SHIMADZU
FDA Regulatory Compliance

C191-E003A

Shimadzu Total Support for FDA Compliance

21 CFR Part 11
Computer Validation Network System

Manage the future

Creating Partnerships

Integrated Strategies

Measuring Values

SHIMADZU presents FDA 21 CFR Part 11／Computer Validation Global Support

All Shimadzu network system products incorporate functions for the Part 11 compliance and computer validation functions required by GxP. Shimadzu provides documentation including IQ/OQ, Certificates of Compliance, and Inspection Test Result Reports based on Shimadzu ISO9001 certified system. Shimadzu's accredited service personnel offer full support for validation of customer's Shimadzu products. Shimadzu provides comprehensive customer support for FDA compliance, including supplying the latest information on FDA regulations through seminars and workshops, participating in vendor audits demanded by the Agency, and actively assisting customers to comply with new FDA regulations.

Validation Support

Validation Support

Systematic validation support for creating system operation and management procedures required for FDA compliance

- Providing DQ templates
- IQ/OQ computer validation
- Accredited service support

Vendor Audit

Vendor Audit

Vendor audits based on extensive and worldwide experience

- ISO-9001 certified quality control system
- Supply of documentation, including Certificates of Compliance and Inspection Test Result Reports

ISO9001 Registered

ISO 14001 JACO — CERTIFICATION ORGANIZATION FOR ENVIRONMENTAL AND QUALITY · JAPAN AUDIT AND

UKAS ENVIRONMENTAL MANAGEMENT 051

Part 11 compliant Network System

Network System

Software and other products provide the functions required for FDA compliance.

- Data Processing Workstations and network systems for meeting Part 11/GxP demands
- Support for creating system operation and management procedures
- On-site/off-site user training

Shimadzu Total Support for FDA 21 CFR Part11 and Computer Validation

Reliability and Security

FTIR · Other vendor's instruments · Balance · MS · HPLC · UV · GC

FDA Latest Information

Latest Information

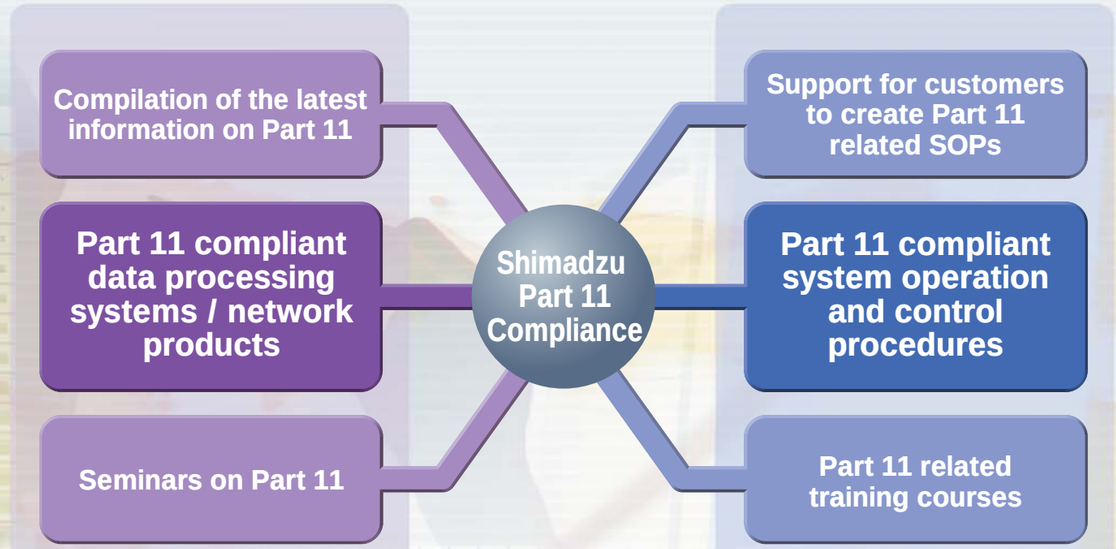
Timely issuing and supply of the latest information on FDA regulations and guidelines

- Shimadzu US Marketing Center collects and provides the latest information about FDA
- Contracted FDA regulation consultants supply the latest information and provide technical instruction
- Shimadzu actively participates in FDA seminars along with ISPE and other organizations

Shimadzu Global Resources Provide Local Support for FDA Compliance

Shimadzu Total Support for Part 11 Compliance

Shimadzu HPLC, GC, Mass Spectrometers, UV-VIS spectrophotometer and other spectrophotometer products and their associated data processing systems all incorporate sophisticated, leading-edge technology for **audit trail, security, and integrity** functions to comply with GLP and cGMP demands.
In addition to offering products and network-compatible software products, Shimadzu offers total support for creating system operation and management procedures, provides information, organizes seminars, and offers post-installation training on Part 11.



