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FDA 21 CFR Part 11 and Compliance for FTIR

No.3

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Here I will give an overview of FDA 21 CFR Part 11, which has been an important topic in the pharmaceutical industry for several years, and consider its observance in the field of FTIR.

FDA 21 CFR Part 11

In the 1990's, in order to promote a reduction in the amount of paper used for documentation, the FDA (Food and Drug Administration,USA) established requirements related to the transfer of conventional paper-based records to electronic media. These came into effect in 1997. Electronic documentation is easier to falsify than paper-based documentation and so these requirements establish criteria for recognizing electronic records and electronic signatures as credible and of an equal standing to paper-based

FDA 21 CFR Part 11 applies to the following corporations:

- Pharmaceutical companies conducting business in the U.S.
- Companies providing products and raw materials to these pharmaceutical companies
- Contract laboratories commissioned by these companies to perform analysis work

FDA 21 CFR Part 11 applies to records and systems in the following cases:

- Cases where a PC is used to create, correct, save, restore, and transfer data
- Cases where data is saved in electronic format
  Examples include analytical instruments, balances, laboratory information management systems (LIMS), electronic document management systems, manufacturing management systems, equipment control management systems, manufacturing environment monitoring systems, and entrance/exit management systems.

FDA 21 CFR Part 11 and Requirements

The items required by FDA 21 CFR Part 11 are organized into sections.

Subpart A – General Provisions
- 11.1 Scope
- 11.2 Implementation
- 11.3 Definitions

Subpart B – Electronic Records
- 11.10 Controls for closed systems
- 11.30 Controls for open systems
- 11.50 Signature manifestations
- 11.70 Signature/record linking

Subpart C – Electronic Signatures
- 11.100 General requirements
- 11.200 Electronic signature components and controls
- 11.300 Controls for identification codes/passwords

The contents of these sections, however, are not very specific. Details can be confirmed by referring to other documentation, such as the GAMP Guide.
I will leave detailed explanations of each section to be covered in other documentation. Broadly speaking, the requirements of FDA 21 CFR Part 11 can be categorized as follows:

1. Access control
2. Data integrity
3. Data security
4. Audit trail
5. Electronic signature
6. Validation

Shimadzu Corporation's Response to FDA 21 CFR Part 11

At Shimadzu Corporation, in order to comply with FDA 21 CFR Part 11, we have suggested the following steps:

1. Use Windows 2000 Professional or Windows XP Professional, which offer a high level of security.
2. Increase the security level (e.g., access control and log functions) of client software (e.g., IRsolution) that performs device control and measurement/data processing.
3. Use in combination with CLASS-Agent data management software, which has database-management and electronic-signature functions.
4. Store and manage all measured and processed data in the CLASS-Agent database.

The following are also carried out:

- Validation of software and hardware
- Support and implementation of installation qualification and operational qualification
- Support of system construction

Taking the field of FTIR as an example, let us look at how we can comply with FDA 21 CFR Part 11.

Compliance with FDA 21 CFR Part 11 for Shimadzu FTIR Systems

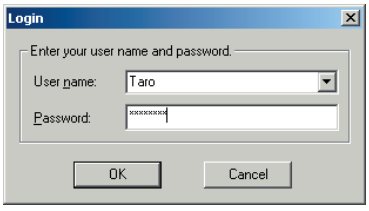
In order to comply with FDA 21 CFR Part 11 when using a Shimadzu FTIR system, IRsolution software and IRsolution Agent software are used in combination.
Both IRsolution and IRsolution Agent have high-level security-control functions, and measured and processed data is stored and managed in CLASS-Agent, which has high-level security functions.

(1) Access Control

FDA 21 CFR Part 11 demands the following with respect to access control:

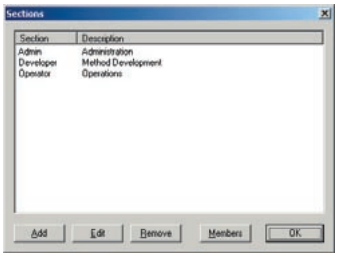
- Access must be restricted to authorized users.
- Available functions must be restricted according to the user.
- It must be possible to change the password regularly.
- There must be functions for preventing illegal access.

IRsolution and IRsolution Agent have a software security function that prompts the user for a user name and password at startup.

