SHIMADZU
Excellence in Science

Mass Spectrometer Business Presentation Materials

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Contents

Expansion of Mass Spectrometry (1)

Why Mass Spectrometry?

Mass spectrometry is able to analyze a wide variety of compounds with high accuracy and high efficiency (simultaneous multicomponent analysis). It offers superior characteristics that are especially beneficial in the following fields, where demand continues to expand.

✓ Analysis of biological molecules

Amino acids, proteins, lipids, sugars → Drug discovery
→ Diagnosis

✓ Analysis of hazardous trace substances remaining in the environment

Dioxins, pesticides, veterinary drugs, volatile organic compounds (VOCs)

✓ Materials research

New material development, functional enhancement of materials, etc.





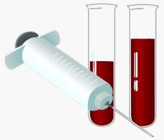
Expansion of Mass Spectrometry (2)

How Did the Mass Spectrometry Develop?

- ✓ Mass spectrometry started being researched at the beginning of the twentieth century, for analyzing isotopes of inorganic elements in Europe and the United States.
- ✓ 1950s-1960s: Mass spectrometry progressed to analyzing organic compounds, such as fossil fuels, synthetic compounds, and biological molecules.
- ✓ 1970s: Combined with chromatography, mass spectrometry development progressed significantly when the characteristics of both technologies were merged.
- ✓ 1980s: Advancements in computerization resulted in dramatic improvements in instrument control and data processing capabilities.

In Which Fields Will Mass Spectrometry Use Increase?

- ✓ Fields with hazardous chemical substance regulations (foods, environmental testing, banned substances, etc.)
- ✓ Healthcare fields: Development of biopharmaceuticals and other drugs, examination of diseases, etc.

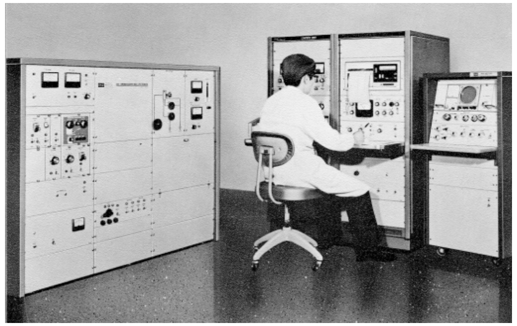


- ✓ Functionally engineered materials and functionally enhanced food fields

I. Introduction

History of Shimadzu's Growth in Mass Spectrometry (1)

		Magnetic Sector MS	Events
Period I	About 1965	Started preliminary investigation of mass spectrometry.	1965 Shinichiro Tomonaga wins the Nobel Prize in Physics. 1969 Apollo 11 lands on the Moon.
	1969	Shimadzu collaborates with LKB of Sweden to introduce the **LKB-9000**, the first **magnetic sector** GCMS system in Japan.	
	1971	LKB-9000 production starts at Shimadzu, with first system delivered to the Hokkaido Industrial Research Institute.	1972 Japan-China Joint Communiqué 1973 First oil crisis 1975 Vietnam War ends 1976 Lockheed bribery scandals 1978 China-Japan Treaty of Peace and Friendship signed.
	1972	Released the **GCMSPAC-300** GCMS data processing system.	
	Late 1970s	Mass spectrometry advancements based on LKB-9000 technology resulted in successive development of **GCMS-6020**, **GCMSPAC-90**, and other products.	
	Around 1978	Started developing key technologies for quadrupole mass spectrometry.	



LKB-9000

GCMS-6020

I. Introduction

History of Shimadzu's Growth in Mass Spectrometry (2)

(continued)

		GCMS/LCMS	MALDI-TOF MS	Events
Period II	1982	Release of the **GCMS-QP1000**, the first **quadrupole** GCMS system, which receives a large market response.	R&D on the laser ionization mass spectrometer started, with Koichi Tanaka joining the development team in 1983.	1981 Kenichi Fukui wins the Nobel Prize in Chemistry. 1985 Plaza Accord 1986 Chernobyl Nuclear Accident 1987 Susumu Tonegawa wins the Nobel Prize in Physiology or Medicine.
	1987	—	Released the **LAMS50K**.	
	1988	Released the **LCMS-QP1000** quadrupole system (with some technology adopted).	—	
	1989	—	Purchased Kratos of the UK.	1990 East and West Germany united. 1991 Gulf War starts. Soviet Union collapses. 1995 Great Hanshin Awaji Earthquake Tokyo subway sarin attack 1999 Euro established as a unified European currency.
	1992	Released the **GCMS-QP5000**.	—	
	1994	—	Released **KOMPACT-MALDI I** MALDI-TOF MS system via Kratos.	
	1997	Released the **LCMS-QP8000**.	—	
	2001	Released the **GCMS-QP2010**.	Released **AXIMA** MALDI-TOF MS system via Kratos.	2001 September 11 terrorist attacks in the United States China joins WTO. 2003 Iraq War 2007 Global financial crisis (subprime lending) 2008 Yoichiro Nambu wins the Nobel Prize in Physics with two others and Osamu Shimomura the Nobel Prize in Chemistry.
	2002	Released the **LCMS-2010**.	Koichi Tanaka wins the Nobel Prize in Chemistry for developing the matrix-assisted laser desorption/ionization (MALDI) method.	
	2004	Released the **LCMS-IT-TOF**.		
	Around 2007	Started developing technologies for triple quadrupole mass spectrometry.		


