Recent advances in mass spectrometry for drug discovery and development

Of the numerous types of analytical techniques used in drug discovery and development, mass spectrometry (MS) has become one of the most powerful tools for the analyses of a wide range of chemical and biological entities. Indeed the demands of the pharmaceutical and biotechnology industries have driven vendors to some extraordinary recent advances in mass spectrometry technology.

By Dr Nelson Cooke

In 2001 pharmaceutical companies spent $35 billion on R&D – twice the amount spent in 1997 and three times the amount spent in 1992[1]. However, only 37 new active substances (NAS) were launched to the marketplace which represents a 20-year low (**Figure 1**)[2]. Typically, from the time research begins to develop a new drug until it receives approval from the FDA to market the drug in the US, a drug company spends $800 million over a 10-15 year timeframe[3]. The reason it takes so long and costs so much is because of the complex process required to discover, develop, test, market and monitor a new drug (**Figure 2**). For example, for every 5,000 medicines tested, on average only five are tested in clinical trials and only one is eventually approved for patient use[4]. All of this strongly suggests there is serious lack of R&D productivity, thus pharmaceutical and biotechnology companies are now under intense competitive pressure to accelerate their drug discovery and development processes. These issues have been the subject of several recent reports from the big consulting firms[1,5-8].

In spite of what might seem to be a bleak situation, now is actually a very exciting time in the evolution of the role of the biological sciences and measurements as applied to drug discovery and development. We are now experiencing the rapid emergence of the 'omics' sciences[9]. The omics suffix refers to the measurement of the entire complement of a given level of biological molecules and information. Thus genomics measures the entire

