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GENERAL PAPER

Analytical Methods Committee

Evaluation of analytical instrumentation. Part XXII Instrumentation for liquid chromatography/mass spectrometry

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Abstract The reports of this series tabulate a number of features of analytical instruments that should be considered when making comparison between various systems. Scoring these features in a rational manner allows a scientific comparison to be made between instruments as an aid to selection. This is the XXIInd report of the series and deals with instrumentation for liquid chromatography/mass spectrometry.

Keywords Instrumentation · Overview · Evaluation · Liquid chromatography/mass spectrometry

Introduction

The following report was compiled by the above sub-committee of the AMC, which consists of Professor S. Greenfield (chairman), Dr. M. Barnard, Dr. C. Burgess, Dr. D. Edwards, Professor S. J. Hill, Dr. K. E. Jarvis, Dr. G. Lord, Dr. M. Sargent, Dr. P. J. Potts, and Dr. M. West with Dr. E. J. Newman as secretary. The initial input of the features for consideration was undertaken by a working party comprising Drs. P. J. Potts and M. West to whom the committee expresses its thanks.

The purchase of analytical instrumentation is an important function of many laboratory managers, who may be called upon to choose between wide ranges of competing systems that are not always easily comparable. The objectives of the Instrumental Criteria Sub-Committee are to tabulate a number of features of analytical instruments that should be considered when making a comparison between various systems. As is explained below, it is then possible to score these features in a rational manner, which allows a scientific comparison to be made between instruments as an aid to selection.

The overall object is to assist purchasers in obtaining the best instrument for their analytical requirements. It is hoped that this evaluation will, to some extent, also help manufacturers to supply the instrument best suited to their customers' needs. It is perhaps pertinent to note that a number of teachers have found the reports to be of use as teaching aids.

No attempt has been made to lay down a specification. In fact, the committee considers that it would be invidious to do so: rather it has tried to encourage the purchasers to make up their own minds as to the importance of the features that are on offer by the manufacturers.

The XXIInd report of the Sub-Committee deals with instrumentation for liquid chromatography/mass spectrometry (LC/MS).

Notes on the use of this document

Column 1	The features of interest.
Column 2	What the feature is and how it can be evaluated.
Column 3	The Sub-Committee has indicated the relative importance of each feature and expects users to decide on a weighting factor according to their own application.
Column 4	Here the Sub-Committee has given reasons for its opinion as to the importance of each feature.
Column 5	It is suggested that scores are given for each feature of each instrument and that these scores are modified by a weighting factor and sub-totals obtained. The grand total will give the final score that can contribute to the selection of the instrument that best suits the user's requirements.

Notes on Scoring

1. (PS) Proportional scoring. It will be assumed, unless otherwise stated, that the scoring of features will be by proportion, e.g., Worst/0 to Best/100.
2. (WF) Weighting factor. This will depend on individual requirements. All features mentioned in the tables have some importance. If, in Sub-Committee's opinion, some

features are considered to be of greater importance they are marked I. Those features of greatest importance are marked as VI (very important). A scale should be chosen for the weighting factor that allows the user to discriminate according to needs, e.g., × 1 to × 3 or × 1 to × 10.
3. (ST) Sub-total. Multiplying PS by WF obtains this.
4. In some circumstances, where there is a fundamental incompatibility between a feature of the instrument and the intended application, it may be necessary to exclude an instrument completely from further consideration.

With these requirements in mind, the user should then evaluate the instruments available on the market, taking into account the following guidelines and any financial limitations. In many instances it will quickly become clear that a number of different instruments could be satisfactory and non-instrumental criteria and may then become important. However, in some specialized cases, only one or two instruments will have the ability or necessary features to be used in the intended application.

The guidelines are intended to be used as a checklist of features to be considered, mostly of the instrument itself, but also of service requirements and any existing relationship between the user and the manufacturer. The relative importance of these features will depend on a number of factors, which in some circumstances could be subjective. However, if all the points have been considered, the choice should be informed.