Shimadzu's Response for FDA Compliance

Shimadzu's basic policy is to comply with Part 11 requirements by integrating data management for all instruments used in the laboratory, including chromatographs and mass spectrometers (HPLC, GC, LC-MS, GC-MS), spectrophotometers (UV, FTIR etc.), and balances.
Shimadzu's CLASS-Agent products provide solutions for the Part 11 compliance of all essential laboratory analysis data from chromatographs and spectrophotometers to balances. Shimadzu supports networking for all analytical instruments so that the customer enhances working efficiency and data reliability.

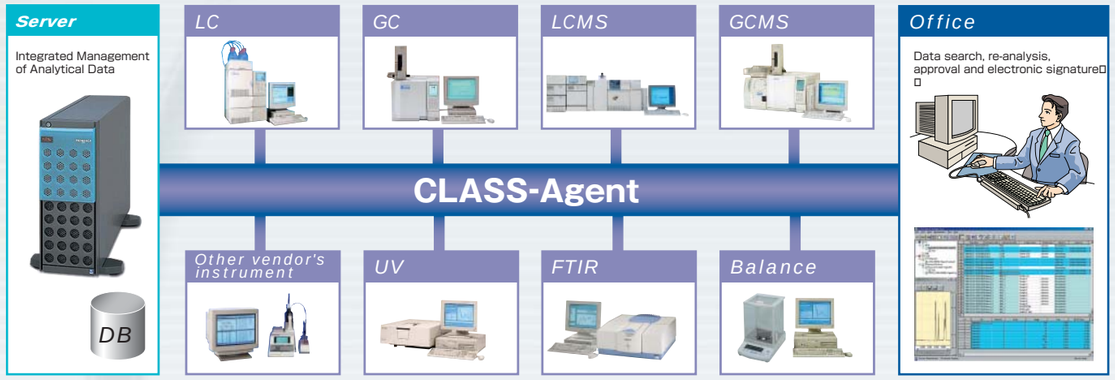
Shimadzu Part 11 compliant network systems ensure data reliability, supporting audit trail, security, and data integrity

1 Total data management with CLASS-Agent
Total management of Shimadzu and other products.

2 "Agent Report" achieves Part 11 compliance for Excel
Use Microsoft Excel that is widely adopted in in the pharmaceutical industry.

3 Total support for Part 11 compliance
Shimadzu total support extends beyond products to assistance in creating system operation and management procedures.

Integrated Management of Analytical Data by CLASS-Agent



21 CFR Part 11 (Electronic Records, Electronic Signatures)

The Part 11 Rule was introduced by the FDA in 1997 to achieve more efficient work practices through paperless operation. It is a compilation of computer validations tackled by the FDA over many years and it establishes the minimum standards for electronic records and signatures to ensure their reliability and equivalence to conventional paper records and handwritten signatures.
As these regulations pertain to all fields of activity under FDA jurisdiction, they apply to all US drug-related businesses, including US pharmaceutical manufacturers and exporters of drugs and raw materials to the US.

Part 11 Requirements

- Electronic records are essential; electronic signatures are arbitrary
  Even if operation is handled using handwritten signatures on records printed on paper, when the original of the record is in an electronic form it is considered to be an electronic record, and it must conform to Part 11.
- Systems and operation procedures to prevent modification of electronic records
  Introducing systems and creating operation procedures for Part 11 support.
- Electronic records are audited by the FDA!
  Audit trail, security, and integrity must be maintained to ensure the reliability of electronic records.

Actual Procedure for Implementing Part 11

- The business clarifies its policies and establishes a master plan.
- Pharmaceutical users establish systems according to the FDA guidelines.
- Select manufacturers / vendors with the capacity to support system establishment.