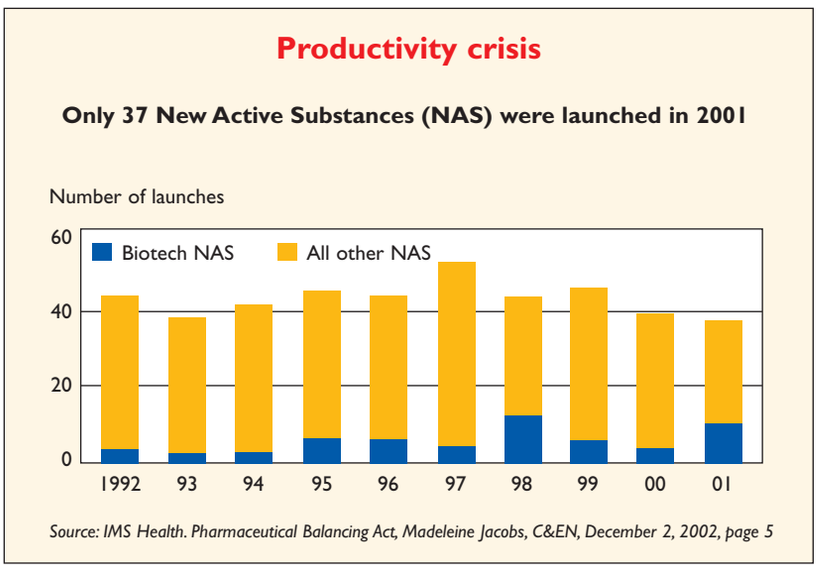
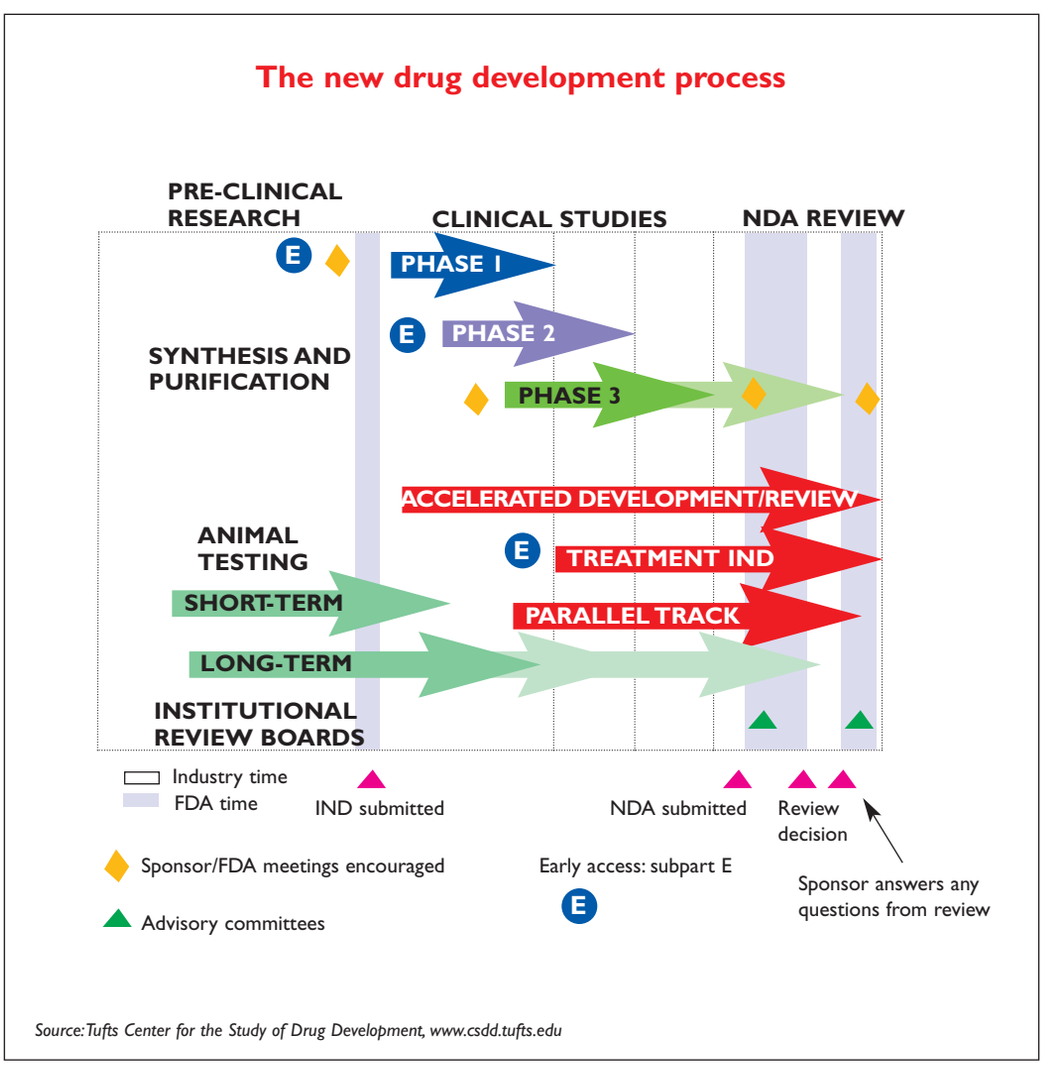


Figure 1

genetic make-up of an organism, proteomics measures all the proteins expressed under a given set of conditions and metabonomics measures the complete metabolic response. These new sciences and the data and information being derived from them, are reshaping the drug discovery and development process and promise to dramatically reduce the time and costs of launching a new drug. The biggest challenge now facing scientists is integrating the information from all the various omics together, this is the goal of 'Systems Biology'[10]. It is fair to say that a new paradigm is being born and will ultimately lead to a more efficient and effective personalised medicine health care system[11-12].

Of the many different types of analytical techniques used in the omics sciences, mass spectrometry (MS) has become one of the most powerful tools for the analyses of a broad range of chemical and biological entities of pharmaceutical interest. It is such a powerful technique since it measures a

Figure 2



fundamental characteristic of a molecule, its molecular weight. The demands of the life sciences applications have led to the improvement of MS technologies and rapid growth of new types of instruments[13]. Modern instruments feature very powerful analytical capabilities – sensitivity, selectivity, resolution, throughput, mass range, mass accuracy, cost-effectiveness. In the remainder of this article, the basic types of instruments used in the pharmaceutical industry are highlighted and some recent advancements discussed.

