

Development of Shimadzu's HPLC Business



Pressing the VP key on each VP module will output the validation records for the unit, including maintenance log, consumable replacement record and auto-diagnostics.

Providing Solutions for Superior Customer Satisfaction

High-performance liquid chromatography (HPLC) is a highly versatile instrumental analysis method used in many scientific fields, and has undergone remarkable developments over the last 30 years. Recent achievements in HPLC have been made possible by advances in separation and detection technologies, as well as the instruments developed to take full advantage of those advancements. In the HPLC field, Shimadzu has continuously introduced new technologies, researched market demands to provide customers with the instruments they need and has energetically promoted research into HPLC applications in a number of areas.

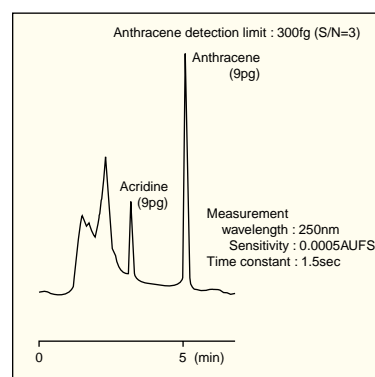
Shimadzu HPLC Product Line-up

Shimadzu offers a large array of HPLC instruments, ranging from micro LCs to preparative LCs, and specializes in the modular type LC-VP series and integrated type LC-2010. In addition, supporting software, such as the CLASS-VP workstation and system networking, also forms a major part of Shimadzu's contribution to HPLC technology.

This article provides a brief introduction to the full range of Shimadzu's HPLC products.

LC-VP Series Validation and Productivity

The LC-VP series is a modular type HPLC system designed for validation and productivity. Each unit is equipped with a special VP key that enables quick execution of various checks for the unit, including periodic and routine checks for compliance with GLP/GMP regulations. Product information, maintenance information, validation support and calibration support are controlled by the VP key. Users can utilize the key to display



Spectacularly low noise level to $\pm 0.35 \times 10^{-5}$ AU for high sensitivity analyses.

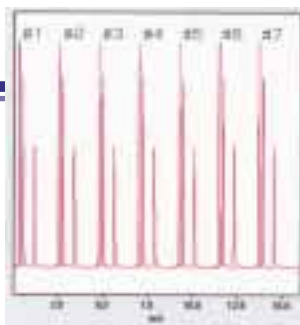
and record instrumental information and output validation results to the Chromatopac (C-R7A) or LC workstation (CLASS-VP) through the system controller, making validation and calibration work more automated and efficient. The LC-VP series units provide a high level of performance. The solvent delivery unit LC-10AD_{VP}, which makes full use of new micro plunger technology, enables highly accurate pulseless solvent delivery that fully utilizes the capacity of detectors sensitive to pulsation.



The powerful VP Series was developed to satisfy all of your "Validation and Productivity" requirements.



The LC-2010 is a next-generation HPLC based on the concept of high-throughput analysis and automated validation.



Seven analyses all done in 15 minutes thanks to high-speed injection and an ultra fast column. This enables major improvements in analysis throughput in the field of drug discovery.

The autoinjector SIL-10AD_{VP}, which employs a plunger type lightweight pump with 6nL/step resolution, has superb reproducibility even for micro volume injections. The recently marketed high-throughput autoinjector SIL-HT has the industry's shortest sample injection time, just 15 seconds, and enables the loading of up to four microplates, to assure an optimum HPLC environment as the front end for LC-MS or LC-MSMS systems. The LC-VP series also provides a choice of high-sensitivity detectors, including the UV-VIS detector SPD-10A_{VP}, the spectrofluorometric detector RF-10A_{XL} and the refractive index detector RID-10A. The photodiode array detector SPD-M10A_{VP} has both high sensitivity and high resolution without changing the slit width.

The LC-VP series can be used for various applications as a truly reliable HPLC system with excellent expandability.

LC-2010 High-Throughput

The LC-2010, designed with productivity, reliability and efficiency as the core concept, is a next-generation intelligent HPLC that integrates many advanced technologies. It stands out in the HPLC field for

many reasons including high throughput, automation, validation and ease of use.

- High Throughput

World's fastest sample injection at 15 sec/10mL.