LAMS50K


GCMS-QP1000


LCMS-QP1000


MALDI-TOF AXIMA

I. Introduction

History of Shimadzu's Growth in Mass Spectrometry (3)

(continued)

		GCMS/LCMS/ICPMS	**MALDI-TOF MS**	**Events**
Period III	2010	Released the **LCMS-8030**, the first **triple quadrupole** LCMS system.	Started supplying MALDI-TOF MS systems to bioMērieux in France.	2011 China becomes the second largest economy in the world. Great East Japan Earthquake 2012 Shinya Yamanaka wins the Nobel Prize in Physiology or Medicine. 2014 Crimean Crisis Isamu Akasaki wins the Nobel Prize in Physics with two others. 2015 Diplomatic relations restored between the United States and Cuba. 2016 Britain announces departure from the EU. 2017 Trump is inaugurated as President of the United States.
	2012	Released the **GCMS-TQ8030** and **LCMS-8040** triple quadrupole systems.	—	
	2013	Released the **LCMS-8050** triple quadrupole system.	**MALDI-7090** (high resolution)	
	2014	Released the **GCMS-TQ8040** triple quadrupole system.	Released the **iMScope** imaging mass microscope (based on IT-TOF technology).	
	2015	Released the **LCMS-8060** and **GCMS-QP2020** triple quadrupole systems.	—	
	2016	Released the **ICPMS-2030**, and the **LCMS-8045** and **GCMS-TQ8050** triple quadrupole systems.	—	
	2017	Released the **DPiMS-2020**.	Released the **MALDI-8020** (compact tabletop model).	
Period IV	2018	Developed the high-resolution market by releasing the first **LCMS-9030 quadrupole time-of-flight** LCMS system.	—	
	…	…	—	

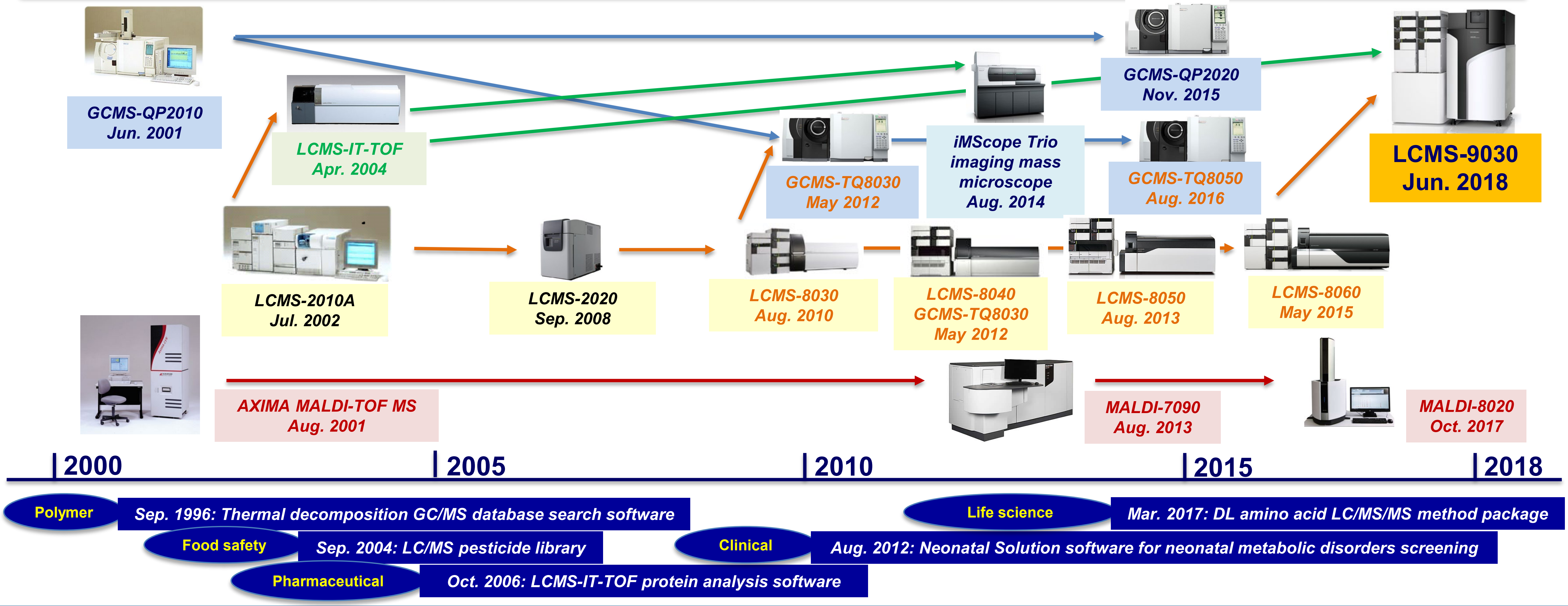

iMScope


MALDI-8020

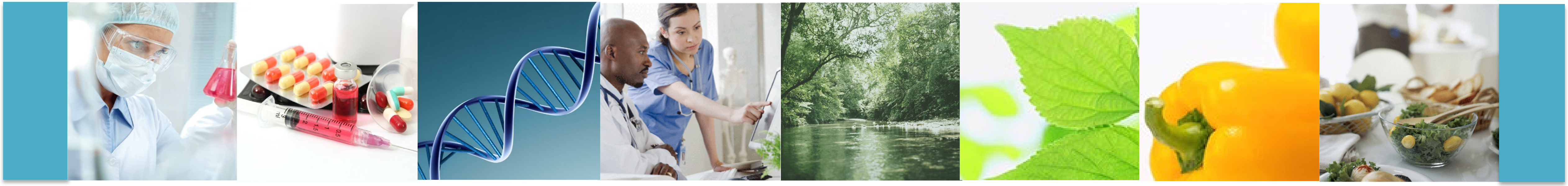
I. Introduction

History of Shimadzu's Growth in Mass Spectrometry (4)

Shimadzu has constantly accumulated state-of-the-art key technologies by continuously researching, developing, and adopting new technologies. By integrating such technologies, Shimadzu has released new products in a timely manner and simultaneously supplied market-oriented applications to develop new demand.



Operating Principle, Demand Trends, and Vendors



Principle of Mass Spectrometry

Mass spectrometers 1) ionize molecular compounds, 2) electrically or magnetically separate the compounds by the type of mass/charge (m/z) ratio, and 3) detect the separated ions.
The resulting mass spectra (with detection intensity, which indicates the concentration contained, plotted on the vertical axis for each m/z ratio, which indicates the mass type, on the horizontal axis) provide information that is extremely useful for identifying known substances or determining the structure of unknown substances.