Types of mass spectrometers

A mass spectrometer is an analytical instrument that separates and detects molecular ions on the basis of their mass to charge ratio (m/z). All MS instruments consist of three main components: an ion source that generates ions, a mass analyser which separates ions according to their m/z ratio, and an ion detector (**Figure 3**). There are three types of mass spectrometers that are most widely used in the pharmaceutical industry: triple quadrupoles (triple quads), quadrupole ion traps (ion traps) and time of flights (TOF). There are unique advantages and disadvantages as well as price points associated with each type of instrument and no one instrument can do everything, thus many labs have more than one type. A detailed comparison of the different types of mass spectrometers available is beyond the scope of this article, however, a general overview is provided. For a more comprehensive comparison there are a number of excellent recent books[14-18] that review mass spectrometry and its application to the omics as well as drug discovery and development. See **Table 1** for a completive matrix of Mass Spec products from companies mentioned in this article.

Currently, quadrapole type mass spectrometers are the most widely used for LC-MS experiments and have become the analytical workhorses of pharmaceutical R&D. Quadrupole mass analysers consist of two pairs of electrically conducting rods, on to which radio frequency (RF) and direct current (DC) voltages are applied. A quadrupole is essentially a mass filter that isolates ions of a selected m/z for detection and a mass spectrum is acquired by scanning the m/z range to detect ions of different masses. Quadrupoles are most commonly configured with three in tandem (triple quadrupoles) which significantly increases the capability of the instrument. Triple quadrupoles can perform single quadrupole experiments such as full scan and single ion monitoring (SIM) experiments and have the capability of specialised tandem (MS/MS) scans modes such as product ion scanning, precursor ion scanning, constant neutral loss and multiple reaction monitoring. Triple quadrupoles are excellent instruments for quantitative analyses experiments and some of the specialised scans such as precursor and constant neutral loss allow characterisation of molecular structure, eg drug metabolite characterisation. However, when doing fast HPLC runs slow scanning speeds may limit the ability to analyse molecules that are co-eluting and sensitivity can be limited by ion beam transmission losses.

Together with triple quadrupole instruments, quadrupole ion traps (ion traps) are also among the most widely used mass spectrometers analysers and the physics behind both of these analysers is quite similar. Ion traps are about the size of a tennis ball and consist of three hyperbolic electrodes: a donut-shaped electrode called the ring electrode and two disk-like electrodes called end cap electrodes, the end caps are perforated and allow injection and ejection (and subsequent detection) of ions. Ions of different mass are stored together within the three-dimensional traps and released one at a time by scanning the applied voltages to destabilise their orbits and eject the ions into the detector. The motion of ions in the trap is dampened by introducing Helium gas and the ions move closely around the centre of the trap which prevents ion loss from collisions with the electrodes and improves resolution. The biggest advantages