Guidance for Industry: Part 11 Validation (draft 9/20/2001)

Computer systems must be validated according to an appropriate procedure to ensure the reliability of electronic records and electronic signatures. This draft Guidance for Industry indicates the current FDA philosophy on computer validation and provides important guidance for implementing

Key Points

- The specification requirements for the starting point. Check that the computer system meets the specification requirements
- It is important that the specification requirements meet the demands on the system and operating environment, and also incorporate the technical elements to satisfy Part 11.
- The documentation of plans, procedures, and reports and appropriate review, approval, and management are key points.

In addition to the functions required for compliance with all regulations including Part 11, the FDA has added basic requirements for the computer system itself such as number of clients connected to the network, disk capacity, network expandability, etc. When creating the specification requirements, it is important to reconfirm such basic information in addition to standard regulatory items.

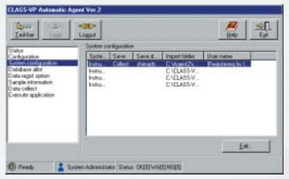
Shimadzu Part 11 Network Supporting Database Management Software CLASS-Agent Features

CLASS-Agent offers total data management of all laboratory instruments from chromatographs to balances.

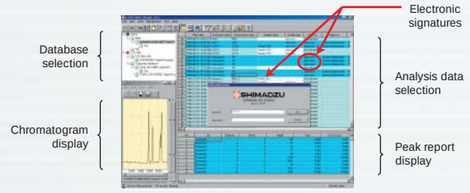
CLASS-Agent complies requirements of the FDA 21 CFR Part 11 (Electronic Records, Electronic Signatures). CLASS-Agent provides secure data management and electronic signature operations for measurement results registered in a database acquired from a range of instruments, including HPLC, GC, GC-MS, LC-MS, UV, FTIR, and balances, as well as other manufacturers' products. The data is automatically saved in the database for subsequent easy searching of desired data. Additionally, the associated method and schedule information, date of measurement, operator's name, and analytical report image files (in PDF format) are stored together to meet Part 11 requirements for storage of machine and human-readable data. Client/server capability allows centralized management of data from all instruments and simple data referencing from a client PC.

● Database Management over the Network provides easy display of peak reports and chromatogram on screen (machine-readable data)

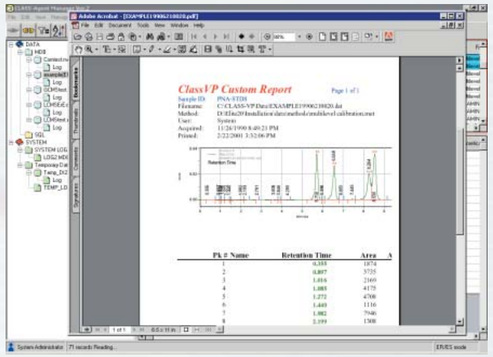
Analytical instruments are connected to a network, permitting centralized management of the analytical data (machine and human-readable data) together with searchable sample and measured value information.



Data review and electronic signatures with Agent Manager data browsing and approval software

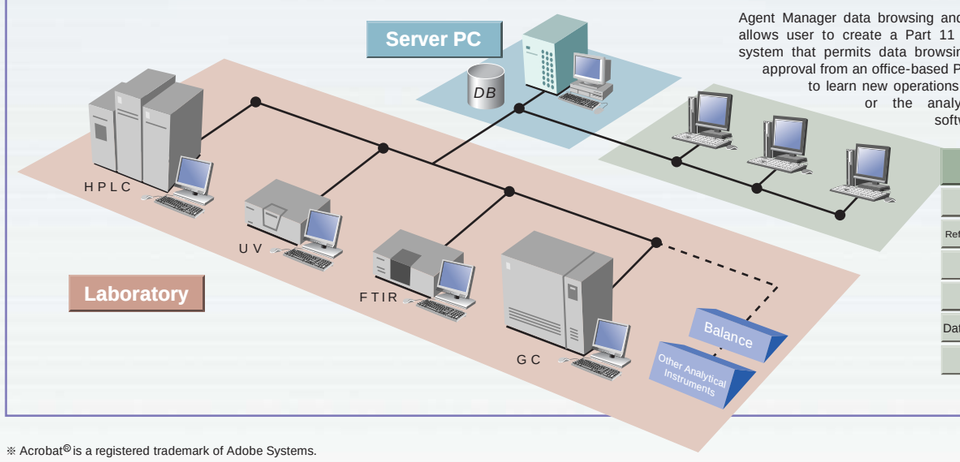


● PDF and AIA files are stored in the same database (human-readable data)



PDF files can be registered in the Agent database if the analytical instrument workstation incorporates a PDF export function.
Agent Manager automatically runs Acrobat to browse PDF files stored in the database.