The LC-2010 autosampler can handle up to 350 vials of 1mL volume. When the 384-well microtiter plates are incorporated into the system, the LC-2010 can process 1536 samples at once.

- Automation

All analysis procedures, from system startup to shutdown, can be completely automated. This automation includes a baseline stability check as well as opening and closing of the drain valve.

- Validation

System validation and verification of operation have both been automated by the auto validation function.

- Ease of operation

Wizard functions simplify operations and allow even a beginning user to easily perform any analysis. Micro plunger technology and dynamic inlet valve further improve reproducibility, while the cell temperature control function and new optical processing technology achieve high detection

linearity and stability.

The LC-2010 is the optimum HPLC for standardized analyses.

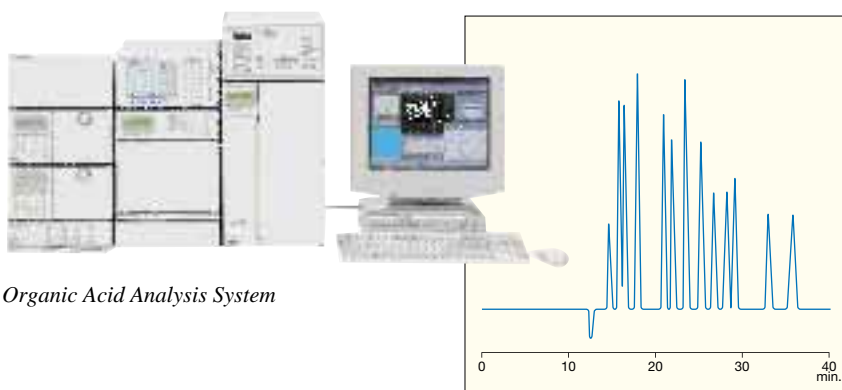
Application Systems for Specific Needs

Most HPLC models are multipurpose analyzers with a broad range of applications. There is also great demand, however, for specialist HPLC models customized for specific uses. Early on, Shimadzu began developing such application systems and currently produces a wide range:

- Amino acid analysis system
- Organic acid analysis system
- Sugar analysis system
- Ion chromatograph
- Transition metal analysis system
- Cyan analysis system
- Carbamate pesticides analysis system
- Bromic acid analysis system
- GPC analysis system
- Auto sample pretreatment system for NMR/MS
- Cleaning validation support system
- Bio-sample analysis system
- GPC cleanup system
- Dioxins cleanup system

While application systems were once developed simply to meet requirements for analyzing specific compounds, they are now regarded as total systems that enhance the efficiency of analyses in specific fields. For example, the automatic sample pretreatment system for NMR/MS, cleaning validation support system and bio-sample analysis system were jointly developed with users to make pharmaceutical analysis more efficient, and have enabled swifter development of pharmaceuticals. The following are brief introductions to three major application systems.

Development of Shimadzu's HPLC Business



Organic Acid Analysis System



The Co-Sense systems offer significant advantages for investigation of *in vivo* and *in vitro* metabolism and analysis of side reactions in chemical analysis.









Automatic Sample Pretreatment System for NMR/MS (Co-Sense for LC-NMR/MS)

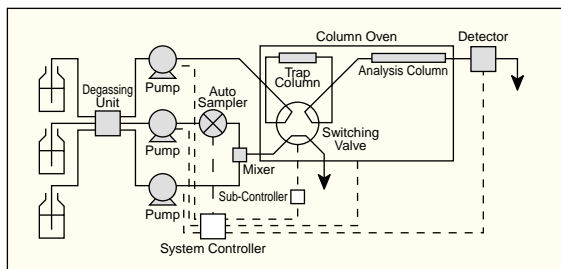
Co-Sense for LC-NMR/MS, a sample pretreatment system for LC/NMR (liquid chromatography - nuclear magnetic resonance) or LC/MS (liquid chromatography - mass spectrometry) structural analysis of compounds, was developed to reduce measurement time and running cost. Sample processing – separation and concentration of target substances from the sample and solvent substitute (substitution with deuterium solvent for NMR) – is fully automat-

ed, which eliminates complex and expensive manual procedures, as well as increases the reliability of the data. Additionally, the Co-Sense for LC-NMR/MS allows users to set optimum LC parameters independent of the NMR/MS measurement conditions. Co-Sense for LC-NMR/MS, originally designed specifically for structural analysis of impurities in pharmaceuticals, has also proven to be a powerful tool for NMR/MS measurement in life science and chemical industry fields, including research into metabolic substances in organisms and analysis of side reactions in chemical synthesis.

