# Mass Spectrometry Road Map

Presented to EPSRC by

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# Recommendations

Mass spectrometry is a highly sensitive analytical technique with high mass accuracy and specificity derived from the fragmentation patterns of molecules. These characteristics mean it is the technique of choice in many applications underpinning progress in research fields across chemistry, biology and medicine as well as directly responsible for routine mass analysis and process quality control, toxicology, forensic analysis integrity in many industries throughout society.

Currently RCUK invests £15m ± 6m per year (37% yearly variation) in mass spectrometry research grants. However, support for mass spectrometry comes from other sources such as industry, EU and charities. A survey of the mass spectrometry community (92 responses) suggests RCUK contribute 25% annual expenditure. This observation suggests a UK mass spectrometry annual investment of ~£60m, from both research and infrastructure. The global market for mass spectrometry is estimated to be $7.3bn by 2020 and expected to show compound annual growth at a rate (CAGR) of 8.1% to 2020 (M&M, 2015)[1].

1) Market growth of 8.1% CAGR is a reasonable target for the academic infrastructure base 2016-2020. RCUK contributions to mass spectrometry research would rise to £21m in 2020: a total UK academic investment of £82m by 2020. This growth would preserve the RCUK 25% contribution to mass spectrometry activity.
2) RCUK should move to 100% support of RCUK-infrastructure through properly charged costs on grants and planned infrastructure bids.
3) The UK mass spectrometry community needs to be amongst the early adopters of new technologies to report the high-impact studies and set the research agenda. The early-adopter strategy requires RCUK to respond promptly to new products that significantly enhance performance.
4) Independent research activity of lone PIs needs to be funded innovatively.
5) Sustainable Mass Spectrometry Centres of 30PIs or more should have transparent accounting of FEC, QR, RCUK consumables income and other sources. The instrument replacement costs should form part of the sample charges.
6) Return on the Investment and impact need to be recorded with countable metrics, noting however the latent impact of mass spectrometry to many fields.
7) Training and Continuing Professional Development are critical in supporting the infrastructure with skilled technical staff, PDRAs, PhD and undergraduates. Training and Continuing Professional development needs to be in place for scientific officers and technical staff to ensure the return on the capital investment.

[1] Markets and Markets Report, "Mass Spectrometry Market" Date: November 2015 Report Code: AST 3787
http://www.marketsandmarkets.com/PressReleases/mass-spectrometry-market.asp

## Contents

# 1. Background to the Road Map

## 1.1 Terms of Reference and Consultation

Mass spectrometry is found in many universities as a technique for fundamental molecular characterisation both of small molecules in chemical synthesis and, increasingly, with large biological molecules in biological samples. Its sensitivity and accuracy coupled with the specificity derived from molecular fragmentation patterns make it a critical analytical technique that supports many if not all research fields and all activities in society.

The Mass Spectrometry Roadmap was commissioned by the EPSRC with the following terms of reference:

- Review the capital equipment infrastructure investment in mass spectrometry in the UK academic sector ('Universities')
- Consider future funding requirements and opportunities
- The requirements for a sustainable mass spectrometry technology base

These Road Map findings have been based on consultation with both academic and industrial users and the instrument manufacturers. A number of site visits were made and additional information was sought electronically, Table 1. The British Mass Spectrometry Society (BMSS) committee members were consulted and an electronic survey of the 2000 subscribers to the JISC mailing list was performed from which there were 92 responders.

**Table 1 Consultations during the preparation of the Road Map (Appendix 1)**

| *Organisation* | *Comments* |
|---|---|
| Universities | |
| Imperial College | Mass Spectrometry in Chemistry |
| Nottingham University | Mass Spectrometry in Chemistry |
| University of Exeter | Mass Spectrometry in Biosciences |
| University of Southampton | Mass Spectrometry in Chemistry |
| University of Bath | Centralised Mass Spectrometry Facility |
| Industry | GSK Stevenage |
| BMSS Committee | |
| British Mass Spec Society | 92 Responses in an on-line survey |
| Individuals (Academic and Industry) | 10 |

The final report has been shared with the members of the community before submission. (See Appendix 1)

## 1.2 Mass Spectrometry User Communities

The field of mass spectrometry is important to many disciplines and is routinely used in molecular characterisation of small molecules in organic and inorganic synthesis but increasingly in the biological –omic subjects. The wide application of mass spectrometry derives from significant improvements in both mass measurement and separation science. The survey results show activity in many fields and are shown in Table 2.