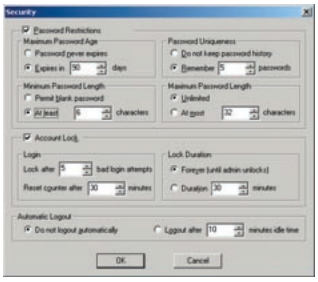


Logon Window

Users are divided into at least 3 groups (Administrators, Developers, Operators, etc.) and the functions that can be used by each group are restricted. There are also functions for setting the validity period of passwords, locking accounts, and automatically logging out, which can be used to prevent illegal access.



Access Groups



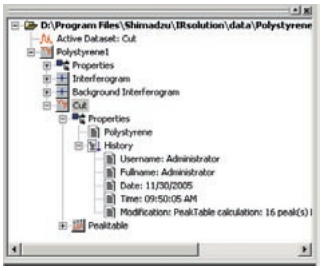
Password Management

(2) Data Integrity

FDA 21 CFR Part 11 demands the following with respect to data integrity:

- Raw data must be recorded together with the metadata that is used for measurement and data processing.

With IRsolution, in addition to information on the measurement conditions, times/dates, the user name, and device names, interferograms, which represent the real "raw data", are recorded and stored together in data files (container files). Also, because all data is stored together in container files after data processing, raw data and partly processed data can be recovered from processed data.



Tree-Structured Container File

Also, all measured and processed data is automatically stored in the CLASS-Agent database, which has high-level security functions, and is therefore reliably protected from falsification and corruption.

(3) Data Security

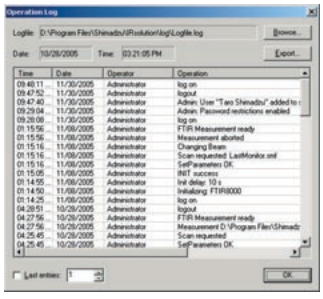
In FDA 21 CFR Part 11 systems, sampled raw data must be reliably protected from deletion, overwriting, alteration, and accidents.
With IRsolution, all measured raw data is automatically stored in the hard disk. Deletion and overwriting of data is prohibited and so the loss of data due to processing or accidents is prevented.

(4) Audit Trail

FDA 21 CFR Part 11 demands the following with respect to audit trails:

- An operation log for devices that includes information on logon activity and details of operations must be recorded.

With IRsolution and IRsolution Agent, a history of operations, including user names and details on measurements and data processing, is recorded and displayed in the operation (system) log. The times and dates at which measurements are performed and details of the data processing carried out are recorded in the data log.



IRsolution's Operation Log

(5) Electronic Signature

FDA 21 CFR Part 11 demands the following with respect to electronic signatures:

- Electronic signatures are unique to individuals and must not be reused by or reassigned to other parties.
- There must be at least two identification components (e.g., an ID and a password).
- Signed electronic records must contain signature information detailing the full name of the signer, the time and date of the signature, and the reason for signing.
- Electronic signatures must be linked to the electronic records to which they apply.
- There must be mechanisms for preventing the use of signatures to disguise electronic records.

Electronic signatures are used with IRsolution. Electronic signing requires the input of a user name and password.

(6) Validation

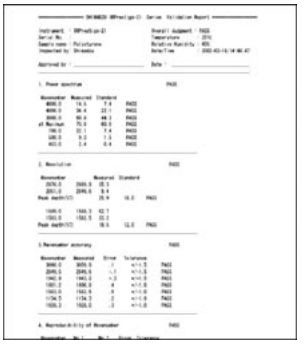
FDA 21 CFR Part 11 demands the following with respect to validation:

- Validation is required for elements that may affect the results of experiments, such as hardware and software.

IRsolution and IRsolution Agent are equipped with an alteration check program that can be used to check whether or not software has been installed correctly.

Results of Alteration Check

Validation of hardware (e.g., IRPrestige-21 or FTIR-8400S) is performed with a validation program that complies with the Japanese and European Pharmacopoeia and ASTM.



Example of Validation Report

There is also support for the installation qualification and operational qualification that is carried out at installation and in periodic inspections.