The committee considers that instrumentation for energy dispersive X-ray spectrometry is safe in normal use, but care should be taken to avoid exposure to X-ray radiation by ensuring that all safety features are fully operational and that instrumentation is used strictly in accordance with the manufacturer's instructions.

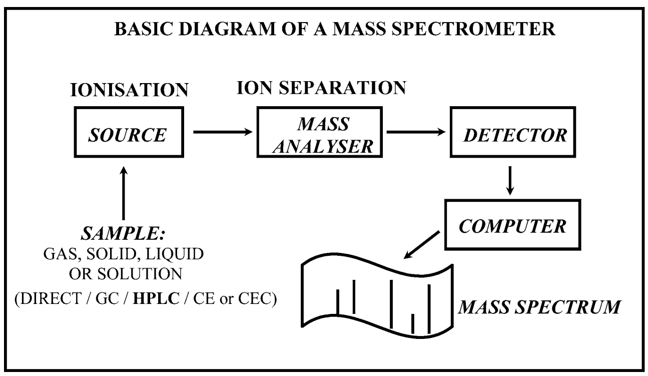
Finally, as many laboratories are now working to established quality standards, some consideration should be given to third-party certification of the manufacturer to standards such as the ISO Guide 9000 series. Such certification should extend to the service organisation.

An overview of liquid chromatography/mass spectrometry (LC/MS)

Liquid chromatography is good for separating mixtures but poor at the identification of compounds, while mass spectrometry offers the converse. Thus, the combination of these two analytical techniques results in a powerful synergistic relationship. At the present time, no instrument manufacturer offers an integrated LC/MS system as may be found for GC/MS, although there is a trend in the industry via collaboration or mergers to provide more complete systems with shared software, for example. However, at the present time, it is still probably best to consider the purchase of the HPLC and mass spectrometer separately, with the proviso of the desirability of software that is compatible between the two instruments. This report will therefore only be concerned with the mass spectrometry aspect of instruments suitable for LC/MS, but will include interface considerations. An earlier report by the committee is concerned purely with instrumentation for HPLC and is listed above.

There is a wide range of about 60 mass spectrometry instruments on the market available from about a dozen manufacturers, with differing ionisation methods, various mass analysers and wide variation in price. There is no single 'black box' instrument, making selection of a suitable instrument difficult. The purpose of these notes is to provide some guidance to areas which should be considered, so that the choice is based on a full consideration of available options. The first task in the selection of an instrument is to examine the range of analyses that it will be expected to perform. Care should be taken not to specify these requirements too closely as use can change with time. The use of LC/MS can be divided into three main areas: (1) Molecular weight determination, possibly with fragmentation of the molecule for structural information and where the quantitative aspect is of little or no importance; (2) Selective and sensitive detection of specific molecules, where the quantitative aspect is important, but molecular weight is of secondary importance; (3) Quantification and confirmation of the identity of a specific molecule, where molecular weight, specific fragmentation together with sensitivity and selectivity are all important.

So-called *accurate mass* measurements, which may be misleading to non-practitioners, can be performed on instruments with high-resolution mass analysers. This involves determining mass to within a sufficient number of significant figures that uncertainties are in the low parts-per-million (ppm) range, implying higher levels of accuracy and precision. Empirical formulae may be determined by such measurements, especially for low molecular weight compounds.



Having decided on the requirements, the user should evaluate the instruments available on the market while bearing in mind the guidelines and financial limitations. In many cases it will quickly become clear that a number of different instruments could be satisfactory and non-instrumental criteria may then be important.

Background of LC/MS

A block diagram of a mass spectrometer is shown in the diagram above. Mass spectrometers measure the mass-to-charge (m/z) ratio of ionised molecules. The analyte must be converted into the gas phase if not already so (for LC/MS the analyte is in solution, of course) and simultaneously or subsequently ionised, if not already present as an ionic species, which is a prerequisite for electrospray ionisation. This process takes place in the *source* of the mass spectrometer and may occur at atmospheric pressure or in vacuum, depending on the type of ionisation employed. Ions are then separated on the basis of their mass and charge (m/z) in the mass analyser, of which there are several types, at high vacuum. The separated ions then pass to the detector, again of which there are several types.