Product Types and Demand Trends

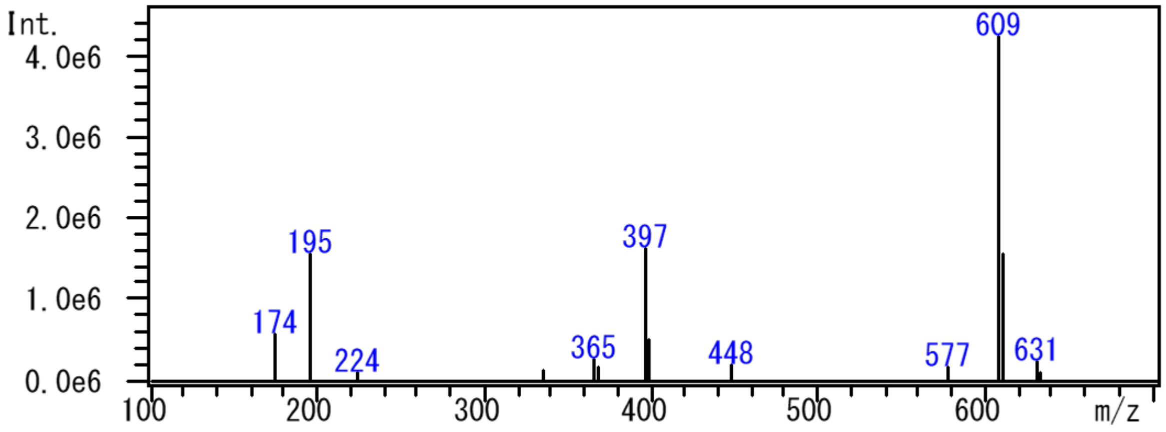
There are basically nine types of mass spectrometers, which use different mass separation methods. ☛ *p. 17*
Due to efforts to increase sensitivity and resolution, demand has been expanding (6 % to 7 % CAGR is predicted for the next five years).

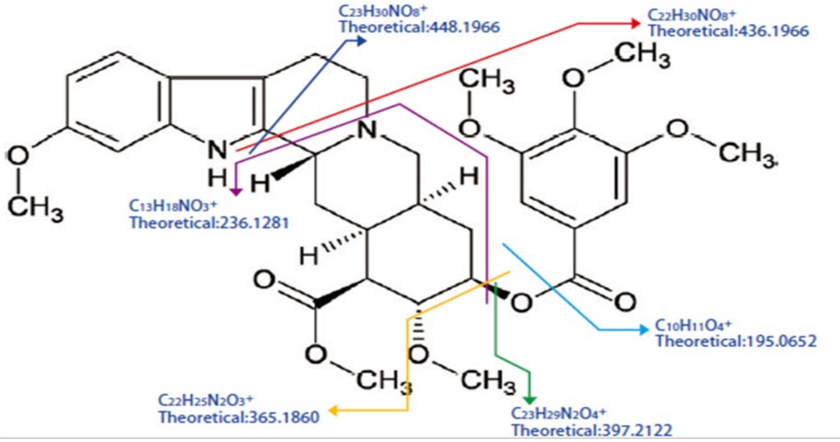
Global Vendors

In addition to Shimadzu, there are five other major global vendors, including four from the United States and one from Germany. ☛ *p. 17*
Vendors are expected to offer comprehensive capabilities, including sophisticated technology, diverse applications, and extensive maintenance and service capabilities. Consequently, barriers to new entry are considered very high.

Mass Spectra

Mass spectra are the data obtained from mass spectrometers. The mass spectrum below shows the presence of reserpine (a tranquilizer or an antihypertensive drug) at an m/z value of 609.2802.





Configuration of Mass Spectrometers

1) Ionization
Ionize atoms and molecules.

2) Separation
Separate ions by type based on m/z.

3) Detection
Detect separated ions.

High vacuum

High vacuum

Exhaust pump

4) Analysis
Analyze the MS spectrum on the computer screen.
☛ *See p.10.*

Note: A high vacuum environment increases ion detection efficiency by eliminating the effects of oxygen and other molecules.

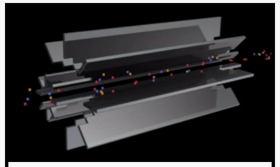
Configuration of LCMS

1) Ionization unit

2) Separation unit: Triple quadrupole

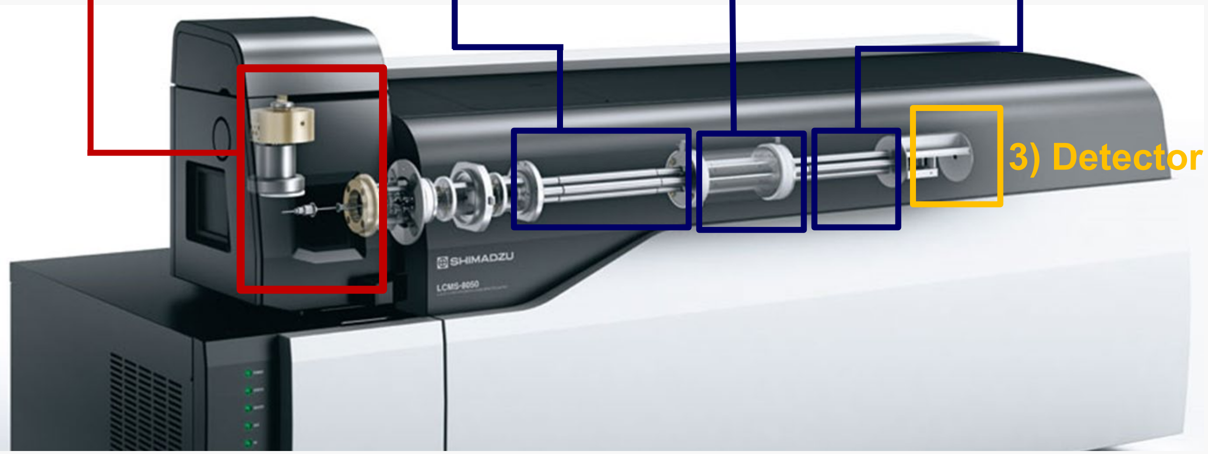
Ion loading unit
Ionize samples separated by HPLC.