Compliance with FDA 21 CFR Part 11 Using IRsolution

The following components are required for compliance with FDA 21 CFR Part 11 when using a Shimadzu FTIR system:

- IRsolution Ver. 1.10 or later
- IRsolution Agent Ver. 2.11 or later (equipped with Agent Manager, User Authentication Tool, and MSDE)

Networked Systems and Stand-Alone Systems

If there is only one FTIR instrument, it is convenient to use a stand-alone system where an Agent database is created on the FTIR computer and data measured and processed with FTIR is stored and managed on the database. In this case, MSDE (Microsoft Data Engine) is used as the database.

Alternatively, when using Shimadzu analytical instruments, such as UV-VIS spectrophotometers and liquid chromatographs, it is possible to construct a network system where computers used to control the analytical instruments are connected via a network. In this case, a database can be created on a server and all data can be centrally managed on this database. Also, performing user management1) at the server makes management considerably easier. In this case, Microsoft SQL Server or Oracle is used as the server. At present, there are many types of instrument that use software compatible with the CLASS-Agent system. These include the following:

UV-VIS spectrophotometers, atomic absorption spectrophotometers, LC, GC, LC-MS, GC-MS, balances, thermal analyzers, TOC, Karl Fischer moisture titrators (Kyoto Electronics), and general titrators (Kyoto Electronics).

Select a system that is suitable for the type and number of analytical instruments used.

1) IRsolution's user-management functions cannot be shared with CLASS-Agent or other software. This functionality is due to be added in the future.

Future Developments

FDA 21 CFR Part 11 was established in order to promote a reduction in the amount of paper used for documentation and to increase the reliability of data and systems. In the U.S., in accordance with the Government Paper Elimination Act (GPEA), a project to render all government documentation into electronic format is being promoted. The Environmental Protection Agency (EPA) and the U.S. Patent and Trademark Office are working towards the establishment of similar regulations. Japan's Ministry of Health, Labour and Welfare implemented similar regulations.

In practice, there are many things that have to be done in order to construct a system that complies with FDA 21 CRF Part 11. These include the establishment of the required specifications for devices and software, discussions prior to system construction and installation, installation, installation qualification, operational qualification, training, and the establishment of equipment management methods and SOP. At Shimadzu Corporation, we are providing support for our customers in order to facilitate compliance with FDA 21 CFR Part 11.

Sampling Accessories Used for Microscope Measurement

Kyoto CSC, Analytical Applications Department, Analytical & Measuring Instruments Division Seiji Takeuchi

The ability to obtain high-quality spectra with infrared microscope measurement depends, to a large extent, on the efficacy of the technique used to obtain samples. Even if high-performance devices are used, it may not be possible to obtain the required information if the sampling method is unsuitable. In order to perform sampling effectively, the minimum requirement of accessories must be prepared beforehand and the analyst must be able to use them effectively. Here, I will describe the minimum accessory requirement and extra accessories that may be useful.

1. Minimum Accessory Requirement

Stereo Microscope

Infrared microscope measurement often involves the measurement of samples with dimensions of less than 100 μm, and stereo microscopes are required to check the samples. The ideal type of stereo microscope is the binocular type with an adjustable magnification factor in the single-digit to two-digit range. Recently, microscopes incorporating digital cameras and digital CCD systems that can be attached to microscope tubes have become commercially available.

Sampling Tools

3-piece sets consisting of precision tweezers, precision needles, and precision knives, which are required for sampling foreign substances, are available. Tools with sharper ends are more suitable for obtaining smaller samples. Precision needles are available in sizes such as 1 μm and 5 μm, and it is convenient to use needles that can be held in a holder and changed when necessary. It is recommended that the necessary tools are purchased together with reference to laboratory-instrument catalogs.
When cutting out a thin section of a sample in order to perform transmission measurement, as thin a blade as possible is used. A safety razor or a stainless-steel replacement microtome blade is suitable.

Transmission Window

In order to measure samples using the transmission method, they must be placed on transmission windows. KBr or BaF2 windows of diameter 13 mm and thickness 2 mm are often used. KBr is relatively inexpensive but is prone to scratching. It is also deliquescent and has a low resistance to water and so the BaF2 window is more suitable in cases where water-resistance is required. Diamond windows (see Fig. 2) are available for cases where a high level of durability is required.

