentration

A sample with concentration above the validated range of the analytical **method** (> **upper limit of quantitation [ULOQ]**).

236 parallelism

A condition in which **dilution** of test **samples** does not result in biased measurements of the **analyte** concentration. Determined for immunoassays by comparison of the responses from the **calibration standard** curve and serially diluted study samples in order to detect possible **matrix effect** or differing affinities for metabolites.

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237 parallel-line analysis (PLA)

A statistical **method** for the comparison of potency between a reference product and test product. It is used to calculate relative potency by comparing the dose–response curves of the two products.

238 paratope

The part of an antibody that recognizes an **antigen**.

239 parent ion

In mass spectrometry, an electrically charged molecular moiety that may dissociate to form fragments, one or more of which may be electrically charged, and one or more neutral species. Also called "**precursor ion**".

240 partial least squares regression (PLS)

Well-established regression-based **method** thanks to its ability to deal with many correlated variables or in situations where fewer observations than measured variables are available. PLS builds a low-dimensional sub-space by maximizing the covariance between the data and the class assignment. **Orthogonal** partial least squares analysis (O-PLS) and O2-PLS are recent extensions of the PLS **method** applied to metabolomic data.

241 partial validation

Series of analytical experiments where only relevant parts of the validation are repeated after **method** modifications or transfer are made to an existing fully validated bioanalytical method.

242 peak area

The area of the peak on a **chromatogram** produced by a substance subjected to chromatographic analysis. Proportional to the concentration of the substance.

243 peak area ratio

Ratio of the instrument response **peak area** of the target compound in the sample or sample extract to the peak area of the **internal standard**.

244 peak capacity

Chromatographic selectivity demonstrated by showing the maximal numbers of peaks that can be **baseline** resolved in a given chromatographic time window.

245 peak height

The instrument response height of the peak on a **chromatogram** produced by a substance subjected to chromatographic analysis. Proportional to the concentration of the substance.

246 peak height ratio

Ratio of the instrument response **peak height** of the target compound in the sample or sample extract to the peak height of the **internal standard**.

247 peak tailing

Distortion of the form of a chromatographic peak, which deviates from its theoretical Gaussian form due to one or more factors, including secondary interactions of the **analyte** with separation materials.

248 peak tailing factor

Also known as 'symmetry factor'; a chromatographic term that shows the asymmetry of a chromatographic peak.

249 peripheral compartment

The sum of all body regions to which a drug eventually distributes, but are less perfused and therefore are not in instantaneous equilibrium with the concentration in blood or **plasma**.

250 pharmacodynamics (PD)

The relationship between drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor.

251 pharmacokinetics (PK)

The kinetics of drug **absorption** distribution, and elimination (i.e., excretion and metabolism).

252 pharmacometabonomics/pharmacometabolomics

Analysis of endogenous metabolites in bodily fluids used to predict or evaluate the metabolism of pharmaceutical drugs, and to understand the pharmacokinetic profile of a drug. Alternatively, it is applied to measure **metabolite** levels following the administration of a pharmaceutical drug, in order to monitor the effects of the compound on certain biochemical pathways.

253 phospholipids

A class of lipids that are the major components of cell membrane bilayers. In **bioanalysis**, these have been identified as one of the major endogenous components that can cause **matrix effects**.

254 pipette

A manual or automated mechanical device that can accurately and repeatedly transfer liquid volumes of biological fluids, **stock solutions,** solvents, among others.

255 placebo

A substance containing no medication and prescribed or given to humans or animals in clinical or **preclinical trials** as a control treatment.

256 plasma

The pale yellow liquid component of blood that holds the blood cells in suspension.

257 plasma protein binding

The extent to which a drug binds to endogenous **plasma** proteins, often expressed as the fraction of the drug that is protein-bound (in percentage).

258 point-of-care testing

Also known as 'bedside testing'; bioanalytical testing near or at the site of patient care.

259 polymerase chain reaction (PCR)

A molecular biological **method** used to enzymatically amplify a single or few copies of a particular DNA sequence using short DNA sequences called DNA primers.