The coupling of liquid chromatographic techniques with mass spectrometry is an important development and continues to evolve. Interfacing began in the early 1970s and involved techniques to evaporate solvent or split the flow from HPLC columns to admit eluent into the high vacuum sources in use at the time, but it was not until 1987 and the commercialisation of atmospheric pressure ionisation (API) that LC/MS became prominent. Other interfaces such as thermospray, particle-beam and continuous-flow fast-atom bombardment, involving sources at vacuum are still in use, but API interfaces are by far the most widely used and would be first choice in a new instrument purchase. Thermospray interfaces are no longer available on the market, but particle-beam is available and has a niche where electron impact ionization-type spectra may be desired from applicable, relatively non-polar molecules. This report will consider only API-based interfaces, being the most inherently suitable for coupling liquid chromatographic techniques with mass spectrometry and representing well over 90% of the LC/MS market.

API is a general name for ionisation techniques where ions are formed at atmospheric pressure and involve ‘soft’ ionisation, producing little fragmentation and mainly providing molecular weight information. However, fragmentation may be induced in-source, in a ‘collision cell’ placed between two mass analysers in a tandem MS/MS instrument or in an ion-trap mass spectrometer. Fragmentation of a molecule provides structural information or may be used quantitatively where specific fragmentations are monitored, leading to improved sensitivity.

There are three main API techniques: electrospray ionisation (ESI), atmospheric pressure chemical ionisation (APCI), and the relatively new technique of atmospheric pressure photo-ionisation (APPI). ESI can be subdivided into pneumatically assisted electrospray (nitrogen gas is used for nebulization), nanospray and multiple-sprayer electrospray, together with a number of trade names, but all rely on the same mechanism of ion formation. In ESI, ionised droplets are produced by applying high-voltage (typically 3–5 kV), to the outlet of a capillary carrying the HPLC eluent (or analyte in solution for direct infusion). A fine mist of charged droplets is produced and this takes place at atmospheric pressure. Nitrogen gas is also used as a ‘curtain’ gas to aid de-solvation of the droplets, together with source heating and de-solvated ions are guided through ‘skimmers’ into the high vacuum region of the mass analyser by application of appropriate electric fields. Nanospray is a later development of electrospray, using sub-μl/min flow rates and where the outlet of the capillary is narrower and often tapered, resulting in smaller droplets and more efficient ionisation. Multiple sprayers (2–8) may be used in either technique, where independent liquid streams are fed into the MS source and sampled sequentially into the mass analyser. This allows coupling of several HPLC systems into one mass spectrometer and/or use of a standard reference solution, for ‘accurate mass’ determinations, for example.

APCI is another development of ESI, where the HPLC eluent is rapidly evaporated by passing through a nebulizer at high temperature. Ionisation is produced by corona discharge in the spray and solvent ions are produced which can react with the analytes in the gas phase (chemical ionisation).

APPI is a newer technique with the claim of fewer matrix effects than ESI or APCI. HPLC eluent is sprayed with a nebulizing gas into a heated probe, as in APCI and a ‘dopant’ compound is vaporised and ionised by UV radiation, forming ‘photo-ions’. The photo-ions initiate a cascade of ion-molecule reactions, forming ionised analytes.

ESI is generally most suitable for relatively polar molecules, across a wide range of molecular mass, while APCI and APPI are most suitable for small (less than 1,000 Da), relatively non-polar molecules. Applications of these techniques cover a vast range, including drug metabolism studies often involving quantitation as well as molecular structural studies, natural products, chemical synthesis structure confirmation and many others. Of particular note is the use of MS and LC/MS in the relatively new area of proteomics to determine protein structures and this is a fast-growing and large application area.