Mass spectrometer unit (1)
Exclude unnecessary ions and select specific ions based on mass number.



Collision cell
Decompose selected ions by spraying gas on the ions.

Mass spectrometer unit (2)
Select specific ions based on mass number.



Ionization (1)

To expand the range of compound types that can be analyzed by mass spectrometry, a variety of ionization methods have been suggested and used in practical applications.

- **Generate ions in a gas phase.**

Advancements toward biochemistry ↓

Electron impact (EI) ionization → GCMS

Chemical ionization (CI) → GCMS
Atmospheric pressure chemical ionization (APCI): LCMS
Atmospheric pressure photoionization (APPI): LCMS

Toward achieving even more sophisticated analysis, such as of chemical modifications
- MS/MS
- High resolution
- Improved quantitative sensitivity

- **Generate ions in a liquid phase (spray methods).**

Thermospray
Electrospray: LCMS

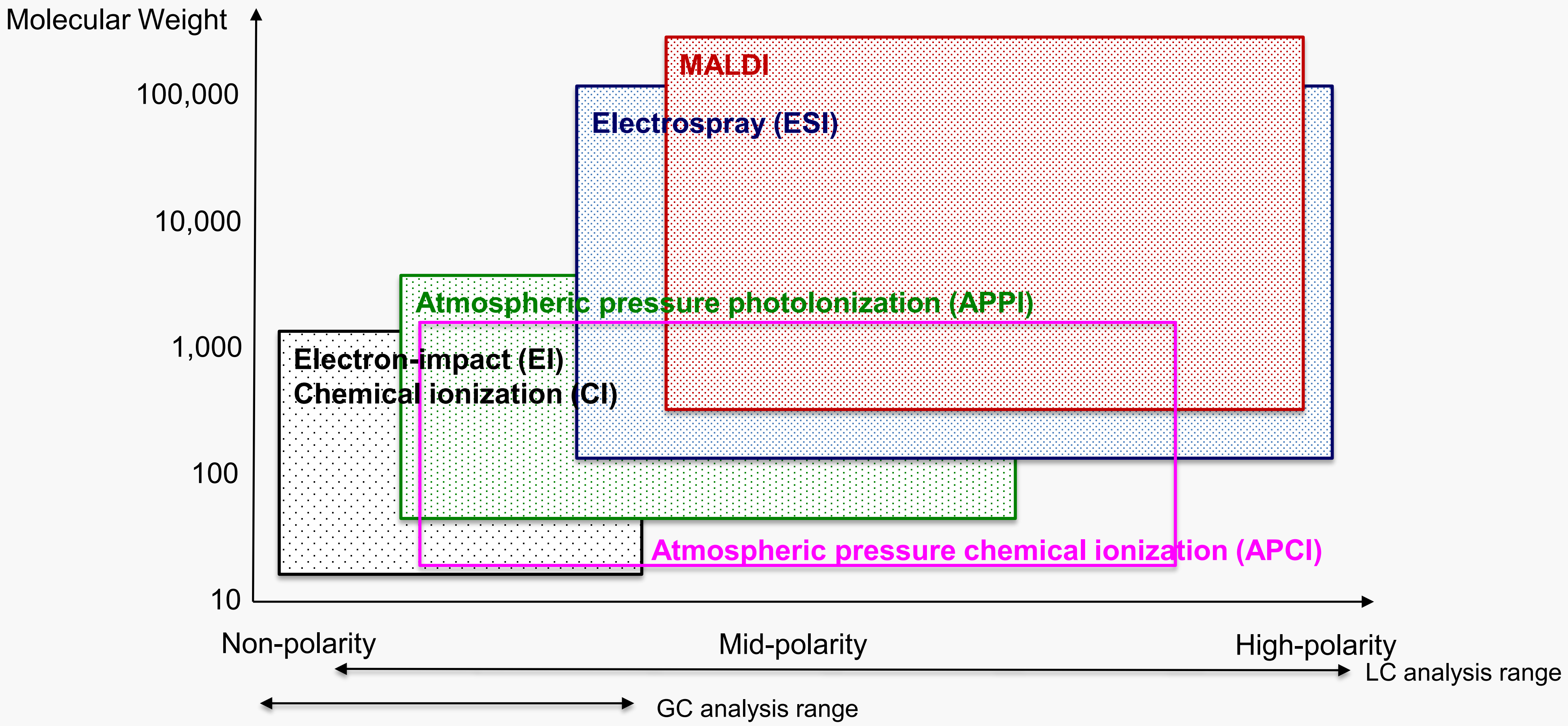
- **Generate ions in a solid phase (desorption methods).**

Field desorption (FD)
Fast atom bombardment (SIMS/FAB)
Matrix assisted laser desorption/ionization: MALDI and iMScope

II. Overview of Mass Spectrometers

Ionization (2)

The number of fields that use mass spectrometry has been expanding, such as for analyzing polymer compounds.



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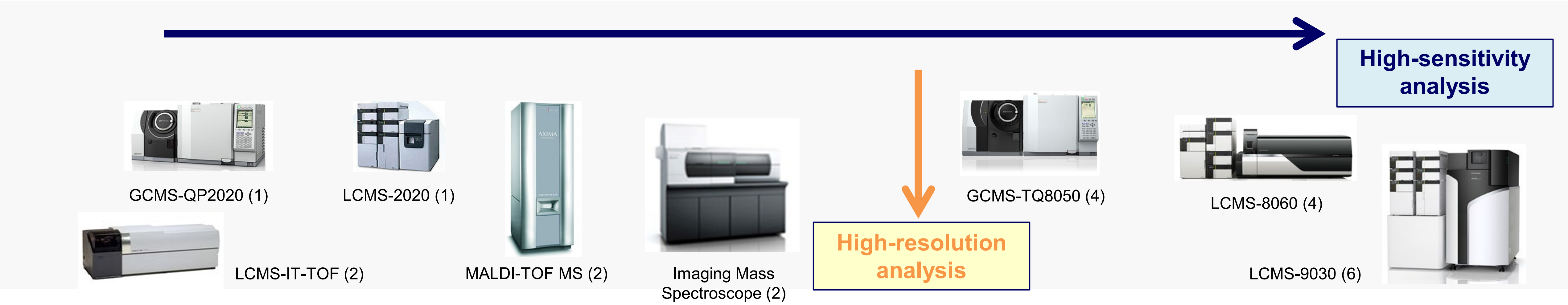
II. Overview of Mass Spectrometers

Mass Separation (1): Classification by Separation Method

By developing practical applications for a wide variety of separation methods, applications for mass spectrometry have expanded from general purpose fields, such as environmental testing and food safety, to more advanced fields, such as drug discovery and healthcare, which require especially high sensitivity and high resolution.