Cleaning Validation Support System (Co-Sense for CV)

Co-Sense for CV, being developed to increase efficiency in cleaning validation of pharmaceutical manufacturing equipment, automatically performs consecutive operations from sample pretreatment to residue and threshold calculations to pass/fail judgments, with specially developed software and a unique system configuration based on column switching technology. The hardware for the Co-Sense for CV consists of a concentration unit to concentrate samples and an analysis unit that detects target components. These are connected

<p>1978 TECHNOLOGY BREAKTHROUGH Constant Displacement Quick Return [CDQR] Solvent Delivery System LC-3A</p> 	<p>1981 TECHNOLOGY BREAKTHROUGH Totally Microprocessor Controlled Ternary Gradient HPLC with Electrically Driven Autosampler LC-4A</p> 	<p>1982 FIRST Dedicated HPLC System for 1 mm Microbore Column Analysis LC-5A</p> 	<p>1984 TECHNOLOGY BREAKTHROUGH Compact, Versatile, HPLC System with Modular Components Controller LC-6A</p> 	<p>1982 FIRST High Resolution, High Sensitivity, Dual Lamp Photodiode Array Detector SPD-M1A</p> 	<p>1991 FIRST Advanced, Modular HPLC System with Exclusive Fiber Optic Interface LC-10A</p> 	<p>1995 UNPARALLELED WORLDWIDE ACCEPTANCE More than 50,000 LC-10A Units Shipped Since Introduction</p>  <p>1996 PERFORMANCE BREAKTHROUGH High Sensitivity Photodiode Array Detector SPD-M10AVP</p> 
---	--	--	--	--	---	--



Example of flow diagram of Co-Sense Series.



The LCMS-2010 responds to demands for trace analysis and ultra high-sensitivity analysis on complex matrices.

with a switching valve. In the concentration unit, the desired solvent is used to dilute the sample for concentration of target components in a concentration column. In the analysis unit, target components from the concentration column are inducted into the analysis column, and then separately detected and quantified. The software calculates the amount of pharmaceutical substances remaining in the equipment after the production process, using data acquired from the LC workstation CLASS-VP version 6.1, and then compares it with the threshold set by the user to evaluate pass/fail of the equipment.

Bio-sample Analysis System (Co-Sense for BA)

Co-Sense for BA, an analysis system for drugs in bio-samples, smoothly performs all operations from sample pretreatment to analysis, taking advantage of a unique system configuration based on column switching technology and the pretreatment column. Co-Sense for BA enables direct injection of bio-samples such as plasma, as well as removal of substances that hinder MS measurement, including proteins and ionic substances.

LC/MS Liquid Chromatograph-Mass Spectrometer

The LC/MS detects the molecular weights of a compound in just a few minutes, demonstrating its superiority for research work in the development of new drugs and analysis of the environment. Shimadzu LCMS-2010 is a high-sensitivity LC/MS. For more details, please refer to Innovation No. 28, 2001.



1997 VALIDATION AND PRODUCTIVITY
Comprehensive GLP/GMP regulatory compliance
LC-VP Series

1997 NEW DIMENSION
Simplicity, Ease of use, Ruggedness, Compactness and Affordability
LCMS-QP8000



2000 NEW CONCEPT HPLC
High Throughput Automation, Validation and Ease of use
LC-2010



2001 DESIGNED FOR CHROMATOGRAPHERS
Compact, High performance, Great value
LCMS-2010



2001 ON-LINE SAMPLE PROCESSING
For LC-MS, LC-NMR, Cleaning Validation, and Bio-Samples
Co-Sense Series

*Morimasa Hayashi, HPLC Product Manager, Analytical Instruments Division, Shimadzu Corporation

Aiming to be the Best Technology Partner Through HPLC Products and Services

Shimadzu Corporation aims to continue to serve its customers as a reliable and trusted partner by actively providing extensive technological assistance in the form of products, services, and information. We have the capability to bring extensive technology resources directly to the customer's laboratory regardless of the location.