**Table 2 Reported activity in Mass Spectrometry**

| *Activity* | *Percentage* |
|---|---|
| Organic, Physical and Inorganic Chemistry | 18% |
| Proteomics | 26% |
| Metabolomics | 14% |
| Other | 42% |
| Other Activities Include: | |
| Food and the Environment | Instrumentation |
| Instrumentation | Structural Biology |
| Interdisciplinary (supramolecular chemistry, | Biochemistry |
| origin of life, inorganic/organic) | Drug Assays and Pharmaceuticals |
| Environmental Science | Cancer Biology |
| Analytical Chemistry | Biogeochemistry |
| Biomarker Discovery | Glycomics |
| Defence | |

For comparison, a segmented market analysis (M&M, 2015) based on application suggests the major global applications are pharmaceutical, biotechnology, industrial chemistry, environmental testing, food and beverage testing and others.

Universities have groups of academics and individual PIs some using routine analysis and others developing techniques and mathematics, the latter is important in the interpretation of protein, metabolomics and post-translational modifications data. There are consequently centres for routine analysis, clusters of PIs and lone PIs. The division boundaries between these user groups are blurred and require flexible funding responses. The individual research initiatives must be supported on demand and peer-reviewed to develop international advantage. Larger groups rapidly become part of an infrastructure commitment making it important to maintain the local centres and difficult for new centres to establish. Clustering of University activity seems to be evolving with regional groupings such as Midlands Innovation and GW4.

The role of a small number of national centres in –oimics analysis is interesting. Such centres would bring equipment investment with critical mass in PIs developing the sample preparation techniques, separation science and data analytics. Centres of expertise are already evolving and momentum in these research fields needs to be driven by the PIs and support on demand. There is a case for RCUK investment in developing expertise and supporting a successful bid for such a centre but the demand should be PI-driven.

## *1.3 RCUK Investment*

Funded grant applications containing the key words “mass spectrometry” or “mass spectroscopy” (*sic*) have received total funding support of £151.2M during the period 2006 - 2015, Table 3. For the period 2006 – 2013 the mean expenditure by RCUK and TSB was £15 ± 6 M, stated as mean and one standard deviation. The standard deviation is a good estimate of year-on-year fluctuations, 38.7% of total expenditure.

Additional sources of research grant funding include EU, industry, research charities such as Gates and CRUK. The survey data showed 70% of responders had bought new equipment in the last 2 years, only 25% funded by the EPSRC/BBSRC. This would suggest that the RCUK expenditure on grants of £15m is 25% of the total expenditure: a total UK Universities investment in mass spectrometry annually is ~£60m ± 11m.