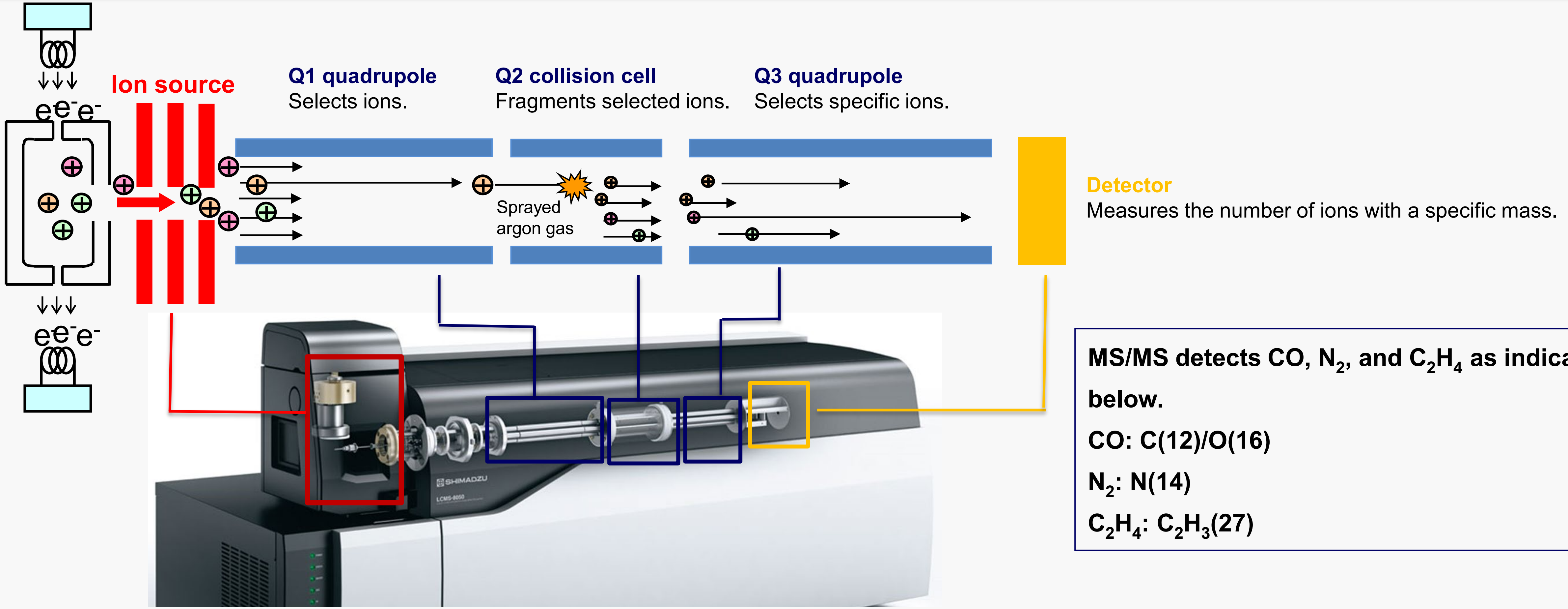
	MS	MS/MS
General-Purpose Analysis	(1) SQ (single quadrupole) model	(4) TQ (triple quadrupole) model (5) Ion-trap model
High-Resolution Analysis	(2) TOF (time-of-flight) model (3) Magnetic sector model	(6) Q-TOF (triple quadrupole time-of-flight) model (7) Orbitrap model



II. Overview of Mass Spectrometers

Mass Separation (2): Principle of MS/MS Mass Spectrometry

The ions separated in Q1 are fragmented in Q2 and the ion fragments are then separated in Q3. The system can differentiate between molecules with the same molecular weight, based on how the molecules fragment. It can also quantitate trace quantities and predict the structure of molecules.



MS/MS detects CO, N_2, and C_2H_4 as indicated below.

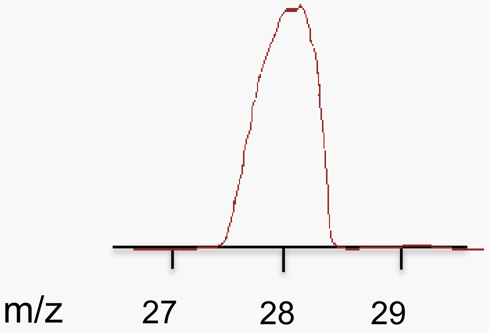
CO: C(12)/O(16)

N_2: N(14)

C_2H_4: C_2H_3(27)

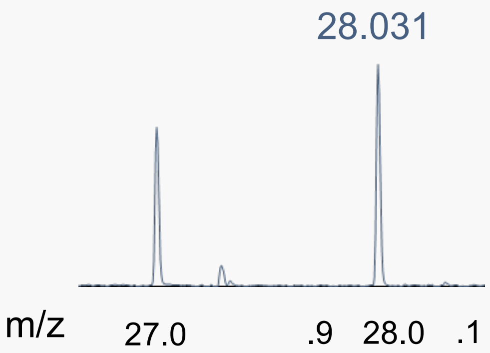
II. Overview of Mass Spectrometers

Mass Separation (3): High Resolution



LCMS-8045
(Triple quadrupole LC/MS)

High-resolution analysis



LCMS-9030
(Q-TOF LC/MS)

Quadrupole and other mass spectrometers can determine integer information about molecular weight, such as a molecular weight of 28, which is the weight of CO, N_2, and C_2H_4, for example, but they cannot identify exactly which of those molecules are in the substance. ☞ *p.15*
Therefore, quadrupole mass spectrometers are best suited for quantitative analysis of known samples.