Instrumental criteria sub-committee instrument evaluation form

Type of instrument: liquid chromatography/mass spectrometer
Manufacturer:
Model no:

Feature	Definition and/or test procedures and guidance for assessment	Importance	Reason	Score		
A. Non Instrumental Criteria						
Selection of manufacturer	Laboratories in possession of other mass spectrometers should score highest for the manufacturer with the best past record based on the following sub-features:			PS WF ST		
(a) Previous instruments						
(i) Innovation	Company's record for developing instruments with innovative features.	I	The manufacturer should be alert to developments in chromatography and MS technology.	PS WF ST		
(ii) Reliability record	Company's record for instrument reliability.	I	Indicates history of sound design/manufacturing concepts.	PS WF ST		
(iii) Similarity of operation, layout and design (including software) to existing instruments in the laboratory	For routine purposes, this may be important. However, this may be less important for research applications.	I	Similarity of design and operation means that operators can draw on in-house expertise, resulting in reduced costs and time for training. It may also maximise the use of spares and fittings.	PS WF ST		
(iv) Ability to upgrade instrument and software	Availability and ease of upgrades to the instrument.	I	Improvements in technology with gains in performance, extends instrument life and capability.	PS WF ST		
	Availability and ease of software upgrades and compatibility with earlier versions.	I	Extends instrument life, also important that old data remains accessible.			
(v) Confidence in the supplier	Confidence gained from past personal experience.	I	The benefits arising from good working relationship already in place.	PS WF ST		
(b) Servicing	Score according to manufacturers' claims and past record, judged by the sub-features (i) to (v) below					
(i) Service contract	Availability and cost of a suitable service contract from the supplier or agent. Reliability of service provided.	VI	Essential to ensure reliable operation over the planned working life of the instrument. Often ensures preferential service and guarantees a specific response time to call-outs.	PS WF ST		
(ii) Availability and delivery of spares	Range of stock carried by, or quickly available to, the manufacturer or agent.	I/VI	Rapid delivery of spares reduces instrument down time.	PS WF ST		
(iii) Call-out time	The time for the engineer to reach the laboratory following a call.	I	A rapid response reduces instrument down time. Nb. The guaranteed call out time may vary, depending on the type of service contract chosen.	PS WF ST		
(iv) Effectiveness of service engineers	The ability of the service engineer to identify and repair faults as judged from previous experience and reports of others, including the carrying of 'common' spares.	I	Ability to repair on-site avoids return visit or removal of equipment for off-site repair, reducing down time and cost.	PS WF ST		
(v) Cost of call out and spares	It may be inappropriate to score this feature if in-house servicing is contemplated or the call out is included in the service contract.	I	The proximity of the service centre may be a factor in travel costs. Note that many service contracts exclude 'consumables', the provision of which may contribute a significant additional cost.	PS WF ST		
(c) Technical support	Score according to manufacturers' claims and past record, judged by the sub-features (i) to (vii) below.					
(i) Applications department	The advice and training available from the manufacturer's applications department.	I	This helps in-house staff to optimise use of the equipment and with new applications.	PS WF ST		
(ii) Technical literature	The range and quality of technical literature including the operating manual. Availability of updates.	I	The availability of good technical literature helps operators optimise the use of the instrument. Note that many instruments have operating instructions incorporated into the instrument operating software.	PS WF ST		
(iii) Telephone assistance	Willingness of the manufacturer, supplier or contractor to give effective advice over the telephone. This can normally only be evaluated by reference to existing users.	I	Rapidly available technical help reduces the number of call outs.	PS WF ST		
(iv) Remote diagnostics	Facility that allows an engineer to assess the status of an instrument by telephone/modem access from a remote location. Score for the availability of this feature if appropriate.	I	Remote diagnostics often help in reducing downtime by facilitating rapid identification of faults. Networking may also enable engineers based in the manufacturer's factory to interrogate the instrument from a distance.	PS WF ST		