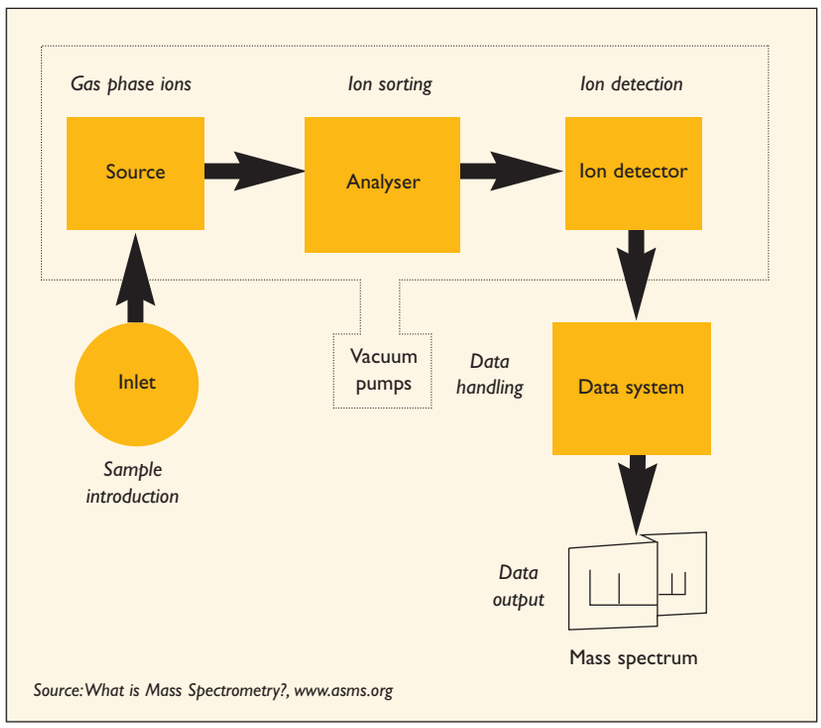


Figure 3
The components of a mass spectrometer

Table 1: Commercial matrix of mass spectrometers

	Applied Biosystems 850 Lincoln Center Drive, Foster City, CA www.appliedbiosystems.com	Agilent Technologies 395 Page Mill Road, Palo Alto, CA 94303 www.agilent.com	Bruker Daltonics 40 Manning Road, Billerica, MA www.bdal.com	ThermoFinnigan 355 River Oaks Parkway, San Jose, CA www.thermofinnigan.com	Waters/Micromass 34 Maple Street, Milford, MA www.waters.com
Single Quads				Surveyor MSQ	EMD 1000 ZQ Mass Spectrometer
Triple Quads	API 4000 API 3000 API 2000			TSQ Quantum Ultra TSQ Quantum Ultra AM TSQ Quantrum Discovery	Quattro Premier Quattro Ultima Quattro Micro
Ion Traps		1100 LC/MSD VL 1100 LC/MSD SL Nanoflow Proteomics Sol	Esquire HCT Esquire 3000 Esquire 3200	LTQ (2D) LCQ Decca XP plus LCQ Advantage	
TOF	Voyager-DE PRO MALDI-TOF	LC/MDS TOF	Bio TOF III Micro TOF		LCT Premier MS LCT MS
Hybrid Traps	4000 Q TRAP Q TRAP			MAT95XL-TRAP	
Hybrid TOF	Qstar XL		BioTof Q		Q-tof Ultima Global Q-tof Ultima MALDI Q-tof Micro
TOF-TOF	Voyager TOF-TOF 4700 Proteomics Analyser		UltraFlex		
MALDI TOF MS	Voyager DE		AutoFlex OmniFlex Reflex IV		TOF Spec
FTMS			APEX-Q APEX III	LTQ-FT	

of ion traps is their small size and the inherent tandem MS capabilities allowing MSn (with n=up to 10) experiments, thus increasing the amount of structural information obtainable for a molecule. Some limitations of ion traps are that product ions at the lower end of the mass range are not detectable (one-third rule) and sensitivity can be diminished during the ion ejection process since only half of the trapped ions are ejected into the detector. Another possible issue is, if the concentration of ions in the trap is too high, ions will repel each other resulting in the degradation of resolution. This is called space charging but many instrument manufacturers have either software or hardware features to minimise this effect.

The time of flight mass spectrometer (TOF) is one of the simplest mass analysers and is based on accelerating a set of ions to a detector with the

Figure 4

Applied Biosystems
4000 Q TRAP™ LC/MS/MS system

KEY FEATURES

High sensitivity full scan MS, MS/MS and MS3 combined with true triple-quadrupole capabilities.
Highest sensitivity triple quadrupole with MRM for quantitation and Precursor Ion and Neutral Loss scans for selectivity.
Advanced scan functions which can be combined for maximum PTM and metabolite information in a single IDA analysis.
Advanced Application Software including Metabolite ID, BioAnalyst, Pro ID, Pro BLAST, Pro ICAT, Fragment Interpretation, Library Searching, Automaton, 21 CFR Part 11.