Fig. 2 Diamond Window

2. Useful Accessories

Diamond Cell

A diamond cell consists of two discs into which diamonds with dimensions of 2 to 3 mm are embedded. Samples can be inserted between the discs and compressed. (See Fig. 3.) This accessory is useful for making hard or irregularly shaped samples thinner. After the sample has been compressed with the two discs, measurement is carried out using only the single window to which the sample has adhered. This is in order to reduce the affect of absorption by the diamond and to prevent interference fringes.

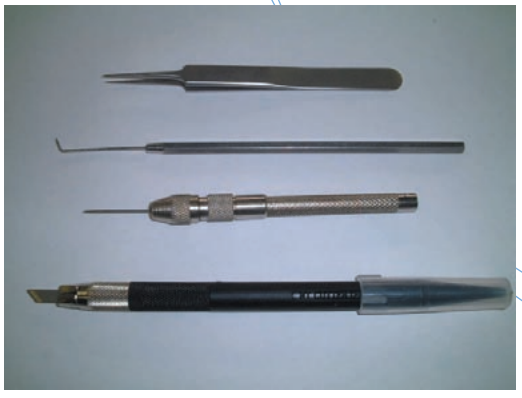


Fig. 1 Sampling Tools

Fig. 3 Diamond Cell

Micro-Vice Holder

When analyzing a sample on a curved surface using microscopic ATR or microscopic reflectance, the analyzed part must be held in a horizontal state. In such cases, a micro-vice holder is a convenient accessory. (See Fig. 4.) For example, when analyzing a foreign substance on the surface of a tablet using ATR, the sample can be turned so that the foreign matter is at the top and then secured in position. This accessory can also be used when analyzing the cross section of bulk samples. Rotation on the stage in the horizontal direction is also possible, making it easy to adjust the angle of the sample for line mapping.

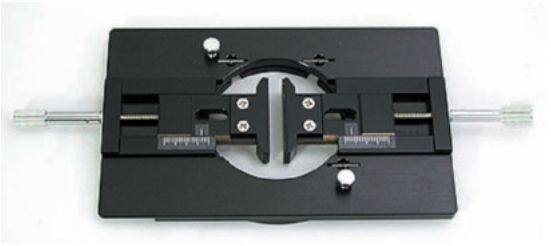


Fig. 4 Micro-Vice Holder

Microtome

There are various types of microtome. The rotary microtome, however, is recommended when performing pretreatment for FTIR. It is used when, for example, cutting out cross sections of multilayered film and analyzing the layers or when analyzing foreign substances contained inside resins. If the sample is small and cannot be held by itself, it must be embedded in epoxy resin or some other appropriate material. There are resins that are specifically used for embedding but epoxy adhesives consisting of two-liquid mixtures can also be used.

A thin section cut at a setting of 10 μm will give an appropriate peak intensity when analyzed using the transmission method. Also, a microtome can be used to cut out a cross section that is suitable for measurement using microscopic ATR.

Micro-Manipulation System

The micro-manipulation system is used to perform the sampling of minute quantities. (See Fig. 5.) This system makes it possible to move the needle attached to an arm freely along 3 axes using a joystick while viewing it with the microscope. Two arms (left and right), to which metal needles, glass needles, or bio-cutters are attached, are usually used. Samples with dimensions as small as approx. 10 μm can be obtained.

Fig. 5 Micro-Manipulation System

EZ-Pick

Although the micro-manipulation system enables precise manipulation, it is relatively expensive and there are restrictions on the installation location. In contrast, EZ-Pick uses a simple mechanism and is easy to operate. Whereas manipulators control the position of a needle with respect to a fixed sample, EZ-Pick controls the position of a stage holding the sample with respect to a fixed needle. As shown in Fig. 6, the holder with the needle is attached to the objective lens so that the needle tip is visible within the field of view and sampling is performed by moving the stage so that the sample makes contact with the needle tip. The portion of sample that adheres to the needle tip is dropped onto the window by rubbing it against a needle that was fixed to the stage beforehand.

Systems in which EZ-Pick is applied to stereo microscopes are commercially available. (See Fig. 7.) These systems are equipped with software for loading digital images into a PC and scaling functions. The magnification factor is in the two-digit range, making it difficult to extract of foreign substances with dimensions of less than 50 μm.