Feature	Definition and/or test procedures and guidance for assessment	Importance	Reason	Score		
(v) Training	This includes initial training when setting up the instrumentation and follow up courses for more advanced users.	VI	A comprehensive training scheme will ensure that operators and instrumentation are working effectively.	PS WF ST		
(vi) Installation	Installation and site requirements.	I	Specifying fittings, gases required and any water cooling, together with site requirements such as ambient temperature and floor weight loadings before installation will save time.	PS WF ST		
(vii) User group	Informal newsletters, meetings etc. organised by manufacturer or agent.	I	Other users are often a good source of advice.	PS WF ST		
B. Instrumental criteria	The specific tests recommended in this report should be discussed with the instrument manufacturer in advance of any evaluation to ensure that any testing is undertaken in a practical and effective manner.					
1. General features Facilities required for:						
(a) Access, and location of the connections and controls on the instrument	Score according to convenient access taking into account the proposed location of the instrument.	I	Instrument may be free standing, or increasingly, bench mounted. Depending on bench position and layout, connections and controls may limit accessibility for servicing and installation particularly at the rear of the instrument.	PS WF ST		
(b) Power requirements	Score maximum for compatibility with existing electrical supply, both with regard to loading and stability	Varies with users' circumstances	Additional power requirements may significantly increase installation costs. Most modern instruments only require a standard 13-A electrical supply, not 3-phase.	PS WF ST		
(c) Size and weight of equipment	Score according to practicality of installation.	I/VI	The instrument must be compatible with existing laboratory accommodation otherwise expensive alterations will be required. The size of instrumentation may be critical if space is limited.	PS WF ST		
(d) Environmental control	Score according to the tolerance of the instrument to factors such as temperature, and humidity, as relevant to the environment in which the instrument is to be installed. Accurate mass measurements, especially with TOF mass spectrometers require stable temperatures for best accuracy.	VI	Additional installation costs may be considerable, if control of environmental factors is necessary. Air-conditioning is often necessary.	PS WF ST		
2. Gas supplies	Constant mass flow of gases is desirable, especially nitrogen nebulizer gas, but also including collision gases like argon, where applicable. The score is highest for systems using electronic mass-flow controllers. Nitrogen is often provided by a gas generator because of the high requirement.	VI	Variations in the stability of the nebulizer spray can give rise to errors in mass accuracy and chromatographic peak integrity.	PS WF ST		
Vacuum system						
Time to achieve instrument operating vacuum and to vent to atmosphere	Score highest for instrumentation that can achieve operating vacuum, or conversely, be vented to atmosphere in the shortest time.	I	Achieving an operating vacuum can delay analysis. More recent MCP detectors require longer time.	PS WF ST		
Power failure protection	Score for protection system that automatically vents instrument safely in the event of power failure. Where appropriate, safely shuts down instrument in event of water supply failure.	I	Avoids instrument downtime and repair costs.	PS WF ST		
3. Ionization sources						
Compatibility	Score for availability of non LC/MS type interfaces, such as electron ionization (EI), where required.	I	The instrument may need to be multitasking, being able to perform GC/MS, for example.	PS WF ST		
Source voltage	Score for earthed electrospray capillary where appropriate. This may be very important.		Electrospray capillary usually at high voltage (3–5 kV), but can result in electrochemical reactions of susceptible analytes. For capillary electrophoresis (CE) or capillary electrochromatography (CEC) coupling, earthed source is useful.	PS WF ST		
Polarity switching	Score highest for ability to switch between positive and negative mode ionisation during acquisition.	I	Analytes preferentially ionise in positive or negative mode, depending on compound type. Prediction not possible with 'unknown' compounds.	PS WF ST		