**Table 3 Current Grant Expenditure by RCUK (to end of 2015)**

| *Start Date Year* | *AHRC /£* | *BBSRC /£* | *EPSRC /£* | *MRC /£* | *NERC /£* | *STFC /£* | *Innovate UK /£* | *Total /£M* |
|---|---|---|---|---|---|---|---|---|
| 2006 | | 2,919,285 | 7,927,673 | 163,826 | 719,394 | 303,141 | - | 12.0333 |
| 2007 | | 2,898,700 | 4,551,343 | | 406,054 | | - | 7.8561 |
| 2008 | | 3,372,234 | 9,186,892 | | 670,031 | | 1,118,710 | 14.3479 |
| 2009 | 141,164 | 5,142,019 | 4,082,165 | 1,102,967 | 1,833,742 | 116,203 | - | 12.4183 |
| 2010 | | 5,367,017 | 1,409,694 | 205,462 | 3,052,930 | 111,557 | 99,025 | 10.2457 |
| 2011 | | 3,520,426 | 8,068,403 | 2,818,810 | 1,833,431 | | 85,285 | 16.3264 |
| 2012 | | 4,031,641 | 2,726,424 | 1,094,248 | 1,493,632 | 699,279 | 1,596,255 | 11.6415 |
| 2013 | | 6,873,822 | 8,104,494 | | 1,408,575 | | - | 16.3869 |
| 2014 | | 6,900,221 | 14,327,889 | 1,622,225 | 1,464,648 | 199,734 | 784,719 | 25.299436 |
| 2015 | | 6,294,285 | 3,718,080 | 13,197,355 | 587,548 | 734,556 | 99,645 | 24.631469 |
| **Total \£M** | 0.141 | 47.31965 | 64.103057 | 20.20489 | 13.46998 | 2.16447 | 3.783639 | **151.2** |
| **Percentage** | 0.09 | 31.30 | 42.40 | 13.36 | 8.91 | 1.43 | 2.50 | |

The key questions for the Road Map are:

1) Is £60m annual expenditure sufficient to maintain a globally competitive UK mass spectrometry activity?
2) Is 25% RCUK contribution to UK mass spectrometry activity an appropriate level of support?
3) What is the return on the Investment (ROI) in UK mass spectrometry?
4) What are the future requirements of the Mass Spectrometry Infrastructure?

The global markets in mass spectrometry is set to reach $7.3bn by 2020 and expected to show compound annual growth rate (CAGR) of 8.1% to 2020 (M&M, 2015). **RCUK investment should at least match the expected growth rate in the market taking its annual commitment from £15m to £21m by 2020**. The total University mass spectrometry expenditure would rise from £60m to £82m by 2020 to keep pace with the market. These are challenging increments. The growth rate of 8.1% reflects the increase in the prices of the instrument as well as growth in the numbers of instruments used. The market growth rate however is a benchmark of RCUK and University expenditure in mass spectrometer research.

Preserving the RCUK contribution at 25% is more challenging and depends on how many high quality applications are submitted for funding to RCUK. Strategically RCUK should be ready for the increasing cost-of-doing-business; the infrastructure element of which is reflected in the 8.1% CAGR, however the number of grant applications that would increase the total RCUK investment will depend on how many grants are funded. If the community writes more competitive proposals they become more likely to be funded: this is unpredictable.

The community believes strongly that it is underfunded and lagging behind in facilities, although the UK community is globally competitive. The number of mass-spectrometry awarded grants is increasing but the EPSRC can only respond to applications.

From time to time, the EPSRC launches dedicated equipment calls to support research infrastructure usually inviting larger scale applications sorted at and approved at an institutional level. One such call in 2014 was launched as an "Experimental Equipment Call" across the remit of the EPSRC. The call specified bundles of requests funded at 100% with one, multiple-bundle, application for each university. The panel ranked the bundles and not the overall grants. 43 organisations submitted 179 bundles with a total value of ~£166m; 117 bundles were ranked above the quality cut-off or ~£105m. The EPSRC funded £31m corresponding to 31 bundles or 26% of the call request. However, the manufacturers report some unsophisticated purchasing against a budget. **The *ad hoc* nature of the infrastructure calls should be refined, allowing for planned capital expenditure and accurate purchasing to a required specification.**

In addition to infrastructure grants mass spectrometry facilities should be sustainably managed. The income of a mass spectrometry facility is rarely identified accurately (see below) and is in part supported by consumables income, FEC and QR to the host University. A pay-as-you-go funding strategy could amortise the cost of the instrument over 3 or 5 years adding a cost to the consumables of grants that are funded by the EPSRC. The support for mass spectrometry would then be funded only as a sustainable service. Project grants would continue to support new equipment in new fields of interest.

Industrial support for equipment investment will depend on the economic cycle and the growth in their respective markets. Mass spectrometry sales are dominated by pharmaceutics, biotechnology, industrial chemistry, environmental testing, and food and drink monitoring (M&M, 2015). These market fluctuations are unpredictable. Continuing EU membership and EU support of research, EU Regional Development funding is a clear risk. Charity sector support depends on changing mission objectives.