Source: www.appliedbiosystems.com

same amount of energy. Since the ions have the same energy but different masses (m/z) they reach the detector at different times, thus the smaller ions reach the detector first because of their greater velocity. Since the dimensions of the mass spectrometer and the energies of the ions are known, a calculation is performed to determine the m/z value of the ion. The resolution of TOF analysers have been improved by adding a reflectron in the flight tube to reduce the kinetic energy distribution of ions that reach the detector and with orthogonal injection to reduce spatial distributions. Since ion detection is not limited by the mass range of the analyser, these instruments have a very wide mass range, which is especially useful for the characterisation of large molecules such as peptides and proteins. TOFs can generate full scan spectral data without instrument scanning resulting in improved sensitivity compared to scanning instruments and also have the important capability of accurate mass measurements (+/-5ppm). The main advantages are high scan rates, high resolution (with reflectron), very wide mass range and high sensitivity because of no ion loss due to scanning, and accurate mass. However, a limitation is the single-stage capability and thus the loss of tandem mass spectrometry capabilities. Newer instruments couple a separate mass selective analyser in front of the TOF to circumvent this problem (see discussion on hybrids).

With respect to ion sources the two most widely used in the pharmaceutical industry are: electrospray (ESI) and matrix-assisted laser desorption ionisation (MALDI). ESI works with samples in solution and is used when coupling high performance liquid chromatography (HPLC) to mass spectrometers while MALDI is used for solid samples. The development of these two 'mild' ionisation techniques was very significant since it extended the application of MS to large biological molecules such as proteins and even noncovalent complexes. One half of the 2002 Nobel Prize was awarded to John Fenn and Koichi Tanaka who independently developed techniques to ionise large biomolecules – electrospray and soft-laser desorption, respectively, for mass spectrometry of proteins[19].

With ESI, the sample enters the source though a flow stream from the HPLC and passes through a stainless steel needle held at high voltage. As the flow stream exits the needle it sprays into a fine mist of highly charged droplets that are electrostatically attracted to the MS inlet. The droplets then either pass through a heated capillary to help the desolvation process before entering the vacuum region of the MS or a curtain of dry gas is passed across the spray to cause desolvation. An important feature of electrospray is the formation of multiply charged molecules making it possible to analyse very large molecules since the mass spectrometer measures the m/z value. Triple quads are very compatible with ESI sources since they can handle the continuous ion currents and elevated ion pressures produced by the source. With MALDI, the sample is mixed with a chemical matrix containing an organic molecule that has a chromophore which absorbs light at a specific wavelength. The mixture is spotted on to a small target plate which is then evaporated and placed into the MS source. The source has a laser which is fired at the target and the matrix absorbs the energy and transfers it to the biological sample molecules causing them to vapourise, ionise and be ejected from the target into the MS. The TOF mass spectrometer is an ideal analyser for the MALDI source since they are both pulsed techniques. A

Figure 5

Bruker Daltronics
APEX-Q

New 9.4 and 12 Tesla magnets and data-dependent LC-MS/FTMS

KEY FEATURES

Provides high field performance needed for proteomics

The new high-field APEX-Q can deliver sub-ppm mass accuracy, enormous resolving power for peptide mixtures, wide bandwidth detection, high dynamic range, and fast automated data-dependent MS/MS for detailed proteome characterisation when coupled online to liquid chromatography. With the APEX-Q, the life science researcher now has access to automated data dependent MS/MS functionality operating with dynamic exclusion lists, inclusion lists and other 'smart' MS/MS proteomics protocols with the added benefit of FTMS calibre performance.

Source: www.bdal.com

Figure 6

Thermo Electron Corporation
Finnigan LTQ FT MS

KEY FEATURES

Robust accurate mass determination.
Mass accuracy of better than 2ppm with external calibration.
Very high mass resolution for mixture analysis.
Maximum resolution of greater than 500,000 (FWHM).
Simultaneous high resolution, mass accuracy and sensitivity over one mass decade (eg m/z 200-m/z 2,000).
Fast data acquisition rate (1 second) with very high mass resolution (100,000 at m/z 400) for unprecedented LC/MS performance.
Sub fmol on-column sensitivity (LC-MS).

Source: www.thermofinnigan.com

recent paper contains a good discussion of some developments in MALDI techniques[20].