Feature	Definition and/or test procedures and guidance for assessment	Importance	Reason	Score		
Electrospray (ESI/API)	Score highest for instrumentation that will accept the widest range of eluent flow rate. This will be achieved by use of a source heater with a wide variable temperature control and with nebulizer gas with a wide range of flow rates.	I	HPLC columns used in LC/MS range from 'analytical' at approx. 1 mL/min. flow rates, through 'microbore' at μL/min, to capillary at sub μL/min flow rates (see nanospray).	PS WF ST		
Nanospray	Score highest for instrumentation which has provision of a nanospray source, essential for capillary HPLC capability, where applicable. Alternatively, score for system where 'make-up' flow of liquid can be incorporated into capillary HPLC eluent for conventional electrospray.	I	Electrospray operates at flow rates greater than about 5 uL/min. Flow rates lower than this require 'nanospray' ionisation, which also has higher sensitivity. Addition of 'make-up' flow to bring flow rate up to electrospray requirements is an alternative, but does not benefit from improved sensitivity.	PS WF ST		
Atmospheric pressure chemical ionisation (APCI)	Score for instrumentation where APCI is available and appropriate to type of analyte.	I	APCI operates at higher flow rates (1 mL/min and higher) than ESI and is very suitable for analytes of low-polarity, molecular weight below about 1,500. In addition, it has wider dynamic concentration range and is less susceptible to ion suppression than ESI.	PS WF ST		
Atmospheric pressure photoionisation (APPI)	Score for instrumentation where APPI is available and appropriate to type of analyte.	I	APPI is a new technique, applicable to analytes, as for APCI (low-polarity, molecular weight below about 1,000). Performance is claimed to be better than APCI for suitable compounds, with even wider dynamic concentration range and better sensitivity.	PS WF ST		
Mass analysers	Several types of mass analyser are used in LC/MS applications. These include quadrupole, ion-trap, TOF and Fourier transform ion cyclotron resonance (FT-MS). Sector instruments are not used so much now for LC/MS. Score for most appropriate characteristics for the application.	VI	Choice of mass analyser(s) depends on several factors, especially speed of data acquisition, resolution and if MS/MS is required. Cost of instrumentation is a further factor, since there is a wide variation in price, depending on type.	PS WF ST		
Single mass analysers (as distinct from MS/MS instruments). *m/z* range	Score as appropriate to analytes for minimum and maximum range.	I	A wide *m/z* range will allow analysis of widest range of samples. Lower limit as important as maximum, with some instruments having quite high cut-off for minimum.	PS WF ST		
Quadrupole	Ions separated (filtered.) by their trajectory through axis of four parallel rods to which varying radio and dc electric fields are applied. Different *m/z* ranges available, affecting cost, score appropriate to *m/z* range, sensitivity and scan rates for scanning/ selected ion monitoring (SIM) mode.	VI	Quadrupoles probably most widely used mass analysers for LC/MS, but increasingly being replaced by ion-trap or TOF instruments. Often used in combination with TOF for MS/MS (see below). Able to perform SIM, as well as full scan. Reasonable data acquisition rates, relatively low resolution. Some manufacturers claim ability to perform accurate mass measurements by data manipulation, but will not resolve ions of nominal isobaric mass, resulting in error.	PS WF ST		
Ion-trap	Operates on similar principle to quadrupole, but stores or 'traps' ions for analysis or subsequent MS/MS experiments (see MS/MS section). Mass spectrum produced by scanning rf voltages to eject ions of increasing *m/z* ratio for detection. Score as for quadrupoles.	VI	Similar performance to quadrupole instruments. Resolution can be increased over narrow *m/z* range by slow scanning, but may compromise chromatography. Reasonable cost, though generally higher than quadrupoles, but also able to perform MS/MS. Product ion scan *m/z* range restricted to 70%.	PS WF ST		
Time-of-flight (TOF)	As name implies, ions separated by virtue of their different flight times. Score for *m/z* range, sensitivity and mass accuracy /resolution.	VI	Becoming increasingly popular because of high data acquisition rates, high sensitivity and medium/high resolution. Able to perform accurate mass measurements. More expensive than quadrupoles.	PS WF ST		
Sector	Original mass spectrometers, using magnetic field to separate ions. Score for *m/z* range, mass accuracy/resolution and sensitivity.	VI	Drawbacks for coupling with LC, including slow scan speeds (magnet hysteresis), source arcing and limited sensitivity at high resolution. Instruments are large, complex and expensive. Unlikely choice for LC/MS, except to use their main virtue, high resolution.	PS WF ST		
Fourier transform ion cyclotron resonance (FT-MS)	Ions trapped in cubic cell in a constant magnetic field and cyclotron orbit induced by rf pulse. Orbiting ions generate signal whose frequency is related to *m/z*.	VI	Very high resolution and high cost. Again unlikely LC/MS choice, with very high vacuum requirement and scan speed capability arising from FT data handling. High resolution required for analysing high mass adducts of proteins, for example, but usually by infusion rather than by LC.	PS WF ST		