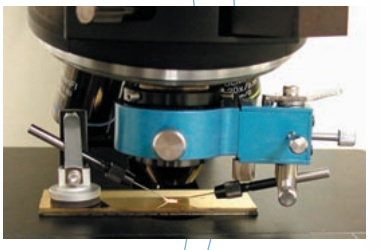


Fig. 6 EZ-Pick

Fig. 7 Prep Scope Ⅱ

Microscope Heating/Cooling Unit

A heating/cooling stage is available to facilitate analysis of the adhesive hardening process or the resin deterioration process that accompanies increases in temperature on the stage of an infrared microscope. (See Fig. 8.) Temperature control is possible between room temperature to 600℃. A cooling unit and liquid nitrogen are required to perform cooling. Using this unit makes it possible to perform transmission or reflectance measurement based on a specified temperature program with an infrared microscope.

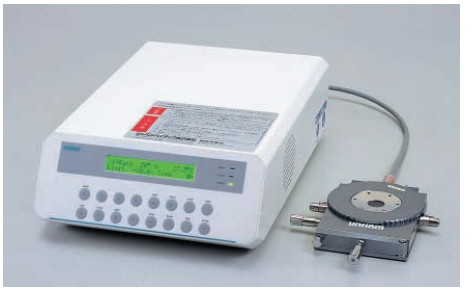


Fig. 8 Microscope Heating/Cooling Unit

3. Summary

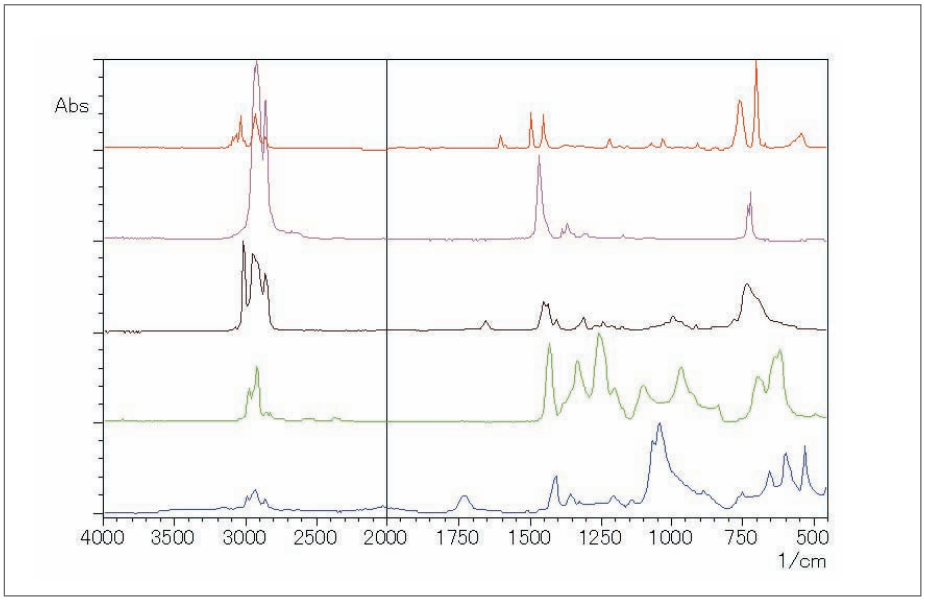
Infrared microscopes allow various types of sample measurement using, for example, the transmission method, the reflectance method, or the ATR method. Furthermore, using the accessories described here makes it possible to perform pretreatment more efficiently and expand the range of application.

Question

There are differences in the wave-number ranges of the MCT detectors used for infrared microscopes. What are the selection criteria?

Answer

In the case of our AIM-8800 infrared microscope, two types of MCT detector are available, type 1 and type 2. The measurable wave-number range for type 1 is 5,000 to 720 cm-1 whereas the range for type 2 is 5,000 to 650 cm-1. In other words, the type-2 range is broader at the lower end. This adjustment was made by changing the mixing ratio of the mercury and cadmium which, together with tellurium, constitute the MCT detector's element. Note that the sensitivity is lower, however, for the larger wave-number range. Therefore, regarding detector selection, if measurement sensitivity in the microscopic range is more important, then type 1 is more suitable, whereas if peaks obtained for the sample in a neighborhood of 700 to 650 cm-1 need to be observed, then type 2 is the better choice. As reference, Fig. 1 shows spectra obtained for polymers with absorbance in a neighborhood of 700 to 650 cm-1. From the top, the figures show spectra for polystyrene (PS), polyethylene (PE), polybutadiene (BR), polyvinyl chloride (PVC), and polyvinylidene chloride (PVDC). The absorption phenomena observed in a neighborhood of 700 to 650 cm-1 include C-H out-of-plane bending vibrations and C-C stretching vibrations.