Selected recent advancements in mass spectrometers

Hybrids

One of the most exciting and powerful developments in the evolution of mass spectrometry technology is the commercialisation of hybrid instruments. Hybrid machines are made by combining two different types of mass analysers together in tandem; one can now choose almost any combination of quadrupole, TOF, ion trap, or FT ion cyclotron resonance (ICR) hybrid. These hybrid instruments promise the ability of combining the best features from the different components and allow tandem mass spectrometry experiments and unique scanning modes that are not possible on a single instrument. The first hybrid instrument was actually introduced several years ago (mid-1990s) by Waters/Micromass and was a quadrupole TOF MS (QTOF) and later by Applied Biosystems/Sciex with its QStar Pulsar. Then in 2002, Shimadzu Biotech introduced an ion trap TOF hybrid (Axima-QIT) and Applied Biosystems/MDS Sciex launched a quadrupole ion trap MS (QTRAP). This year, Bruker Daltonics, IonSpec Corp and ThermoFinnigan launched three new FTICR hybrid type instruments: two quadrupole FTICRs and an ion trap FTICR. Some of the more recent new hybrid products are now discussed, the reader is referred to several published product reviews and the respective companies' websites for more details [21-26] (**Table 1**).

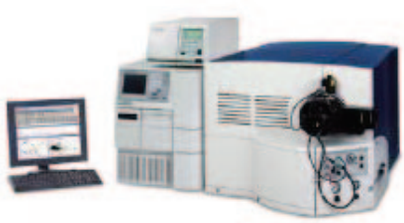
The most recent wave of hybrids started last May at the 50th Annual American Society of Mass Spectrometer (ASMS) conference when AB/MDS Sciex launched the QTRAP. The QTRAP is a hybrid triple quad (API 3000)/ion trap instrument in which Q3 is a linear (2D) ion trap. Precursor ion selection is performed in Q1, fragmentation in Q2 (which is the collision cell) and subsequent injec-

Waters Corporation

Waters Corporation introduces new system for Metabonomics
First-to-market LC/MS solution for metabolic profiling

KEY FEATURES

The Waters Metabonomics MS System consists of the Waters Micromass Q-Tof micro™ mass spectrometer, the Waters 2795 Separations Module, the Waters Metabonomics MS System Applications Kit featuring Symmetry® column chemistry and the MarkerLynx™ Application Manager for MassLynx™ 4.0 software.



Source: www.waters.com

Figure 7

Agilent Technologies
Nanoflow Proteomics Solution

KEY FEATURES

Unsurpassed low-flow performance and stability.
Automated sample clean-up, enrichment and 2D HPLC.
High-efficiency nanoflow separations.
Flow path designed to maximise and maintain separation efficiency.
Superb MSMS sensitivity.
Fully integrated software.
Data-dependent acquisition.
Better quality data for better matches.
Quickly identify and characterise proteins.

Source: www.agilent.com

Figure 8

tion of product ions into the 2D ion trap. The ions can then either be ejected and detected or isolated and further fragmented in the trap to generate MS3 data for more detailed structural information. Unlike traditional 3D ion traps in which ions circle in an enclosed spherical chamber before being ejected and detected, the linear 2D trap stores ions in a two-dimensional quadrupole configuration. The linear trap has a larger trapping volume and thus higher ion capacity which reduces the problems associated with space charging and improves sensitivity. While traditionally triple quads are excellent for quantitative analyses and ion traps excel at qualitative analyses, the hybrid instrument offers the possibility of doing both types of analysis on one machine. Another attractive feature of this type of hybrid is several new and novel scan modes. For example, the multiply-charged scan mode reduces singly charged species yielding a simpler spectrum and revealing the multiply charged precursors that can be selected for further structural analysis. At this year's ASMS conference, the 4000 QTRAP was introduced which is based on the company's API 4000 triple quadrupole platform (**Figure 4**).