● Centralized Data Management for LC, GC, MS, balances, UV, and FTIR
● Supports connection of non-Shimadzu analytical and measuring instruments

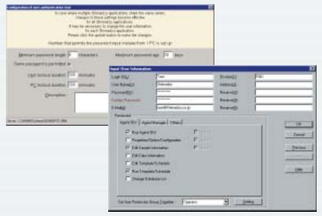


Agent Manager data browsing and approval software allows user to create a Part 11 compliant network system that permits data browsing, inspection, and approval from an office-based PC, without the need to learn new operations for the workstation or the analytical instrument's software.

Office
- Client PC
- Reference chromatograms
- Statistics
- Approvals
- Database management
- Report output

※ Acrobat© is a registered trademark of Adobe Systems.

Access Control, User Management



FDA 21 CFR Part 11 compliance access control provides centralized control of user access to the program, independent of the OS, from a unique Shimadzu user-authentication server. The available functions are set for each registered user to prevent unauthorized people inadvertently changing the settings.

Security, Audit Trail

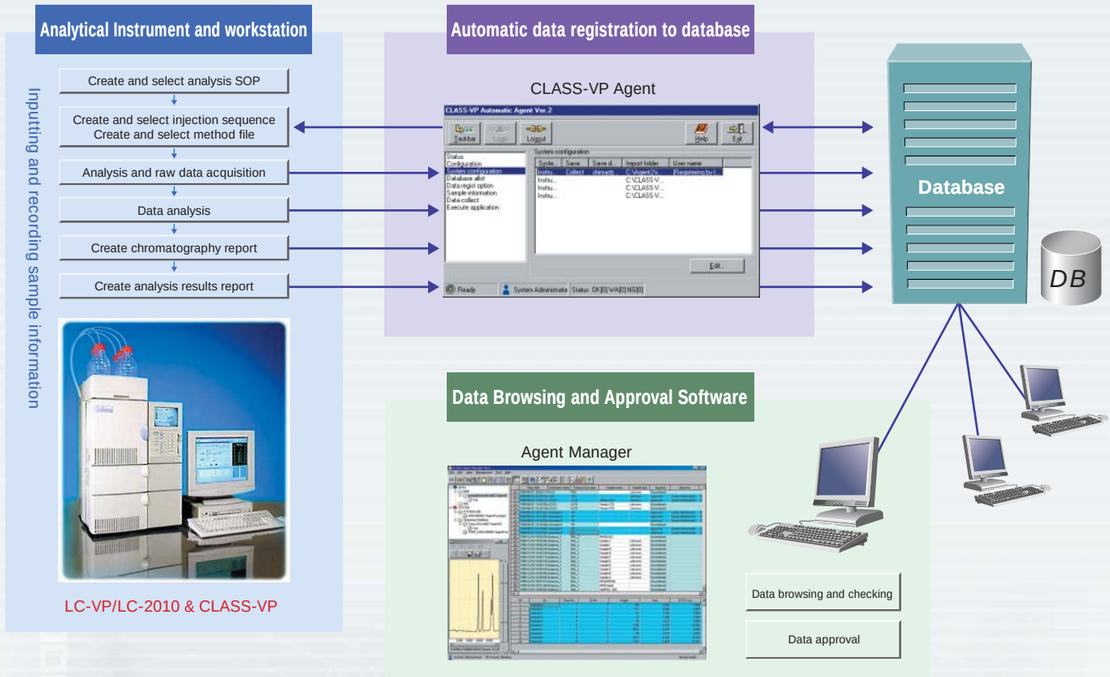
When an illegal login attempt occurs, according to the authentication conditions set in the user-authentication server, access is denied and the illegal login attempt is reported via e-mail.

An operation log is automatically recorded of who did what operation on the registered data and when. The log can be subsequently easily checked. The required information items can be designated for display.