*There is significant resource commitment as capital but this cannot be decoupled from the rest of the skill set requirements. Investment in a large instrument must come with commitment for the life-time of the instrument to permanent technical support and a clear career progression for the Scientific Officer*

## 2. Technology Advancements and Manufacturers

Mass spectrometry consists of two principal parts: the mass analysis instrumentation; and the separation science sample preparation. The instruments are sold with one or more separation technique attached – the performance of the instrument is then a product of both parts. The major instrument manufacturers are listed in Table 4 suggesting a well-populated market place servicing the $3bn global market in 2014. The market leader is Thermo Fisher and developments in transmission, resolution, sensitivity are led by product launches. An example is the launch of Orbitrap in 2005 which quickly entered the literature as can be seen in the publications using Orbitrap technology in *Science* and *Nature*, Figure 1. New products are launched yearly and must be supported for a minimum of 7 years under EU regulations although many university departments still have instruments more than 20 years old.

**Table 4 Instrument Manufacturers**

| | |
|---|---|
| *Thermo Fisher Scientific (US)*<br>*Waters Corporation (US)*<br>*Agilent Technologies (US)*<br>*Kore Technologies (UK)*<br>*Shimadzu Corporation (Japan)*<br>*Siemens(German)*<br>*JEOL (Japan)*<br>*Perkin Elmer (US)*<br>*Sciex (Danaher Corporation) (US)*<br>*Leco Corporation (US)* | *Bruker (US)*<br>*Spectro Analytical Instruments (Germany)*<br>*Hitachi High Tech (Japan)*<br>*Hiden Analytical (US)*<br>*Analytik Jena (Germany)*<br>*Protea Biosciences Group (US)*<br>*Rigaku Corporation (Japan)*<br>*BaySpec (US)*<br>*Extrel (US)*<br>*Dani Instruments SPA (Italy)* |

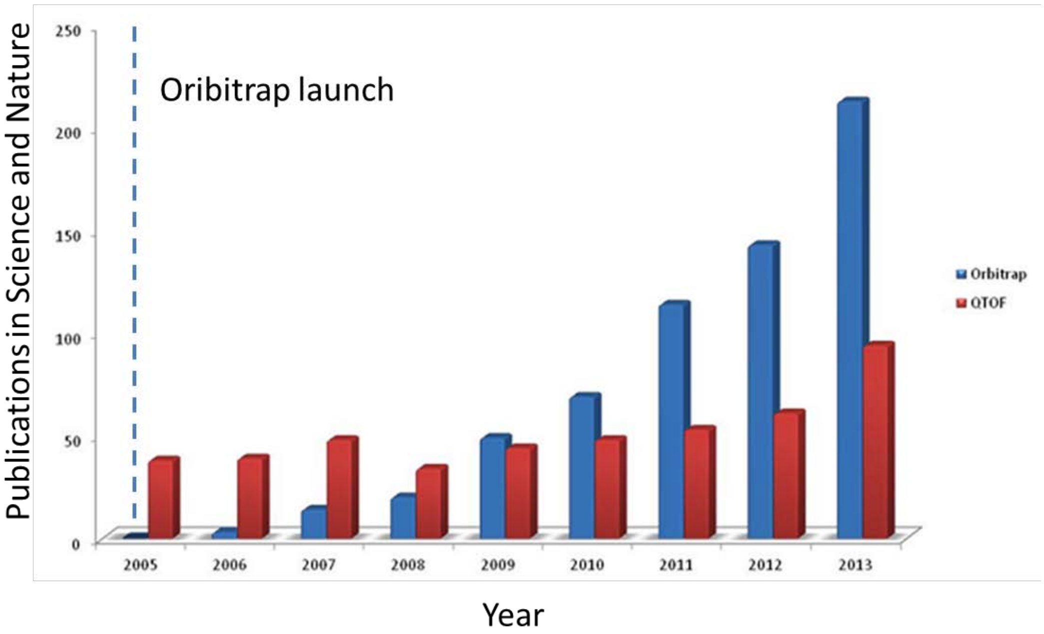


**Figure 1 Publications in Science and Nature citing Orbitrap and QToF technologies since the launch of Orbitrap in 2005. (Data from Thermo Fisher and re-validated for the report)**