This year, Bruker Daltonics and Thermo Electron launched new hybrid Fourier transform mass spectrometers, the APEX-Q and LTQ-FT respectively (**Figures 5 and 6**). These hybrids combine the extremely high resolution and mass accuracy of FTMS with the ion storage and separation capabilities of quadrupoles and linear ion traps. FTMS is based on ion cyclotron resonance (ICR) in which ions are stored and orbit in an ICR cell in the presence of a strong magnetic field. The orbiting ions are excited with a radio frequency (RF) pulse which results in a cyclical motion with a frequency inversely proportional to the ions m/z ratio. A Fourier transform is used to obtain the component frequencies of the different ions and produce a mass spectrum. The mass resolving power of FTMS is proportional to the detection time and

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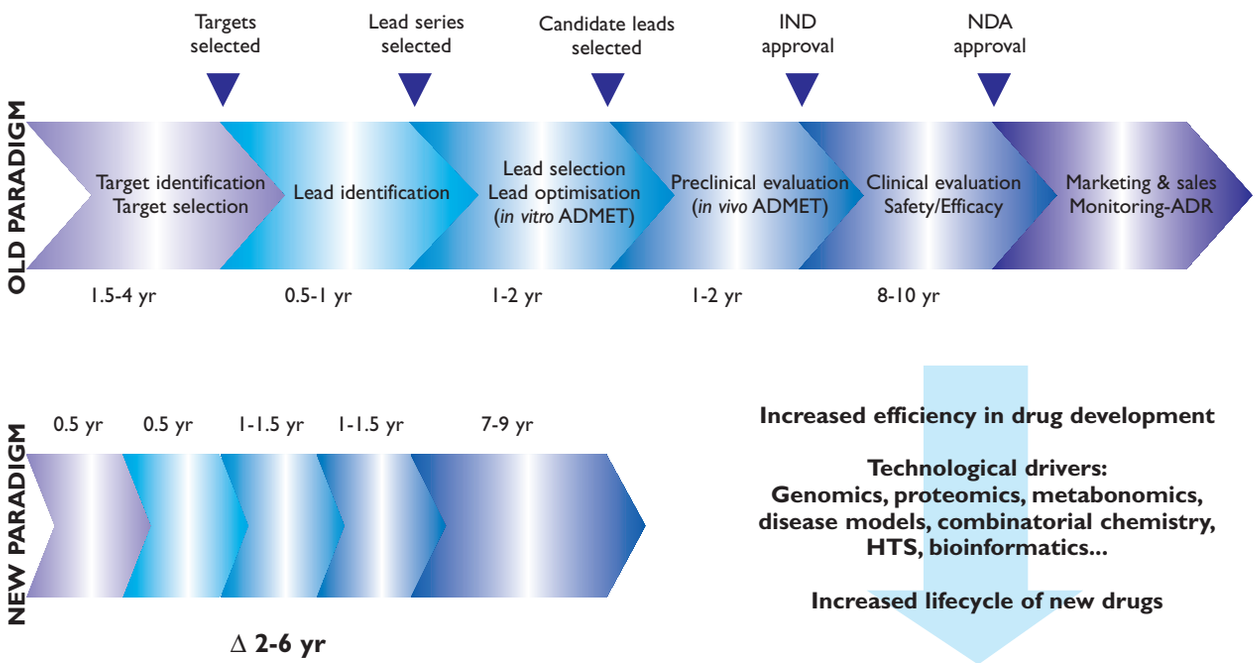

Figure 9

strength of the magnet, the Bruker and Thermo instruments use superconducting magnets with strengths of up to 12 and 7 Tesla respectively. Both instruments use the same strategy of interfacing either Qq quadrupoles or a linear ion trap to the FTMS which allows the ability to store, accumulate and prepare samples before injection into the ICR cell. This strategy allows the user to selectively accumulate ions to increase sensitivity for low abundance proteins, for example, or to separate a peptide or protein of interest out of a complex mixture for analysis by the FTMS. Another advantage of this approach is that one can very precisely control the number of ions going to the ICR cell which is critical for highly accurate mass measurements and for reducing space charging effects. As noted above, the linear trap offers higher storage capacity than 3D ion traps. These types of machines are expected to become very popular since they will provide the ultimate capability for the fields of proteomics and drug metabolism when the best resolution, sensitivity and accurate mass are required.