Data Integrity and Electronic Signatures

When CLASS-Agent saves data, it also saves the associated instrument configuration, method, and operating status. This allows all parameters to be subsequently reproduced and guarantee data integrity.
An electronic signature can be applied to electronically recorded data, which is linked to the analysis data. It saves the name of the signer, the date and time of the signature, and the reason.

Flow of Analysis Operations and Data Browsing and Approval (in case of HPLC)



Workstation and CLASS-Agent

Workstation	Automatic Database-registration Software	Data Browsing and Approval Software
LC workstation	CLASS-VP Agent	Agent Manager
GC workstation	GCsolution Agent	
LCMS workstation	LCMSsolution Agent	
GCMS workstation	GCMSsolution Agent	
UV workstation	UVProve Agent	

Analytical Instrument Workstation	Automatic Database-registration Software	Data Browsing and Approval Software
FTIR workstation	IRsolution Agent	Agent Manager
Balance	Balance Agent	
Non-Shimadzu HPLC workstation	AIA Agent	
Non-Shimadzu instruments	Public Agent	

NEW

Shimadzu Agent Report Achieves Part 11 Compliance for Excel Spreadsheet Software

CLASS-Agent now lets Agent Report solve the Excel Part 11 compliance problems

Excel Problems

1 Audit trail problems
- Difficult to identify the creator, date and time of registered data
- Impossible to know who changed values or formula and when

2 Data security and integrity problems
- No means to prevent overwriting or deleting files

3 Electronic signature problems
- No electronic signature functions available

Solutions by Shimadzu Agent Report

Features of Agent Reports

Simple system creation
Report templates can be created quickly by re-using existing Excel worksheets. Created templates are easily registered to the database for secure management using the registration tool. This reduces the workload before the system can be operated after introduction.

Automatic generation of PDF files
A PDF file is generated automatically at the same time an Excel report file is created. The excellent portability of PDF files is effective for electronic report transfer.

Electronic signature-compatible
Electronic signatures can be applied to reports using standard functions of CLASS-Agent Manager.

Easier report generation
Reports are generated automatically simply by selecting analysis data and report templates registered in the CLASS-Agent database. No manual input is required, saving effort for report generation and checking.

Automatic database registration
Created reports are automatically saved in the database for secure storage. Required reports and analysis data can be easily found and recalled using the associated information that is automatically registered simultaneously.

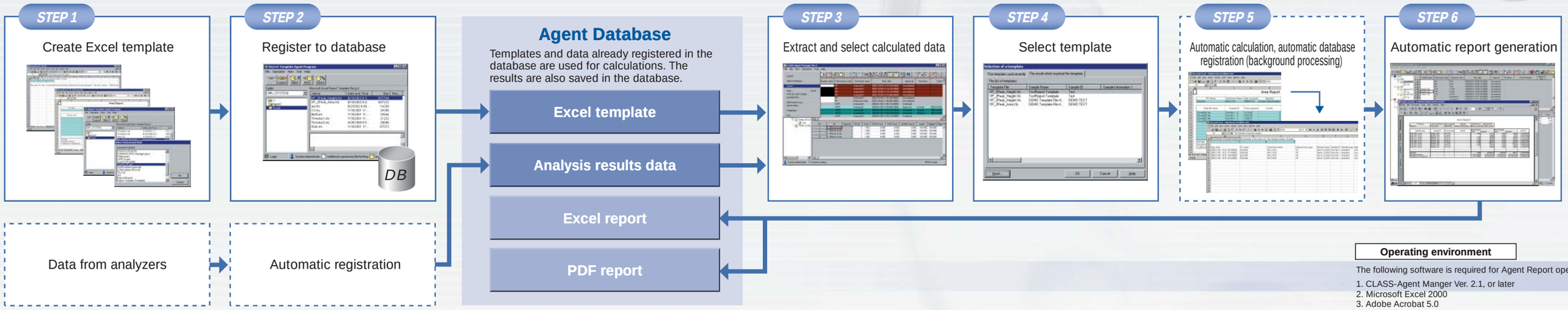
Agent Report Meets All Part 11 Requirements

"Agent Report" registers pre-created templates to a database. When a report is generated, it automatically selects the template, pulls required data from the database and conducts the calculations. Through this procedure, only templates and data already in the database are used for calculations. The Excel spreadsheet that calculated the results is also saved and managed in the database. Consequently, the user does not directly touch the data, thereby maintaining the audit trail, security, and data integrity.