260 population-specific cut point

A threshold level determined for and applied to a target population to define the presence or absence of a response.

261 post-column infusion

Technique for the evaluation of **matrix effect** profiles in LC-MS analysis, by injection of a solvent blank or **matrix** blank into the chromatography column while simultaneously infusing **analyte** by a syringe pump to the column effluent.

262 post-translational modification (PTM)

Chemical modification to polypeptides, such as the attachment of functional groups (phosphate, carbohydrates), during their biosynthesis after their translation from mRNA sequence.

263 precision

The closeness of agreement (i.e., degree of scatter) among a series of measurements obtained from the same homogenous sample under controlled assay conditions. Precision is defined as (standard deviation/mean) × 100%. Three levels can be distinguished:

- **Repeatability**;
- Intermediate precision;
- **Reproducibility**.

264 preclinical trial

A study to test a drug, procedure, or medical treatment in animals.

265 precursor ion

See "**parent ion**".

266 predictive metabolomics

Prediction of quantitative functional value of a treatment by means of multivariate analysis using metabolome data (**metabolite** signatures) as the explanatory variable.

267 predose sample

Biological sample, typically **plasma**, that is taken from the test subjects prior to receiving the study drug(s).

268 preventative maintenance (PM)

Scheduled equipment maintenance in bioanalytical laboratories.

269 principal components analysis (PCA)

A statistical procedure using an **orthogonal** transformation of multivariate data, mostly used for exploratory analyses by extracting and displaying systematic variations. The vast majority of metabolomic studies involve PCA as a first exploratory step.

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270 Principal Investigator

An individual who, for a **multi-site study**, acts on behalf of the **Study Director** and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the **study plan** and its amendments, approval of the final report, and ensuring that all applicable principles of **good laboratory practice (GLP)** are followed.

271 processed sample

The final extract (prior to instrumental analysis) of a sample that has been subjected to various manipulations (e.g., extraction, **dilution**, concentration).

272 prodrug

A substance designed to be rapidly converted to its active ingredient in the body after administration. A prodrug is typically synthesized to enhance the systemic **absorption** of the active drug.

273 product ion

The ion resulting from the fragmentation of a charged molecular species in a mass spectrometer. Also known as a "**daughter ion**".

274 protein binding

The binding of compounds, with typical reference to xenobiotics, to large **plasma** proteins such as albumin. The extent of protein binding of a drug varies according to the chemistry of the drug itself and certain disease states, and only the unbound fraction is considered to be freely able to move into tissues or have activity with cellular surface receptors.

275 protein precipitation

A process for removing proteins from sample matrices involving aggregation and precipitation of proteins by adding a precipitation solvent or reagent, often using organic solvent or strongly acidic solution.

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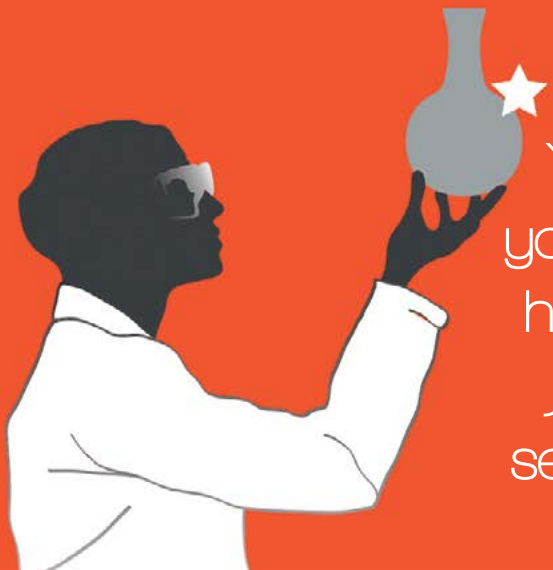

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276 protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial or a study. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

277 protocol amendment

Documentation of an intended change to the **study plan** after the study initiation date.

278 protocol deviation

Documentation of an unintended departure from the **study plan** after the study initiation date.

279 proxy matrix

A suitable **matrix** that can be used in place of an original matrix available in limited amounts.