Shimadzu Global Preferred Accounts Program

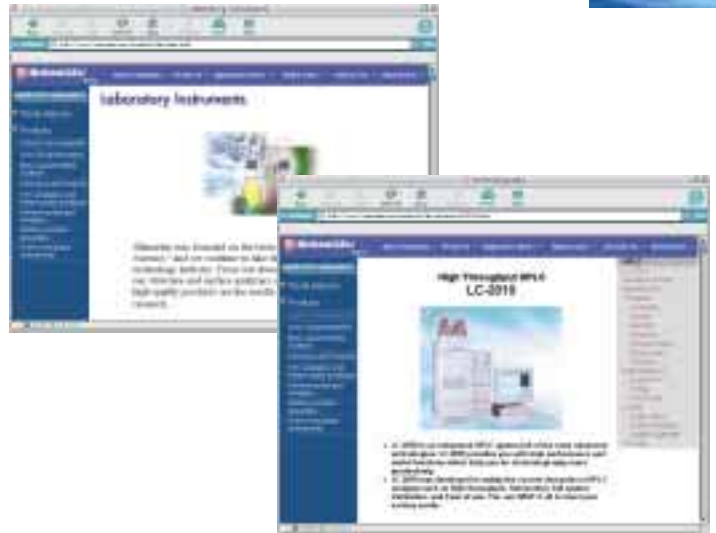
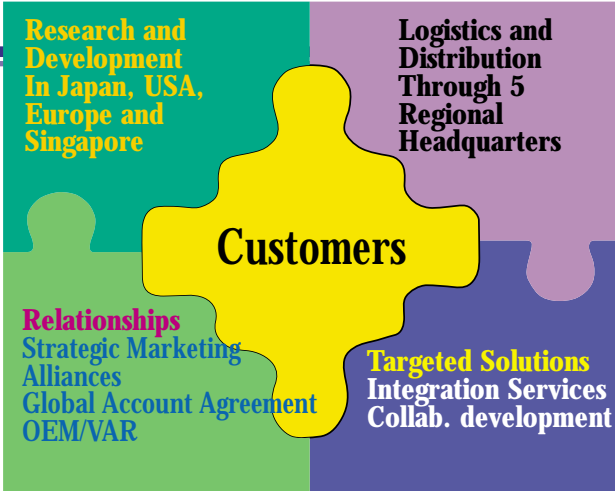
One aspect of the drive to continue long-term partnerships is the promotion of the Shimadzu Global Preferred Accounts Program for Shimadzu analytical instruments. With sales and customer service networks in over 70 countries, Shimadzu provides its international customers with high-performance analytical instruments and top-quality service on-site regardless of location. The Shimadzu Global Preferred Accounts Pro-

gram is designed to accomplish this in the most efficient and cost-effective manner possible, while meeting the specific needs of each company.

HPLC is the core product of this program at present. Major multinational pharmaceutical manufacturers contracted into the program receive fast and uniform service at their local facilities all over the world. As part of the process to forge close relations with the customers, Shimadzu listens to users' needs and incorporates them into the development of new products.

Shimadzu Customer Support Centers

Shimadzu emphasizes customer support as a major part of its efforts to support the user, and holds workshops and seminars at its overseas facilities as part of the customer support programs offered. Shimadzu has Customer Support Centers in the USA, Germany, Singapore, China, Australia and other countries. The training courses provided at these Customer Support Centers include courses on the operational principles of the instruments, their methods of operation, and user-level maintenance. In order to enable Shimadzu distributors around the world to offer this type of user training, Shimadzu is also promoting the establishment of laboratories, the employment of chemists and other relevant technicians, as well as important training for staff members. In addition, Shimadzu holds seminars worldwide, at which new products and their applications are introduced and eminent Shimadzu customers give lectures on interesting topics.



News Media for HPLC Users

The LCWorldTalk newsletter is used as a medium to inform Shimadzu HPLC users about new technologies and important announcements, covering information on the latest HPLC technologies and products, tips on day-to-day analysis, and achievements by users in their research. The Shimadzu home page at www.shimadzu.com is another source of news, providing information on new HPLC products and application data. Lists of maintenance parts are supplied on multimedia CD-ROM.