Audit trail	●CLASS-Agent database control of Excel spreadsheets after calculation ●Possible to apply electronic signatures on calculated Excel spreadsheets.
Validation	●No macros are required, only sheet functions are used, making validation simple. ●Validated Excel templates are controlled in a database.
Security	●Excel templates are saved in a secure database. ●Excel files are protected in the CLASS-Agent database.
Human readable	●Reports are automatically saved as PDF files.
Integrity	●Data in the CLASS-Agent database cannot be changed.
Easy to use	●Existing Excel templates can be used as templates.

Basic Points on Excel Validation
- GAMP classified Excel as "Category 3" - No individual validation of the package required.
- Validation of formula is required, despite being classified as "Category 3".
- Control of the software version number, training, and validation (IQ, OQ, PQ) as the system are required.
- GAMP classification Category 5 is applied if macros are used, such that full validation is required.

How Agent Report Achieves Part 11 Compatibility for Excel



Operating environment

The following software is required for Agent Report operation:

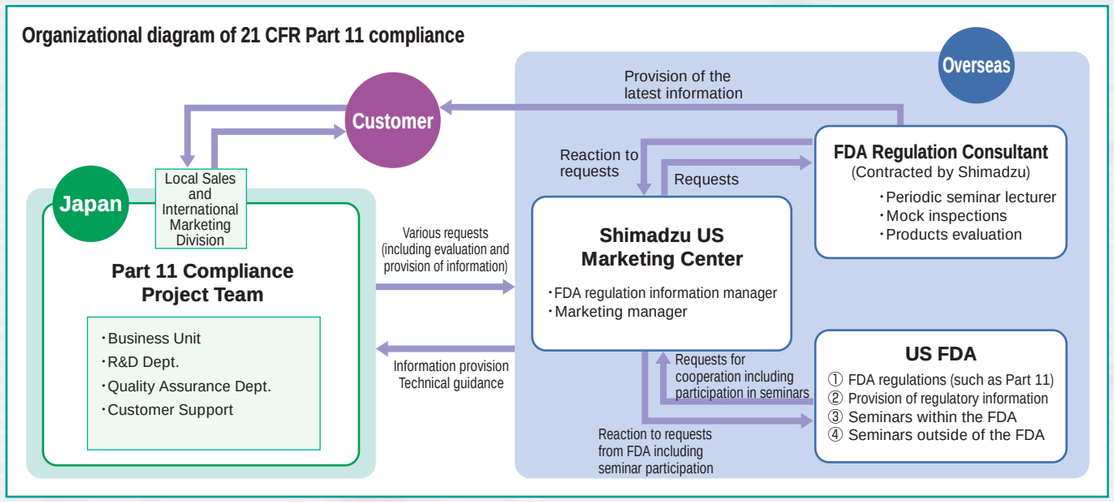
1. CLASS-Agent Manger Ver. 2.1, or later
2. Microsoft Excel 2000
3. Adobe Acrobat 5.0

※ Excel® is a registered trademark of Microsoft Corporation.

Full User Support for Part 11 and Computer Validation ~Shimadzu's commitment~

The FDA does not, and cannot, certify the hardware, software or services of specific manufacturers as Part 11-compliant. The reason being that compliance with the regulations requires management and operating procedures and the associated documentation for the system, which involves operational requirements additional to the functions offered by the product. Consequently, the creation of the company policy and validation master plan by the customer is extremely important for Part 11 compliance.
Therefore, Shimadzu offers the user meticulous total support over the entire lifecycle of the product, from consultations before installing a new system to regular post-installation inspections. Shimadzu in-house systems remain alert to the new requirements of regulatory agencies and national and international trends to continue to offer comprehensive support for customer requirements.