**The UK mass spectrometry sector needs to be amongst the early adopters of new technology as new instrument capabilities rapidly set the standards in research fields and generate the high impact publications.**

The market in mass spectrometry is segmented and includes GC-MS, LC-MS, MALDI-TOF (the fastest growing segment), triple-quadrupole, quadrupole–TOF, ICP-MS and others. MALDI-TOF is the fastest growing sub-segment in global mass spectrometry market. This is attributed to increased usage of the technology in clinical diagnostic field. There is reasonable representation amongst all of the technologies from the responders in the survey. No one instrument is a “must have” for any department and the choice is made by project requirements, instrument performance characteristics and price incentives. **There is no single suite of instruments that should make up the capital expenditure of any particular centre**.

The preparation of samples for MS analysis is critical to the quality of the data and the subsequent interpretation. The sample preparation techniques are often the least expensive component of off-the-shelf instruments and the most difficult to use experimentally for high quality data and are part of the capital expenditure.

New technologies for new fields such as MS imaging of clinical samples by MALDI-TOF, toxicology for nanomaterials, routine medical diagnosis are some of many future areas of importance but should be funded appropriately through a project grant, correctly resourced for equipment. The recurring equipment costs need to be considered as capital expenditure as it evolves into widely adopted technique.

# 3. Sustainable Mass Spectrometry Centres

The community has organised itself into a number of sustainable mass spectrometry centres offering services to PIs within universities and between universities. Fewer than 10% of responders have used the national facility in Swansea indicating preference for local facilities, ultimately at group-level for specific dedicated projects. The centres are associated with expertise at technician and scientific officer levels for sample preparation and instrument operation and management. The necessary skills are usually acquired on the job over extended periods leading to a flat career trajectory that rarely includes continuing professional development. **Experimental officers should attend a conference regularly as part of their continuing professional development**

**The survey responses suggest each centre has a mean of 30 PIs and this may be considered a sustainable centre**. Most centres make a charge per sample although this is not a uniform practice; some institutions make an annual charge to the PI, irrespective of the number of samples. There is some indication of running costs per centre from the survey but this depends on the institution. Ideally, the running costs should be considered at a real FEC including routine consumables.

Most responders to the survey, 75%, had purchased instruments in the last two years with an average expenditure of £350k and there is considerable diversity in the source of funds; some from the host institution and other sources, Table 5. The sustainable mass spectrometry centres are performing 9k sample measurements per year. A sample price of £31 - £23 would allow for running costs of £100k and amortisation of the instrument over 3 or 5 years, Table 5. An appropriate consumables charge appearing on an RCUK grant has some advantages:

- The RCUK grant is peer reviewed and approved expenditure
- The expenditure is FEC
- RCUK infrastructure grants can then be used to expand a centre or support technique innovation.

Sustainable centres can reasonably contribute to capital expenditure with RCUK funding to support expansion or innovative technique development which aligns better with the RCUK mission.

**Table 5 Activities of a Sustainable Mass Spectrometry Centre**

| *Activity* | *Mean* | *Range* | *Comments* |
|---|---|---|---|
| Number of PIs | 30 | 1-80 | Survey results |
| Number of Samples Analysed | 9000 | 10 – 50000 | Survey results |
| Cost structure | £50 per sample | £4-£400 | No consistent charging structure |

| | | | |
|---|---|---|---|
| Commercial Revenue | £22k | £0.5 - £40k | Survey Results |
| Instrument Purchases | 70% of responders in the last 2 years | | |
| Average Spend per instrument | £375k | £10k - £1600k | 76% not funded by EPSRC/BBRSC |
| Funding | RCUK 30% | Other bodies including EU, Gates, Industry, Home University, CRUK | |
| **Sustainable Centre Business Model** | | | |
| Running costs | £100k | Staff+ consumables | |
| Instrument Costs | £500k | Replaced every 3 years or 5 years | |
| Samples per year | 9000 | | |
| Sample price | £12 + £19 | Cover running costs and instrument | |
| | £31 | Replacement instrument in 3 years | |
| | £23 | Replacement instrument in 5 years | |

Sustainable centres with expertise in metabolomics or proteomics can develop experimental and theoretical methods that benefit all PIs but not all projects or universities have a large PI base. Smaller research groupings however will not generate the 9k sample level such as when entering a field where larger capital expenditure contributions are required but justified against a novel justification for the project grant.