Mass spectrometers with high-resolution functionality, such as time-of-flight models, are able to analyze molecular weight to the 1/1000 level. By comparing the data to molecular weight data CO=27.9949, N_2=28.0062, and C_2H_4=28.0312, for example, the substance can be identified as C_2H_4.
In particular, Q-TOF models, which are combined with an MS/MS mass spectrometer, can be used for not only accurate qualitative analysis and structural analysis, but also quantitation of trace quantities.

Product Type: Models Offered by Shimadzu

The market size in 2017 was an estimated $5.4 bil. . Shimadzu offers an extensive product line for satisfying a broad range of market demand.

Note: Model types offered by Shimadzu are indicated in blue.

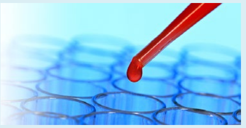
	Model	Major Vendor	Major Field
Quadrupole LCMS	**Triple quadrupole LCMS** **Single quadrupole LCMS**	**Shimadzu**, DHR, A, WAT, TMO	Pharmaceuticals, CROs, universities, hospitals, biotechnology
Time-of-Flight LCMS	**Q-TOF, LC-TOF**	**Shimadzu**, WAT, DHR, BRKR, A	CROs, pharmaceuticals, biotechnology, universities, foods
Trap LCMS	Orbitrap, Ion trap LCMS FT-ICR	TMO, BRKR	Biotechnology, universities, CROs, pharmaceuticals
GCMS	**Single quadrupole GCMS** **Triple quadrupole GCMS** Ion trap GCMS, TOF GCMS	**Shimadzu**, A, TMO, PKI, BRKR	Environmental testing, governmental institutions, foods, universities, petrochemicals, general chemicals
MALDI-TOF	**MALDI-TOF, MALDI-TOF/TOF, MALDI-Q-TOF**	**Shimadzu (Kratos)**, BRKR, DHR	Biotechnology, hospitals, universities, CROs
Magnetic Sector	Isotope ratio, double focusing	TMO, JEOL	Universities, environmental testing, governmental institutions
ICP-MS	**Single quad ICP-MS** Triple quad ICP-MS	**Shimadzu**, A, TMO, Hitachi	Electronics/semiconductors, environmental testing, governmental institutions
Leak Detector	—	**Shimadzu**, IFCN, PFV, A	Electronics/semiconductors, environmental testing, general chemicals
Other	IMS, SIMS, Portable, etc.	—	
Total	—		

TMO: Thermo Fisher Scientific, Inc., DHR: Danaher Corporation, A: Agilent Technologies, Inc., WAT: Waters Corporation, PKI: PerkinElmer, Inc., BRKR: Bruker Corporation
IFCN: INFICON Holding AG, PFV: Pfeiffer Vacuum GmbH

III. Shimadzu's Mass Spectrometer Business

Application Software

Shimadzu offers an extensive selection of application software and databases in an effort to provide user convenience and increase added value in mass spectrometers.

• Foods 	GC/MS method package for residual pesticides in foods Ver. 2 	LC/MS/MS method package for residual pesticides Ver. 3 	LC/MS/MS method package for aminoglycoside antibiotics 	LC/MS/MS method package for mycotoxin 
• Environmental 	Smart Environmental Database 	Screening system for phthalate esters Note: Compliant with RoHS (II) Directive 	LC/MS/MS method package for water quality analysis 	
• Clinical research 	Neonatal Solution Ver. 2.30 (neonatal metabolic disorders screening) 			LabSolutions Insight multi-analyte quantitation software 
• Pharmaceuticals  • Life science	Smart Metabolites Database 	LC/MS/MS method package for primary metabolites Ver. 2 	LC/MS/MS method package for lipid mediators Ver. 2 	LC/MS/MS method package for cell culture profiling 
• Toxicological drugs 	Quick-DB GC/MS/MS forensic toxicological database 	LC/MS/MS rapid toxicology screening system Ver. 2 	LC/MS/MS toxicological database 	