280 qualified assay

Assay that is not validated, but is deemed suitable (scientifically sound) in performance for the purpose of the studies it is used to support. See also "**scientific validated assay**".

281 quality assurance

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in **compliance** with the applicable regulatory requirement(s). May also refer to the independent quality unit required within **good laboratory practices (GLPs)** for quality oversight.

282 quality control

Activities undertaken within the quality management system to verify that operational activities and derived data have been verified.

283 quality control sample (QC)

A sample spiked with a known quantity of **analyte** in the same **matrix** as the **unknown samples** that is used to monitor the performance of a bioanalytical **method** and to assess the integrity and validity of the results of the unknown samples analyzed in an individual run.

284 quantification range

The range of concentrations, including ULOQ and LLOQ, that can be reliably and reproducibly quantified with **accuracy** and **precision** through the use of a concentration–response relationship.

285 radioimmunoassay (RIA)

A sensitive, competitive, **immunoassay** technique whereby a limited amount of radiolabeled **antigen** competes with unlabeled antigen for binding to a limited amount of specific antibody. Competition with increasing amounts of unlabeled antigen provides a **calibration curve** from which concentrations of antigen in study **samples** may be interpolated.

286 raw data

Per the **Organisation for Economic Cooperation and Development (OECD) good laboratory practice (GLP)** regulations, all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. According to the **US FDA**, any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes that have been transcribed verbatim, dated and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data.

287 reactive metabolite

Drugs are generally converted to biologically inactive forms and eliminated from the body, principally by hepatic metabolism. However, certain drugs undergo biotransformation to reactive metabolites that can interfere with cellular functions. These are often electrophilic and can interact with DNA and proteins to form covalently bound products.

288 reanalysis

Repetition of a series of analytical procedures from the processing step on **samples** that have been previously analyzed.

289 recovery (extraction)

The extraction efficiency of an analytical process, reported as a percentage of the known amount of an **analyte** carried through the sample extraction and processing steps of the **method**.

290 reference standard

A substance well-characterized for its chemical and physical properties, accompanied with a **certificate of analysis (CoA)** that provides the purity and expiration (or retest) date.

291 regulated bioanalysis

Bioanalysis conducted in **compliance** with regulatory requirements (e.g., **US FDA**, **EMA**, ANVISA, MHLW).

292 regulatory validation

The conduct and reporting of experimental testing of a **method** to demonstrate that the concentration data are scientifically accurate, reproducible and reconstructable to allow valid decision-making for the intended purpose of the study, and comply with regulated bioanalytical standards as defined in guidance and guidelines.

293 relative bioavailability

The **bioavailability** of a formulation of a drug compared with that of an alternative formulation.

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294 relative standard deviation (RSD)

See "**coefficient of variation**".

295 repeatability

Repeatability expresses the **precision** under the same operating conditions over a short interval of time. Repeatability is also synonymous with **intraassay precision**.

296 reproducibility

Reproducibility expresses the **precision** between multiple measurements of a sample or sample sets, which may include those between laboratories (collaborative studies, usually applied to standardization of methodology).

297 resolution

The extent of separation of two or more compounds using a given technique, such as chromatography or mass spectrometry.

298 response function

A mathematical treatment that adequately describes the relationship between instrument response (e.g., **peak area** or height ratio) and the concentration (amount) of **analyte** in the sample. Response function is defined within a given range.

299 retention time (RT)

Refers to the specific time needed by the **analyte** to be detected after its injection into a separative process (e.g., a **chromatographic column**).

300 reversed-phase chromatography

Type of chromatography employing a nonpolar **stationary phase** and a polar **mobile phase**. Hydrophilic analytes have limited affinity for the stationary phase and are eluted first, while hydrophobic analytes tend to adsorb to the stationary phase and are eluted by decreasing the polarity of the mobile phase.

301 risk-based approach

Has multiple meanings in drug development, all relating to the evaluation of the risk of failure versus the resource investment required to maintain the required quality level. The regulatory guidance and **white papers** by health authority authors support a risk-based approach for companies designing their own tiered testing schemes (i.e., **fit-for-purpose** bioanalytical strategy). This is also used in terms of a **tiered approach** for **metabolite** analyses and in consideration of **biomarker** analyses.