Extensive Shimadzu worldwide customer support network for FDA compliance with flexible and rapid support



Required items and its schedule for Part 11 compliance (new system introduction)

Step 1 — Part 11 unified understandings and corporate consensus
- Goal agreement document for Part 11 compliance
- Internal notification
- Agreement on practical understanding on Part 11
- Internal education program and record management system

Step 2 — Practical works for Part 11 compliance
- System requirement specification and collection of vendor information
- Execution of DQ /IQ/OQ/PQ
- System introduction, trial use, and internal audit

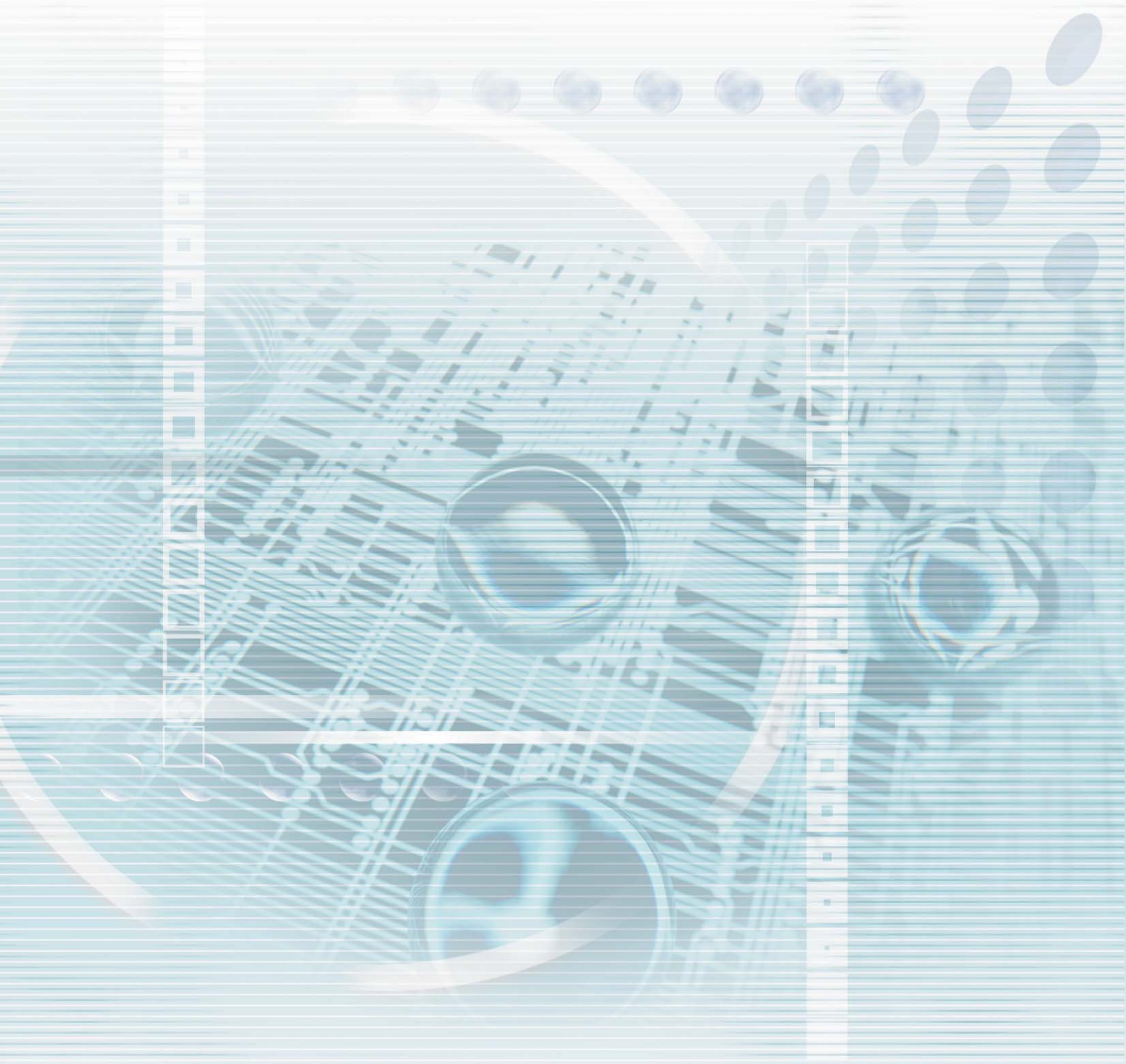
Step 3 — Part 11 compliant system operation
- Change control
- Internal education
- Execution of PM
- Periodic internal audit