Feature	Definition and/or test procedures and guidance for assessment	Importance	Reason	Score		
MS/MS instruments	Ion-trap and FTMS instruments are able to perform MS/MS experiments. Quadrupole, sector and TOF analysers must be combined, either with similar mass analysers or as hybrid instruments. Many MS/MS experiment setups possible. Application will dictate type, but focus here on most used for LC/MS only.					
Quadrupole/quadrupole	Coupled quadrupole mass analysers *via* 'collision cell' where fragmentations are usually induced by collision with inert gas. The collision cell is itself a quadrupole or higher multi- pole, but with radio frequency (rf) only, transmitting all ions, not mass filtering.	I	Most widely used for small molecule LC/MS and quantitation. Several different scan modes. MS1 and MS2 separate analysers can be scanned simultaneously for constant neutral loss/gain (CNL/CNG). MS2 static with MS1 scanning for precursor ion scan. High sensitivity for single/multiple reaction monitoring (SRM /MRM), with MS1 and MS2 both static. Relatively low cost.	PS WF ST		
Quadrupole/TOF	MS2 quadrupole replaced with TOF mass analyser. Score for *m*/*z* range of both analysers, sensitivity and mass accuracy/resolution (TOF).	I	Good combination, especially for proteomics, with high sensitivity and resolution. TOF as obligatory scanning analyser excludes some scans where MS1 is static. However, software manipulation allows equivalent dynamic experiments.	PS WF ST		
Detector Choice of detectors	Detectors in modern instruments are generally based on electron multipliers and two classes of detector are available, point ion collectors and array collectors. There are several types in each class and choice is often dictated by the mass analyser used. Score for compatibility with different types of detector as appropriate.	I	Detectors differ in their attributes and choice may not be available if the manufacturer specifies only a particular type. For example, TOF instruments usually use multichannel plate collectors.	PS WF ST		
Dynamic range	Score for detector with wide dynamic range as appropriate.	I	Electron multipliers should ideally have a wide dynamic range, being efficient at detecting few or many ions. Array detectors are more easily saturated by large numbers of ions and have worse dynamic range than point detectors.	PS WF ST		
Dark current	Score for lowest dark current.	I	Residual electrical current in the detector when no ions are being detected (Electronic noise).	PS WF ST		
Life-time (Use)	Score for long life-time at optimum operating voltage and performance.	I	Detector surface will deteriorate with time.	PS WF ST		
Life-time (Storage)	Score for longest 'shelf life'.	I	Detectors are air/moisture sensitive.	PS WF ST		
Ease of replacement	Score accordingly.	I	Detectors vary in their ease of replacement. Some may be replaced relatively easily by the user, while others need an engineer.	PS WF ST		
Operating characteristics Tuning	Score for generation of report of settings used. Additionally score for automatic tuning.	I	Record of settings needed to comply with quality system requirements and useful for instrument performance checks. Automatic tuning can be useful, but operator ideally needs to understand tuning functions also to optimize and monitor performance.	PS WF ST		
Flow injection	Score for facility, usually *via* 'in-built' syringe driver, to infuse analytes or reference calibration compounds in solution to the ionisation sources listed above.	I	Allows direct infusion of solutions of compounds into the MS without HPLC. These may be analytes to optimize instrument settings or reference compounds to calibrate the instrument *m*/*z* range.			
Reference inlet sprayer	Score for facility to allow flow injection of reference calibration with rapid alternation between analyte and reference streams, this could be very important.		Reference compound allows data from HPLC stream to be corrected for accurate mass measurement. Separate introduction of reference and analyte avoids common problems such as mass interference and ion suppression. Usually used with medium/high resolution TOF instruments.	PS WF ST		
Multiple inlet sprayer	Score for facility to connect several HPLC systems to one mass spectrometer, this may be important.		Development of above, again usually used with fast data acquisition TOF instruments. Especially for high-throughput analysis.	PS WF ST		
Scan modes						
Selected ion monitoring (SIM)	Score for ability to acquire data in SIM mode, where one or more ions are selected, especially for quantitative analysis.	I	SIM maximises data acquisition rate and hence sensitivity.	PS WF ST		
Multiple reaction monitoring (MRM)	Score for this ability with instruments able to perform MS/MS experiments, especially for quantitative analysis.	I	MRM maximises sensitivity and also specificity by monitoring specific fragmentations of precursor to product ion.	PS WF ST		