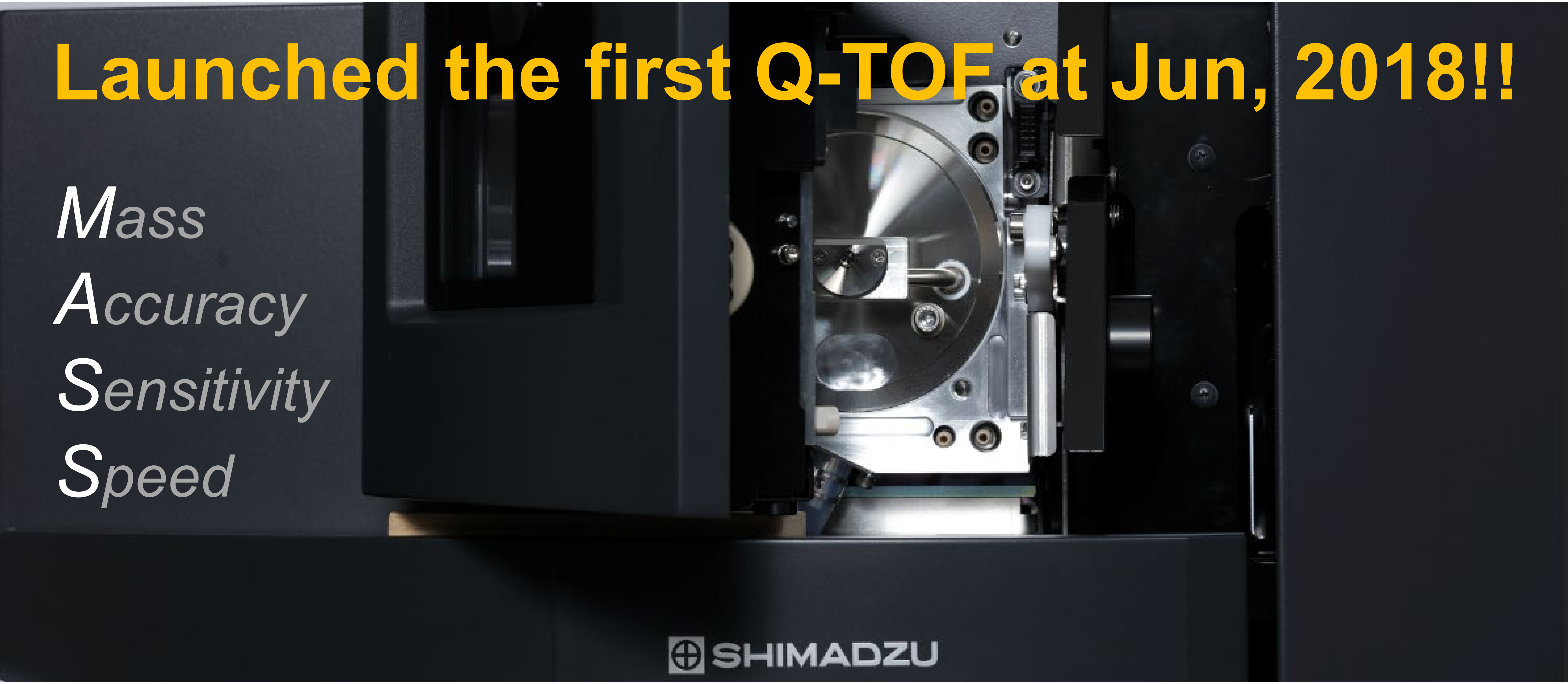
Growth Strategy for Mass Spectrometer Business

Units: Billions of yen	FY 2019 Medium-Term Plan Target	FY 2016	FY 2019 vs. FY 2016		
			Increase	Percent Increase	CAGR
Analytical & Measuring Instruments	**253.0**	209.2	43.8	20.9%	6.5%
Mass Spectrometers (MS)	**45.0**	**33.9**	**11.1**	**32.9%**	**9.9%**

Medium-Term Management Plan: Growth Strategy for Mass Spectrometer Business

1) Expand/improve product lines, such as MS products for rapid screening or high resolution.
2) Develop expert systems based on using AI and ICT technologies for sophisticated data processing and analysis.
3) Expand business based on expanding the range of MS application fields (such as molecular diagnostics and cellular analyses).

Expand/Improve Product Lines (1): LCMS-9030 Q-TOF



III. Shimadzu's Mass Spectrometer Business

Expand/Improve Product Lines (2): LCMS-9030 Q-TOF

1) High Resolution

Identifies compounds with high reliability: Resolution is greater than 30,000 FWHM at m/z 1,972.

2) High Accuracy

Identifies masses with high accuracy: Mass accuracy within 1 ppm at m/z 622.5662

3) High Stability

Maintains high mass accuracy even after operating continuously for long periods in an environment with temperature variations: Maintains 1 ppm mass accuracy after operating continuously for 24 hours in an environment with 6 ˚C temperature variations.

4) High Operability

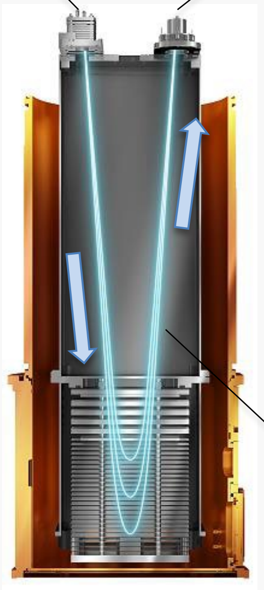
Simple operability: Uses highly rated LabSolutions LCMS software, which has an extensive track record in LC, GC, and quadrupole LCMS systems.

New Fields Being Developed for Q-TOF Mass Spectrometers	
Biopharmaceuticals	Characterization of biopharmaceuticals, identification of impurities, etc.
General Structural Analysis	Structural analysis of impurities in pharmaceuticals and synthetic chemical substances
Food Safety, Environmental Testing, Forensics	Screening for unknown compounds, etc.
Omics Analysis	Biomarker discovery, etc.

Expand/Improve Product Lines (3): LCMS-9030 Q-TOF

Effortless Performance

—High Resolution, High Mass Accuracy, and High Sensitivity—



TOF (time-of-flight) model

Ions fly a given distance toward the detector and ions with a smaller *m/z* value successively reach the detector first. *m/z* values are determined very accurately by measuring the time required for ions to reach the detector.

Internal Configuration of Q-TOF Mass Spectrometers (Reflectron)

UFgrating™ (patented)
High-strength miniature grating electrode achieves high sensitivity and high resolution.

Funnel MCP
Detects all ions that reach the detector, without any losses.

High-speed digitizer
High-speed data acquisition at up to 100 Hz

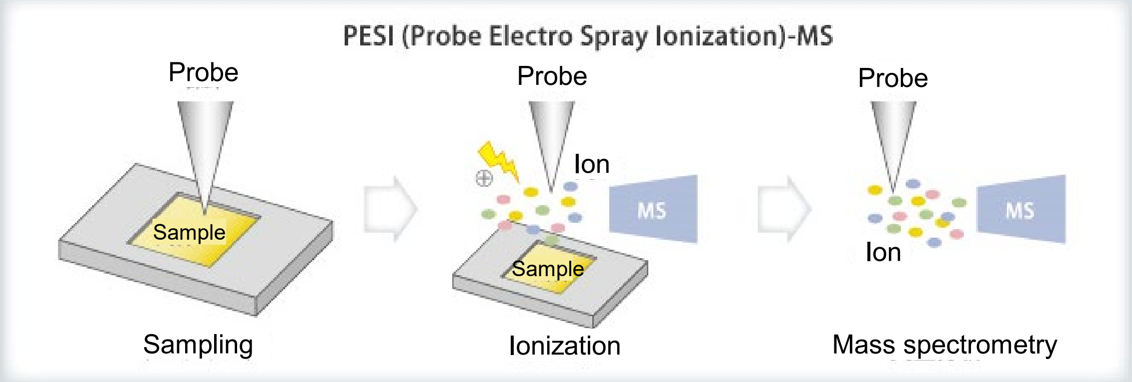
High-precision temperature control system (patented)
Maintains consistent mass accuracy for long periods.

iRefTOF™ (patented)
This ideal reflectron with an optimized electric potential distribution offers high resolution and high sensitivity.