Total support from Shimadzu

		【1】Unified understanding of Part 11, corporate consensus	Output required at minimum	Available Support from Shimadzu
Before introduction	1	●Documented consensus on goals for Part 11 compliance ① Objective of Part 11 compliance ② Scope and time limit (deadline to achieve 100% compliance) ③ Gather Project Team (Objective: to establish process for Part 11 compliance) ④ Preparation of progress report system and templates ⑤ Preparation of corporate internal training materials ⑥ Submission of Corporate Certification to FDA (when Electronic Signature is employed)	・Agreement on goals (document) ・Progress report ・Training materials ・Corporate Certification	・Suggestion for preparation ・Training Materials ・Review of documents ・Support for work
	2	●Proper communication of goals for Part 11 compliance ・notification of the related departments in the company	Corporate internal notice	・Suggestion for procedure ・Support for documentation
	3	●Agreement on understandings on Part 11 clauses ・Practical understandings on each clause of Part 11, and application to analytical systems	・Understanding documents for Part 11 compliance	・Suggestion for procedure ・Support for documentation ・Referential information
	4	●Preparation of the internal training program and record control systems for project team and users	・Education program ・Education record ・Education material lists	・Suggestion for procedure ・List for education materials
	5	●Revision of User SOP ・Addition of new documents to the document management system	・Review of the document management system	・Suggestion for procedure

		【2】Part 11 compliance by employing a new system (before introduction)	Output required at minimum	Available Support from Shimadzu
Before introduction	1	●Personnel trainig and training records	・Preparation of training records ・Review of training materials	・Suggestion for procedure ・Referential information
	2	●Preparation of system requirement specifications	・System requirement specification	・Suggestion for procedure ・Referential information ・Support for reinforcement works
	3	●Collecting information and proposal documents from vendors related to the requirement specifications	・Proposal documents from vendors	・Proposal documents
	4	●Evaluation of vendor's proposal documents	・Gap analysis record	・Suggestion for procedure ・Referential informatio
	5	●Vendor inspection ① Making vendor inspection program, and execution ② Making vendor inspection report	・Vendor inspection program document ・Vendor inspection report	・Suggestion for procedure ・Referential information ・Support for reinforcement works
	6	●Preparation of the Design Qualification (DQ) and validation records	・DQ documents	
	7	●Review of the validation program including Part 11 compliance	・Review of validation SOP	
	8	●Making validation documents additionally required for Part 11 ① Validation master plan ② IQ program document / IQ report ③ OQ program document / OQ report ④ PQ program document / PQ report ⑤ System operation management procedure document (for administrator) ⑥ System operation procedure document (for operator) ⑦ PM program document / PM report	・Validation master plan ・IQ program document ・OQ program document ・PQ program document ・System operation management procedure document (for administrator) ・System operation procedure document (for operator) ・PM program document (including back-up program)	
	9	●Discussion with vendors for system introduction	・Confirmation of document and record content	・Suggestion for procedure
	10	●Making system introduction program document ・including trial period, review of procedure documents	・System introduction program document	・Suggestion for procedure ・Referential information ・Support for reinforcement works
Installation	11	●System installation ① Execution of IQ/OQ/PQ ② Execution of training and making education record	・IQ report (record) ・OQ report (record) ・PQ report (record) ・Education record	・Supprt for IQ/OQ/PQ execution ・Suggestion for practical procedures
	12	●Participation to training course offered by vendor for Part 11 compliance	・Education record	・On-site training ・Off-site training
	13	●Making internal audit program and confirmation of Procedural control	・Internal audit program document	・Support for contents reinforcement
	14	●Internal audit ・to be done at the end of trial period	・Internal audit execution record	・Suggestion for countermeasures for points raised up by the audit

		【3】Part 11 compliance after new system has been employed (after introduction)	Output required at minimum	Available Support from Shimadzu
After starting operation	1	●System change management ・Client/User Addition/deletion etc.	・Change control record	・Suggestion for practical procedure ・Change control document support
	2	●Periodic education, new user education	・Education record	・On-site training ・Off-site training
	3	●Execution of PM (including back-up record)	・PM report (record) (including back-up record)	・Suggestion for practical procedure ・Support for documentation
	4	●Periodic internal audit	・Internal audit execution record (Correction record/Re-education record)	・Suggestion for countermeasure for points raised up by the audit



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