Yet another type of hybrid to emerge during the past couple of years is the tandem time of flight (TOF-TOF) mass spectrometer systems from ABI/MDS Sciex (Biosystems 4700) and Bruker Daltonics (Ultraflex TOF). Although these systems are at the high end of the price spectrum they provide a platform for high throughput screening type applications. Both instruments enable high throughput protein identification by MALDI TOF peptide mass fingerprinting, followed by tandem MALDI TOF/TOF on the same sample for more detailed protein characterisation. The 4700 system was the first commercial instrument to combine MALDI with TOF/TOF optics and was designed for high energy fragmentations which generate information-rich fragmentation patterns for more accurate protein identification and better characterisation.

Other new developments

In this section, we list some selected new products by several different companies not discussed above that also represent new developments and capabilities in the field of mass spectrometry, once again

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the reader is referred to the various companies' websites for more detail.

Ion Trap-based MS systems

- Agilent LC/MSD XCT is a new high capacity 3D ion trap instrument 10 times more sensitive than its predecessor.
- BrukerEsquire HCT high capacity ion trap has a higher trap storage capacity for femtogram small molecule sensitivity, mid attomole peptide sensitivity, high resolution and 50ppm mass accuracy.
- Finnigan LTQ is a 2D linear ion trap with a new ion source, optics and dual detection technology providing increased sensitivity and ultra fast scan speeds ideal for metabolism and proteomics research.

Quadrupole-based MS systems

- Finnigan TSQ Quantum Ultra has a new Ion Max source with enhanced linear dynamic range and sensitivity ideal for pre-clinical and clinical quantification.
- Finnigan TSQ Quantum Ultra AM is the first triple quad that has routine accurate mass capability to 5ppm on a chromatographic timescale ideal for drug metabolism and pharmacokinetic studies.
- Finnigan TSQ Quantum Discovery is a robust and sensitive entry level triple quad for drug discovery labs.
- Waters Quattro Premier is a high-end quadrupole mass spectrometer intended for high sensitivity quantitative analyses in pharmaceutical, industrial environmental, clinical and forensic laboratories.

Time of flight-based MS systems

- ABI 4700 Proteomics Discovery System is based on TOF/TOF optics for the characterisation of proteins from a variety of proteomics workflows – gel-based multidimensional LC, and LC-MALDI.
- Agilent LC/MSD TOF is an easy to use mass spectrometer for high mass accuracy measurements of drug candidates.
- Bruker Bio TOF III research grade ESI-TOF and ESI-Q-q-TOF with high resolution capability.
- Bruker MicroTOF bench top high performance ESO-TOF for exact mass analysis.
- Waters LCT Premier is a high-end, bench top TOF mass spectrometer designed for routine, automated exact mass measurements for the identification of compounds.

Integrated and Hybrid-based MS systems

- Finnigan ProteomeX Workstation with nanospray is a multidimensional LCMS system for proteomics analyses of complex biological samples.
- Waters Metabonomics MS System is the first end-to-end exact mass LCMS solution for metabonomic investigations (**Figure 7**).
- Agilent Nanoflow Proteomics Solution is an integrated nanoflow HPLC ion trap MS system for the identification and characterisation of proteolytically digested proteins (**Figure 8**).

Summary

As pharmaceutical and biotechnology companies embrace the new drug discovery and development paradigm in order to reduce the costs and cycle times of commercialising a new drug they will continue to rely on advancements in analytical tools. The pace of advancement of mass spectrometry technology and its application to drug discovery and development over the past few years has been extraordinary and has reinvigorated these markets. Mass Spectrometry has become one of the most powerful analytical tools for drug discovery and development because of the detailed information it can provide and its speed and sensitivity. MS is now being successfully used at all points along the pharmaceutical value chain and there is a huge opportunity to significantly reduce the cycle times and costs associated with bringing a new drug to the market (**Figure 9**). The pharmaceutical and biotechnology markets will continue to make up the biggest demand for this technology over the next several years and drive vendors to continue to make improvements in performance and user friendliness. As noted in the introduction, we really are at a very exciting time in science and mass spectrometry is at the cornerstone of the new systems biology. DDW

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