Expand/Improve Product Lines (4): DPiMS-2020

In September 2017, Shimadzu released the DPiMS-2020 mass spectrometer, which directly ionizes samples with a probe. That eliminates the need for complicated pretreatment operations.
The system is promoted in fields that require rapid analysis, such as emergency medicine and forensics.
In the future, we will also target cancer and other surgical applications (for support with deciding what areas to remove).
That will establish a new application for mass spectrometry.

DPiMS-2020 Probe Electrospray Ionization Mass Spectrometer



Measures to Expand Application Fields

Introducing Mass Spectrometry for IVD Applications

In vitro diagnostics (IVD) is used to diagnose diseases by examining the blood, urine, stool, saliva, or other liquids (minimally invasive liquid biopsies).

Why Use Mass Spectrometry?

1) **It results in a smaller percent of false negatives and positives than conventional methods. (It measures the relevant molecules directly.)**
2) **It enables simultaneous examination of multiple targets (measuring multiple target molecules at the same time).**
3) **Low operating cost (It does not involve using a special reaction reagent.)**

☞ Mass spectrometry has been used for drug screening, forensic toxicology tests, and sports doping screening from an early stage.
☞ Operating cost is low, but issues remain with high initial investment cost, skill required for operating the system and data analysis.

Examinations That Already Use Mass Spectrometry

1) **Newborn screening (NBS):** Covered by Japanese national insurance for specific analysis
2) **Therapeutic drugs:** Covered by insurance for managing drug administration by measuring drug concentrations in the blood
3) **Bacteriological testing:** Covered by insurance for testing for microorganisms that can cause infectious diseases
4) **Testing for endocrine substances (vitamin D and catecholamine):** LCMS is anticipated as a potential testing method.

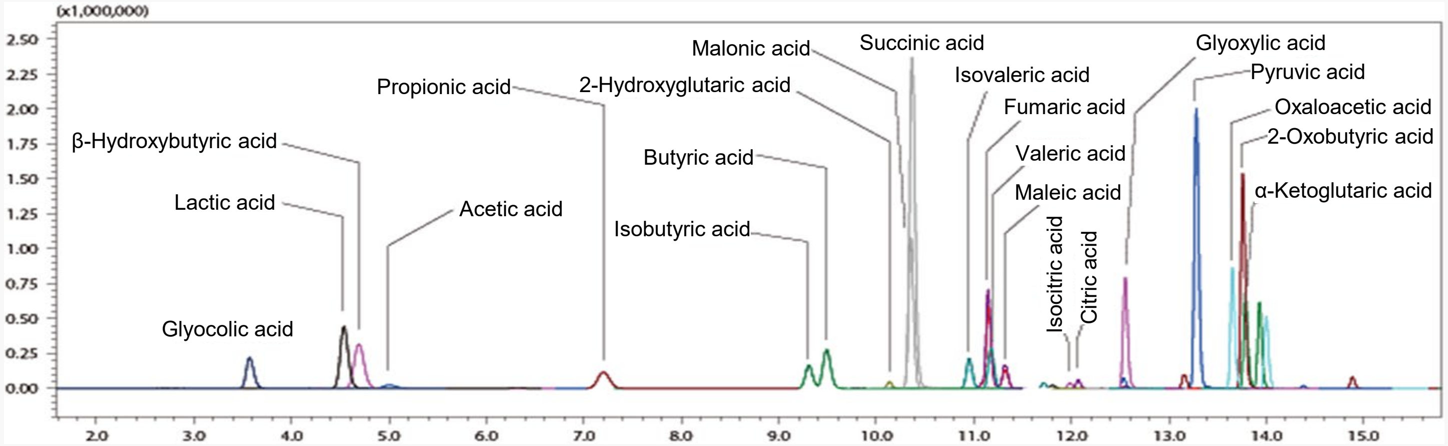
Measures to Automate Data Processing Using AI

The MS chromatogram below is from using the LC/MS/MS method package for short-chain fatty acids to analyze 21 related components. By using the simultaneous multicomponent analysis capability, progress has been made in introducing mass spectrometry even in such metabolomic analysis fields (comprehensive analysis of biological metabolites).

However, due to the massive amounts of data that can be acquired after increasing instrument performance, customers are looking for increased automation for saving time and data analysis functionality that eliminates the need for experience and expertise.

We are currently collaborating with Fujitsu to develop automatic peak-picking (identifying the width and height of peaks) functionality based on using deep learning, which is a type of AI. The aim is to achieve high-precision and fast data analysis software that does not depend on operator experience or expertise.

Mass Spectrometry Data for Short-Chain Fatty Acids



Summary

Future Direction

1) **Relentlessly pursue high sensitivity and high resolution.**
   ⇒ Satisfy high-end needs, such as for new drug development.

2) **Reduce instrument size, make them easier and less time-consuming to operate, and automate data analysis using AI technologies.**
   ⇒ Expand routine applications, such as healthcare examinations and quality control testing.
   ⇒ Enter the smart cell industry (industrial use of cell products).

3) **Build extensive selection of mass spectrometer applications.**
   ⇒ Promote joint development consistent with global demand, mainly at innovation centers.

4) **Develop advanced healthcare technologies.**
   ⇒ Launch the Healthcare R&D Center for promoting joint research with researchers world-wide (construction scheduled for completion in January 2019).

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