302 r-squared

A term, often referred to as the correlation coefficient, used to assess the fitness of a linear relationship when performing regression.

303 signal-to-noise ratio (S/N)

The ratio of actual response signal to the differentiated background signal for a given detector.

304 salting out assisted liquid–liquid extraction (SALLE)

The process by which a solution is supersaturated with salt to cause the formation of a biphasic system between a water sample and a water miscible sample.

305 sample

A generic term encompassing calibrators, controls, blanks, unknowns and **processed samples**.

306 sample diluent

Aqueous or organic fluids used to dilute the **analyte** prior to the analytical process (e.g., chromatographic separation, **derivatization**, binding to a receptor or antibody).

307 sample pretreatment

A process whereby fluid or tissue **samples** are homogenized, lysed, digested, sonicated, pulverized or extracted prior to analysis.

308 scientific validation

To provide concentration data that are scientifically accurate, reproducible and reconstructable to allow valid decision-making for the intended purpose of the study and that can withstand independent review (and, although not following regulated guideline "**standard operating procedure (SOP)**", also review from regulators if so required). Within scientific validation, the following tiers can be defined: "**stage-appropriate scientific validation**" or "**assay-appropriate scientific validation**".

309 selected reaction monitoring (SRM)

The most selective tandem quadrupole operating mode and ideal for quantitative applications. **Precursor ions** are isolated then collision-activated dissociation of the precursor occurs, with **product ion** isolation completing the process.

310 selectivity

The ability of the bioanalytical **method** to measure and differentiate the analytes in the presence of components that may be expected to be present. These could include metabolites, impurities, degradants or **matrix** components.

311 sensitivity

The lowest **analyte** concentration that can be measured above the noise with acceptable **accuracy** and **precision** (i.e., **lower limit of quantification [LLOQ]**).

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312 serum

The liquid that is obtained after clotting of the blood and subsequent **centrifugation**.

313 shotgun proteomics

Identification of proteins in the sample is based on a preliminary enzymatic **digestion** of the mixture followed by **HPLC**–MS/MS characterization of the resulting peptides.

314 significant human metabolite

A **metabolite** seen in humans that is either greater than 10% of all drug-related material in circulation or a metabolite whose exposure in humans is greater than that seen in animal species. A significant human metabolite typically requires additional monitoring or studies to demonstrate its safety.

315 single-dose administration

The next dose of the same drug is administered only after the drug of the previous dose is completed eliminated from the body.

316 size-exclusion chromatography

Chromatographic separation based on the relative sizes of the analytes.

317 solid-phase extraction (SPE)

A sample preparation procedure using packed solid sorbent and defined **protocol** of conditioning, equilibration, **sample pretreatment**, loading and **elution** to provide a separation of analytes from other biological components.

318 solubility

The propensity for an **analyte** to dissolve in a liquid forming a homogeneous solution, dependent on the physical and chemical properties of the solute and solvent.

319 specificity

The ability to measure the **analyte** unequivocally in the presence of other compounds, either exogenous or endogenous, in the **matrix**.

320 specimen

A specifically selected proportion of a material taken from a dynamic system and assumed to be representative of the parent material at the time it is taken. See also "**sample**".

321 spike recovery

The amount of **analyte** that is measured upon analysis of a sample (e.g., **matrix**) to which a known amount of analyte has been added. See also "**recovery**".

322 stability

The chemical stability of an **analyte** in a given **matrix** under specific conditions for given time intervals.

323 stable-labeled isotope

Analyte in which a few atoms are exchanged with heavy isotope counterparts, typically ^{2}H, ^{15}N or ^{13}C. It is commonly used as an **internal standard** in LC–MS **bioanalysis** as it has very similar physical and chemical properties as the analyte and works well to compensate for the variability due to extraction, chromatography and mass spectrometry (MS) detection.