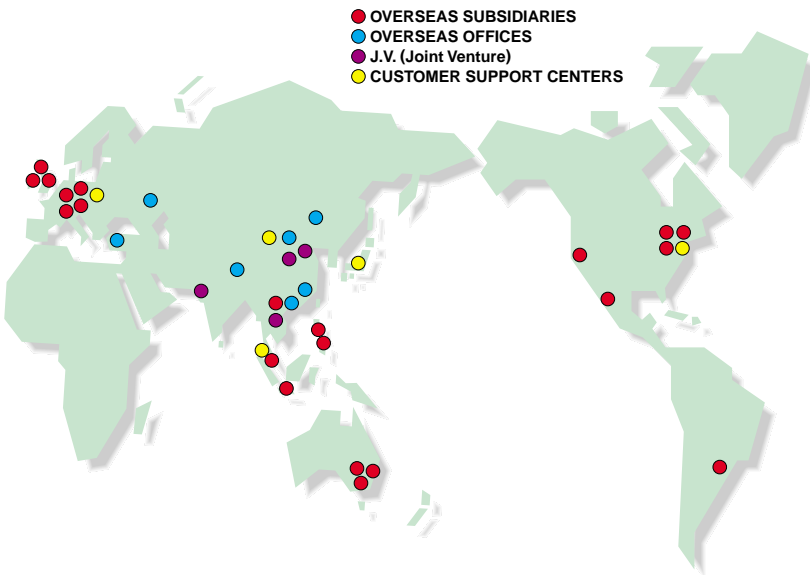
Application data can be down-loaded from the Shimadzu website.



Multimedia CD-ROM for quick search of maintenance parts.



LCWorldTalk is a complimentary newsletter designed to keep the customer abreast of the latest HPLC techniques and applications



*Atsuro Ueyanagi, HPLC Marketing, International Marketing Division, Shimadzu Corporation

Shimadzu Responses to Demands from Pharmaceutical Industry Customers

US FDA put new regulations for pharmaceutical manufacturers

In 1997, the U.S. Food and Drug Administration (FDA) introduced Part 11 of the 21 Code of Federal Regulations (21 CFR Part 11), in order to promote paperless work in processes such as approval checks. This regulation lays down the requirements for use of electronic records and electronic signatures in lieu of paper records (data) as well as the handwritten signatures required in conventional GLP and GMP regulations. FDA, concerned about the possible ease with which electronic records and signatures could be falsified without leaving any traces, made every effort to address this issue and to create regulations that would assure authenticity.

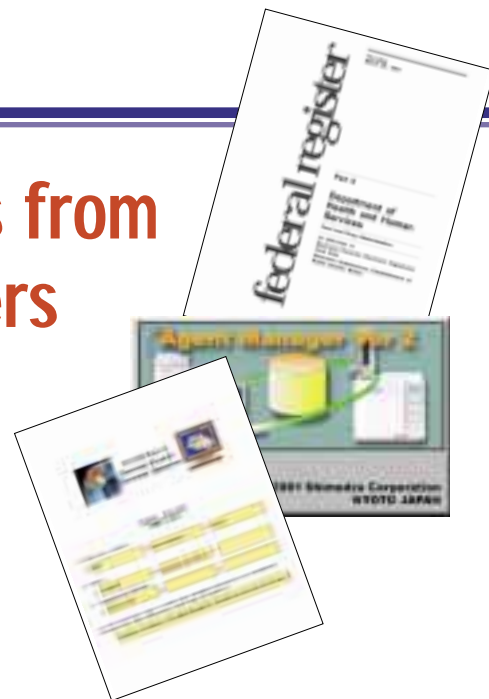
Shimadzu's Responses

The instruments used in pharmaceutical analysis are diverse, ranging from LC and GC in chromatography and UV and FTIR in spectrophotometry to other instruments such as weighing balances, while the data processing for these instruments is nearly always done on computers.

Shimadzu offers the CLASS-Agent Network System, a data management system integrating all analytical instruments, including chromatographs. The CLASS-Agent Network System provides a

secure base for data processing that conforms to the requirements of 21 CFR Part 11.