Maintenance of small research initiatives is RCUK mission-critical and will require additional capital support. The legacy of capital investment needs to be managed as PIs move or retire.

**All mass spectrometry centres need to present transparent accounts.**

## 4. Return on the Investment

All RCUK capital investment needs to consider the ROI including mass spectrometry which is now captured in Impact. Mass spectrometry is explicitly mentioned in 620 Case Studies in the last REF generating spin-out companies with turnover and employment contributions to the economy. The number of publications cited on Pubmed including mass spectrometry in the title is 5859 papers from the UK since 2005 averaging (530 ± 160) per year. The global mass spectrometry paper output is 154104 since 2005, 14,222 ± 4492 per year; on this simple analysis UK publishes ~ 4% of all papers globally. However, mass spectrometry is rarely cited in the title of many papers that depend critically on the characterisation of small molecules, proteins and metabolites.

Latent impact in subjects such as proteomics and metabolomics would add a further 78927 papers since 2005; consideration could be given to biomarkers and their discovery and application. Similarly, total grant income supported, total staff trained (PhD, PDRA) and total undergraduates trained are further measures that populate a healthy mass spectrometry community that find work in Industry and Government laboratories.

Assessing the ROI for an annual RCUK investment of £15m is important and does form part of the case for support for capital expenditure but is likely to be a considerable underestimate of the impact of the technique across society. New ideas in single cell analysis, mass spectrometry imaging, MALDI-ToF cited as the fasted growing market segment (M&M) and biomarker discovery have significant impact leverage and make investment in mass spectrometry compelling.

# 5. Conclusions

The mass spectrometry community is innovative and contributing to the development of a critical technique with wide and hidden impact globally. Current expenditure by RCUK is £15m and should be a coordinated investment across the Councils to ensure value for money, development of techniques and exchange of expertise. The total research activity annually is £35m-£60m. The wholesale upgrade of the capital infrastructure does not appear justified but the resource should be spent where the project demands and innovation (as judged by peer review) has been identified. Transparent accounts with FEC contributions, QR contributions, sample numbers and costs should be available with a cost structure that reflects the amortisation of the instruments. These data would form the basis of a pay-as-you-go funding model replacing routine instruments on a 3-5 year rolling capital expenditure. No facilities manager or PI consulted understood the local cost centre income and consequently whether a University contribution to a grant was fair when matched with EPSRC/RCUK funds. All replacement cost estimates however should reflect the predicted growth rate of the market which is predicted to be 8.1% annually to 2020.

The future requirements of capital expenditure in mass spectrometry are driven by the development of new instruments by the instrument manufactures and research groups innovating in application. The community needs to be amongst the early adopters of new technologies; new capabilities provide quick contributions to the field, setting new standards pushing the research fields rapidly forwards. An early technology adoption strategy requires RCUK and researchers to respond quickly to new developments.

## Appendix Consultation List

Members of the British Mass Spectrometry Society

Committee of the British Mass Spec Society

Neil Oldham, Nottingham University

Gareth Benton, National Mass Spectrometry Facility

Peter O'Connor, Warwick University

Thermofisher, Instrument manufacturer

Waters, Instrument Manufacturer

G. John Langley, University of Southampton

Nick Smirnoff, University of Exeter

Hannah Florence, University of Exeter

Carol Robinson, University of Oxford

Anneke Lubben, University of Bath

Imperial College, mass spectrometry department

Nottingham University, mass spectrometry department

Bill Leavens, GlaxoSmithKline