324 stage-appropriate scientific validation

One process of scientific validation, where, depending on the stage of development in which the study is supported, the proposed assay criteria for scientific validation may be different. In all stages, however, the reported concentrations support valid and documented decisions in the study. When a compound progresses in development, the study could change from nonpivotal (internal decision) into pivotal. **Regulatory validation** can be considered as the ultimate level of stage appropriate scientific validation.

325 standard curve

The relationship between the experimental response values and the analytical concentrations of the calibrants (also called "**calibration curve**"). Is also used for the physical **samples** used to generate the experimental responses.

326 standard operating procedure (SOP)

Document that describes the recurring operations relevant to the quality of an activity that enables proper, consistent execution of the operations by someone knowledgeable in the field.

327 stationary phase

In chromatographic methods of analysis, typically, a solid material (typically modified silica or polymeric material) usually contained in a column, through which a **mobile phase** is moving. Separation of a mixture of analytes is achieved by differences in partitioning, adsorptive, electrostatic or affinity-type interactions between the mobile and stationary phases.

328 steady state

The level of the drug in blood and tissue upon multiple dosing when input and output are at equilibrium during sequential dosing intervals.

329 stock solution

Solution containing **analyte** of interest at a known concentration that can be further diluted to prepare calibration standards and **quality control samples (QCs)** in biological fluids.

330 Study Director

Has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control.

331 Study Monitor

Responsible for overseeing the progress of a clinical study, and for ensuring that it is conducted, recorded, and reported in accordance with the **protocol**, **standard operating procedure (SOP)**, **good clinical practice (GCP)** and applicable regulatory requirement(s).

332 study plan

A document to describe the purpose and procedure of an experiment or a study. A study plan may supersede **standard operating procedure (SOP)** requirements.

333 supercritical fluid chromatography (SFC)

Also known as "convergence chromatography", a chromatographic technique that employs a supercritical fluid as the **mobile phase**.

334 superficially porous (core-shell) particle technology

In LC columns, the use of particles that have a nonporous core but fully porous outer layer.

335 supernatant

The liquid layer resting above a lower layer or solid residue, such as after **centrifugation** following **protein precipitation** from **plasma**.

336 supported-liquid extraction

Sample extraction technique fundamentally analogous to **liquid–liquid extraction** but with a different **protocol** that involves sample application to a solid support, composed of diatomaceous earth, and from which the analytes are subsequently eluted with water-immiscible organic solvent.

337 surface plasmon resonance (SPR)

Change of the reflective index of light reflected off a metallic film resulting from biomolecular binding on the opposite side of the film.

338 surrogate analyte

A compound similar to the **analyte** of interest used to evaluate extraction efficiency and **matrix effects** (e.g., stable-labeled isotope analogs).

339 surrogate matrix

Alternative **matrix** used in **bioanalysis** in place of an endogenous matrix that is difficult to sample, recreate or maintain.

340 system priming

Injection of extracted biological **samples** into a **HPLC** system prior to the run under the chromatographic condition for the **analytical run**. System priming is mainly for blocking active sites that may adversely adsorb the analytes of interest. It should not be confused with **system suitability**.

341 system suitability

Determination of instrument performance (e.g., **sensitivity** and chromatographic retention) by analysis of a specific **samples** conducted prior to the **analytical run**.

342 tandem mass spectrometry

See "**tandem quadrupole mass spectrometry**".

343 tandem quadrupole mass spectrometry

A quantitative tandem mass spectrometer consists of two quadrupole mass spectrometers in series, with a (non-mass-resolving) radio frequency (RF)-only quadrupole between them to act as a cell for collision-induced dissociation. The first (Q1) and third (Q3) quadrupoles serve as mass filters. **Precursor ions** selected in Q1 are dissociated in the collision cell in the presence of an inert gas such as Ar, He or N_2. Resulting fragments are passed through to Q3 where they may be filtered or scanned. This configuration is sometimes referred to as a triple quad mass spec and is often abbreviated QqQ.