CLASS-Agent automatically records data and analytical results in real time to a database in addition to analytical conditions and other environmental information that assure data integrity. The system also provides strong support for password administration by setting a lower limit for the number of characters included in a password and specifying expiry dates for passwords. In addition, CLASS-Agent offers other substantial security functions, such as automatic e-mail notification to the administrator when an incorrect password is entered. Also, the data recorded in the database are further recorded into an Oracle database, where access through



the Explorer is also checked. Since recorded information from all analytical instruments is uniformly managed in the CLASS-Agent database, work required for each data set, such as data authorization, can be performed simply by accessing CLASS-Agent. With CLASS-Agent as the hub of data management, users can significantly simplify their routine work and reduce the time and labor of accustoming themselves to other software.

What are Electronic Records?

21 CFR Part 11 defines an electronic record as "any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system." According to this definition, information generated by an HPLC workstation is also an electronic record, and subject to 21 CFR Part 11. In the case of HPLC technology, the electronic records initially saved in the computer are regarded as the original, while paper printouts are merely copies.

What are Electronic Signatures?

An electronic signature is a way to identify the individual who created or modified an electronic record, and it has legal force equivalent to that of a handwritten signature. In concrete terms, this refers to the input required to login to a computer system or to access saved data, in order to identify the user and ensure that the person is authorized by the system administrator.

There are two types of methods for individual identification: biometric methods (fingerprint validation, etc.) and non-biometric methods, which generally consist of an identification code and password. When using an identification code and password, it is essential that no two individuals have the same combination of identification code and password (in other words, that no two individuals use the same identification code), and also that even the system administrator must not know any other user's password. Electronic signatures are valid only for a closed system (a system where access is controlled by the administrator), while cryptographic digital signatures are required for an open system.

For a secure system of electronic records and electronic signatures, the computer setup must be one that assures security such as access limits. Another necessary feature is automatic recording of audit trail information, such as the time, person, item and reason for creation, alteration or deletion of any electronic record. In addition, a secure system also requires a function to prevent overwriting of original records.

*Morimasa Hayashi, HPLC Product Manager, Analytical Instruments Division, Shimadzu Corporation



Major Global Customers Select Shimadzu as a Preferred Analytical Instruments Supplier

Major Customers Benefit from the Global Preferred Accounts Program

The key elements of the program are Preferred Unified Pricing, Priority Service, and Global Technical Support. These elements, when offered to the global account, must be provided equally, regardless of location. In other words, Shimadzu provides services and pricing to the account at a consistent level at all locations, whether in Europe, the US, the Mideast or in Asian countries. The main benefit for the account is to reduce the overall costs associated with purchase and maintenance of analytical products involved.

The basic objective of the Global Preferred Accounts Program is to meet customers' needs by offering value-added services coupled with a preferred pricing structure, to form a partnership between Shimadzu and the customer. With sales and customer service facilities in over 70 countries, Shimadzu has the capability to offer global customers high performance analytical instrumentation with high priority service and support directly to their laboratories. The Global Preferred Accounts Program is designed to ensure that this is accomplished in the most efficient and cost effective manner possible

while meeting the specific needs of each company.

Major Companies Worldwide Choose Shimadzu

Shimadzu Scientific Instruments, Inc. in the United States has taken an active role in developing the Global Preferred Accounts Program. For example, Eli Lilly and Company (Indianapolis, Indiana) and Bristol Myers Squibb (Princeton, New Jersey) have already chosen Shimadzu as a Selected Preferred Vendor for all Shimadzu analytical products, including HPLC products, for a 3-year period, and as of this writing the contracts were being renewed. In

addition, Dow Chemical has selected Shimadzu as its Preferred Supplier of On-Line and Laboratory TOC products.

The program will continue to expand in 2001 and beyond, with increased R&D spending forecasted particularly in the areas of Biotechnology and Drug Discovery. The major product focus is HPLC, given the business expansion in Pharmaceuticals and Biotechnology. The new LC-2010 and LCMS-2010 will reinforce Shimadzu's position as the leader in these markets, and the Global Preferred Accounts Program will develop long-term partnerships between the Major Account Customer and Shimadzu.



*Leonard J. Poirier, Manager, National & Global Accounts, Shimadzu Scientific Instruments, Inc