Feature	Definition and/or test procedures and guidance for assessment	Importance	Reason	Score		
MS/MS	Score for this capability, depending on requirements.	I	MS/MS fragmentation provides very useful structural information and can be essential in some cases, such as peptide sequence determination in proteomics. See also MRM above.			
Instrument stability	Score for stable response over short (min)/long(hours)-term.	VI	Instrumental drift will compromise data, both qualitative and quantitative. Especially important to avoid drift for 'accurate mass' (low ppm uncertainty) determinations.	PS WF ST		
General maintenance						
Source cleaning	Score for ease of source cleaning and additionally score highest where instrument does not have to be vented.	I	Instrument sources vary in complexity and hence ease of cleaning. Some instruments fitted with source isolation valve to maintain vacuum whilst source is cleaned, reducing down-time.	PS WF ST		
Mass analyser	Score for ease of disassembly for cleaning, although this is usually performed by an engineer.	I	Minimises down-time and maintenance costs.	PS WF ST		
Safety considerations	The provision of appropriate interlocks to prevent accidental exposure to hazardous voltages are statutory requirements, without which an instrument cannot be legally operated. It is inappropriate to score these items.					
Software						
Compatibility	Score for software that allows control and data processing of both mass spectrometer and HPLC system. Additionally score for ability to control HPLC from different manufacturer to that of mass spectrometer.	I	Simplifies instrument control and data acquisition. Also useful for quality assurance.	PS WF ST		
Ease of use	Score for general ease of use and for use by new user.	I	Reduces operator error and reduces time to learn how to use instrument.	PS WF ST		
Availability of validatable software	Score for software developed under recognised quality system and fully documented.	Maybe VI	Essential for quality assurance.	PS WF ST		
Multi-tasking	Score for ability to process results previously acquired during real-time acquisition.	I	Time-saving.	PS WF ST		
Fraction collection	Score where applicable, ability to collect fractions, identified by mass, from post-column, non-MS, split. (mass directed fraction collection).	Maybe VI	Allows further analysis of fractions, etc.	PS WF ST		
MS to MS/MS switching	For MS/MS instruments, score for this capability. Switches automatically from MS to MS/MS mode during chromatographic acquisition to fragment ions identified by set parameters.	Maybe I	Provides structural information from fragmentation MS/MS spectra.	PS WF ST		
HPLC flow control	Score for capability to reduce eluent flow for MS/MS acquisitions during chromatographic run by automatic control of HPLC pump, according to set parameters.	Maybe I	Allows greater acquisition time and enhances MS/MS data quality.	PS WF ST		
Networking	Score for this capability where required.	Maybe VI	Allows data processing, etc., on local network and for example proteomics applications database searching on the Internet.	PS WF ST		
Instrument control	Score for degree of control of the instrument that software gives user. Score additionally for ability to lock settings.	VI	Allows optimisation of the instrument by user.	PS WF ST		
Instrument performance diagnostics	Score maximum for instrument that 'self-checks' on switching on and has validation routine.	I	Important for quality assurance and must be recorded.	PS WF ST		
Instrument malfunction protection	Score highest for greatest degree of flexibility to override instrument controls when associated with a range of potential malfunctions.	VI	Protects instrument from possible damage.	PS WF ST		
Data analysis						
Mass chromatogram/spectra	Score for range and applicability of data manipulation.	VI	Many functions available, such as background subtraction, summing of spectra, etc., enhances data.	PS WF ST Sum of sub-totals		
4. Value for money (points per currency unit)	Sum of the previous sub-totals divided by the purchase price of the instrument. Subject to proportional scoring and weighting factors, including ST in grand total.		'Simple' instruments are often good value for money, whereas those with unnecessary refinements are often more costly.	PS WF ST Grand Total		

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