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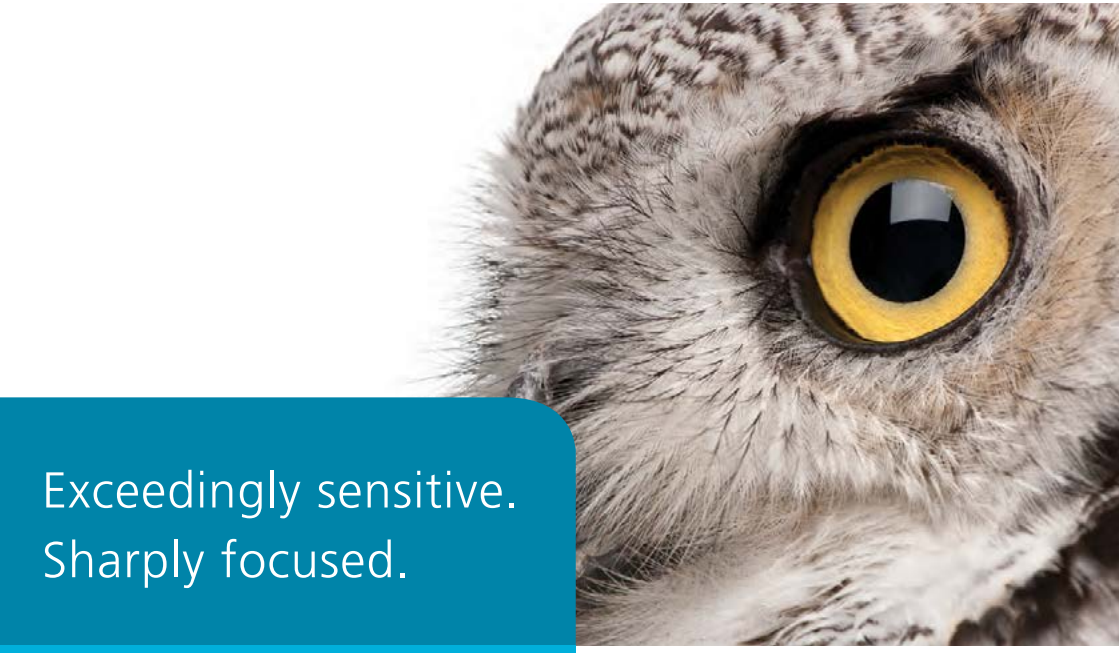

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344 targeted analysis

Analysis of the composition of a complex sample by applying predefined selection criteria with the aim to quantify or verify the occurrence of previously identified sample components.

345 therapeutic drug monitoring

Clinical monitoring of patient drug concentrations in **plasma**, serum or blood in order to enhance treatment efficacy, or reduce toxicity. Typically used to treat patients taking marketed drugs.

346 tiered approach

A science-driven, **fit-for-purpose** strategy for scientific validation applying a predefined appropriate level of bioanalytical quality, for the analysis of biological samples originating from preclinical and clinical studies. Level of pre- or in-study validation, **acceptance criteria** and documentation depend on the intended use of the concentration data, and consider the type of study (**assay-appropriate scientific validation**), and/or the stage of drug development (stage-appropriate scientific validation and **regulatory validation**) in which the study data are generated.

347 time-of-flight mass spectrometry (TOF-MS)

Mass analyzer that utilizes a field-free vacuum chamber to separate ions by their velocity. The time-of-flight is then converted into the **accurate mass** of the observed ion.

348 tissue distribution

The extent of accumulation of a therapeutic agent or chemical substance in various organs.

349 total drug

The sum of the bound and **free drug** within a biological system.

350 total ion chromatogram (TIC)

A **chromatogram** showing the sum of intensities of all mass spectral peaks belonging to the same scan.

351 Ultra-high-performance liquid chromatography (UHPLC)

Makes use of support particles that often have diameters less than 2 µm in size. These smaller particles make it possible to obtain more efficient separations but also increase the pressure that is required to apply the **mobile phase** through a given length of column.

352 unknown

A biological sample that is the subject of the analysis with the goal to determine **analyte**(s) concentrations.

353 upper limit of quantification (ULOQ)

The highest concentration **calibration standard** of an **analyte** that can be quantitatively determined with **precision** and **accuracy**, and represents the concentration above which **incurred samples** must be diluted to achieve a response less than this concentration.