NEW PRODUCTS

1. NIR Measurement Accessories for the IRPrestige-21

We have started the sale of three types of NIR accessories produced by Pike Technologies (U.S.), an NIR fiber coupler, and a fiber probe as NIR measurement accessories for the IRPrestige-21.

①Upward Looking Diffuse Reflectance Accessory

- Powder samples can be analyzed on the stage.
- Pretreatment, such as dilution with KBr, is unnecessary. The powder can be analyzed in its natural state, in a plastic bag, or in a glass bottle.

②IntegratIR A – NIR Integrating Sphere

- Powders, tablets, liquids, and molded products can be analyzed on the stage (reflectance measurement).
- Pretreatment, such as dilution with KBr, is unnecessary. Samples can be analyzed in their natural state, in a plastic bag, or in a glass bottle.
- Equipped with a high-sensitivity InGaAs detector.

③Heating Transmission Cell and Temperature Controller

- Liquid samples can be put into the 6-mm-dia. test tube provided and subjected to transmission measurement while being heated or held at a constant temperature.
- The temperature can be set to a level between room temperature and 120°C.

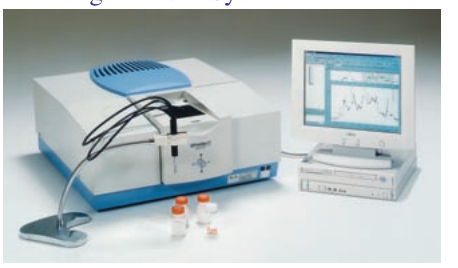
④Fiber Coupler

- Acts as an interface for connecting other companies' fiber probes.
- Equipped with two SMA connectors (In/Out) to allow fiber probes with SMA connectors to be connected.

⑤Reflective Fiber Probe

- NIR rays emitted from the probe head are directed at the sample, and the reflected light is collected for measurement. Pretreatment, such as dilution with KBr, is unnecessary.
- Powder samples can be analyzed directly by inserting the probe, and samples contained in bags or glass bottles can be analyzed in this state.

IRPrestige-21 NIR System



①

Upward Looking Diffuse Reflectance Accessory UpIR A

②

NIR Integrating Sphere IntegratIR A

③

Heating Transmission Cell and Temperature Controller

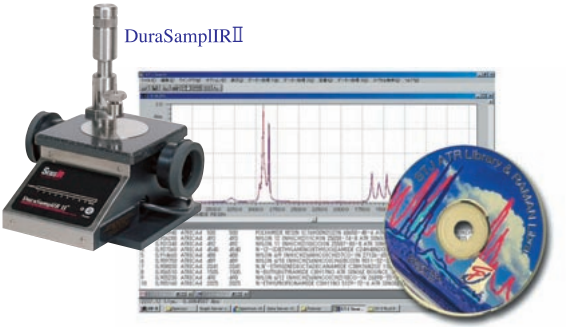
Main Specifications

Measurement range	10,000 to 3,800 cm^{-1}
Connector type	2 × SMA
Probe type	Probe head: 6.4 dia.×50 mm, SUS303
	Handle: 18 dia. ×100 mm, aluminum
Operating temperature	Room temperature
Permissible bending radius	100 mm
Length	1 m from probe head to connector

2. ATR/FT-IR Library

We will be releasing an ATR/FT-IR library containing approx. 11,000 items of data that were measured with single-reflection ATR (DuraSamplIRII). It will be possible to purchase all the data together or to purchase separate sections classified according to the field. The data was measured using a diamond/KRS-5 DuraDisk and so information in the wave-number range 4,000 to 400 cm-1 is available. This library is suitable for the qualitative analysis of unknown samples obtained with DuraSamplIRII.

DuraSamplIRII



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