354 US Food and Drug Administration (US FDA)

An agency within the US Public Health Service that is responsible for approving the safety and efficacy and marketability of medicines, among other health-related services.

355 validation report

A summary of the experimental (assay **method**) validation findings that define the performance characteristics of the method for its intended use. It describes the statistical acceptance of the method.

356 van Deemter equation

H = A + B/u + Cu; the A term represents the contribution from eddy diffusion. Eddy diffusion results from radial flow inequalities through a packed bed. The B term (B/u) represents the contribution from longitudinal diffusion. The C term (Cu) represents the contributions from resistance to mass transfer in the **stationary and mobile phases**. u is mobile phase velocity (mm/s). An optimum mobile phase velocity exists for a column at which its highest efficiency would be realized. While the A term is somewhat fixed for each column, the B and C terms play a significant role in the column efficiency.

357 Very-high-pressure liquid chromatography (VHPLC)

See "**UHPLC**".

358 weighting factor

Weighted least-squares **linear regression** is justified in the commonplace scenario of the statistical **error** or variability of instrumental response being approximately proportional to **analyte** concentration. A weighting factor such as $1/x$ or $1/x^2$, where x denotes concentration, is chosen in accordance with the severity of weighting required.

359 white paper

Authoritative report or guide helping readers understand an issue, solve a problem, or make a decision. Typically written by a panel of subject matter experts to ensure a broad consensus.

360 whole blood

Unmodified or unseparated blood sample. May be drawn from arteries or veins.

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The audience for Future Science titles consists of clinicians, research scientists, decision-makers and a range of professionals in the healthcare community.

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Word limit: 4000–8000 words (excluding Abstract, Executive Summary, References and Figure/Table legends). Mini-reviews are also accepted.
Required sections
(for a more detailed description of these sections go to www.future-science.com):
- Abstract
- Defined key terms
- Future perspective
- Executive summary
- References: target of 150 maximum
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- Financial disclosure/acknowledgements

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Word limit: 1500–3000
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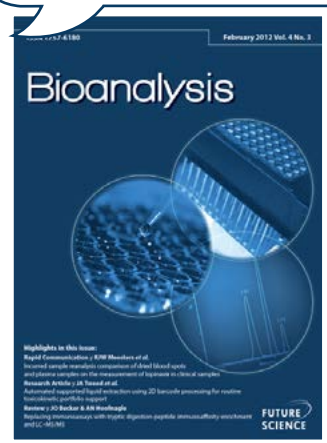

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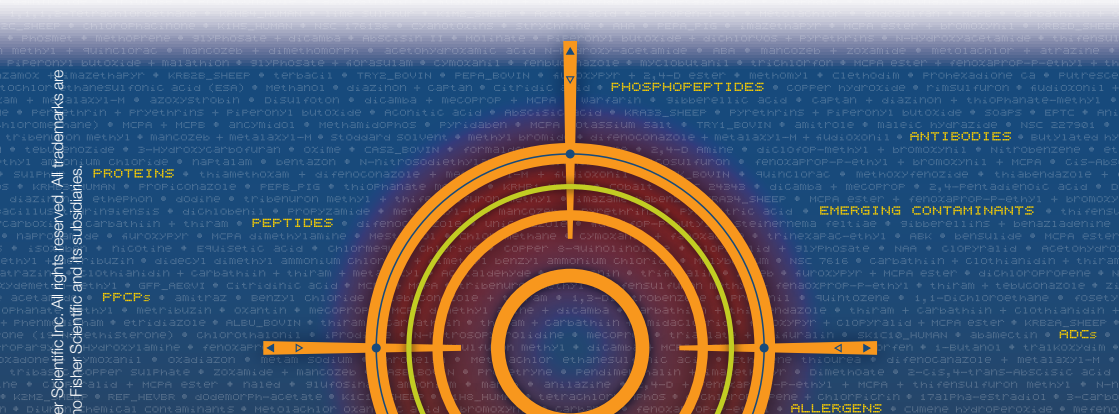

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