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Digitization of Qualification Documents

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Shimadzu Corporation has been progressing toward deployment of the digitization of IQ/OQ documents (services for creating digitized qualification documents) for various systems and has started providing a digitization service for FTIR models. In addition to discussing the relevance of qualification to validation, this article describes changes from the conventional qualification services based on paper documents, as well as features of the service for creating digitized qualification documents.

1. Validation

In recent years, there has been an abrupt increase in the regulations that manufacturing companies are required to comply with, including computer system validation (CSV), PIC/S GMP, 21 CFR Part 11, and ER/ES regulations. Further, the content of these regulations is becoming stricter. FTIR validation was discussed in FTIR TALK LETTER Vol. 4 and Vol. 27. There, validation was referred to as one step in clarifying whether these regulations are being complied with.

According to the Japanese Ministry of Health, Labour and Welfare, validation is defined as the verification and documentation that the structural facilities at manufacturing sites as well as the procedures, processes, and other manufacturing control and quality control methods (referred to hereinafter as the "manufacturing procedures") are achieving the anticipated results.

In other words, validation requires the following with respect to manufacturing control and quality control methods: (1) The anticipated results must be predetermined; (2) It must be verified that the results from Step (1) are obtained; and (3) Steps (1) and (2) must be documented.

2. Relevance of Qualification to Validation

What is the difference between validation and the types of qualification referred to as installation qualification (IQ) and operational qualification (OQ)? In the ICH Q7A (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients), the ICH defines qualification as follows:

Qualification refers to the process of confirming and documenting that analysis instruments and their optional items were installed appropriately, are functioning correctly, and that the anticipated results are actually obtained. Qualification is part of validation. However, the implementation of individual IQ and OQ qualifications on their own does not constitute a process validation.

Accordingly, qualification is considered one element of the process of validation.

To clarify the difference between validation and qualification, we introduce a V model showing the validation flowchart (Fig. 1). This was introduced in the Good Automated Manufacturing Practice (GAMP) Guide. It indicates the sequence of validation procedures with respect to each process, from the introduction of the instruments until just before they begin to be used for routine work after installation. In examining Fig. 1, it is evident that arrows of verification extend from each qualification process (IQ, OQ, and PQ (performance qualification)) to the various required specifications (DS (design specifications), FS (functional specifications), and URS (user required specifications)). Here, verification refers to the process of checking the details of the items required in the DS, FS, and URS. Then, the determination whether the required specifications are satisfied, from the results of the verification process, becomes qualification. Accordingly, validation refers to verifying the validity of the instrument from the results of qualification in this sequence of processes.

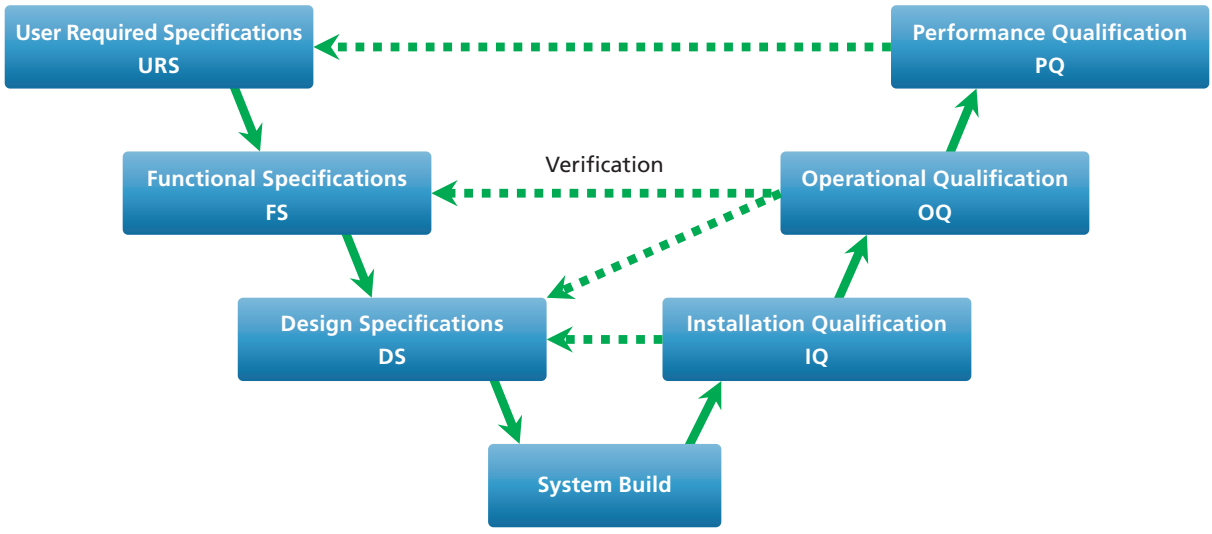

Fig. 1 GAMP V Model

3. Support Provided by Shimadzu for Compliance with Regulations

It is generally assumed that validation will be implemented by the users of the instruments. However, Shimadzu provides products compliant with the CSV guidelines, PIC/S GMP guidelines, and the ER/ES regulations, through a quality assurance system based on ISO 9001:2000 certification. Further, to ensure that validation is implemented effectively, Shimadzu provides qualification (IQ/OQ) documents as well as document creation support services.

The qualification document creation service clearly documents the implementation of IQ/OQ installation and preventative maintenance (PM)/OQ inspections by personnel accredited by Shimadzu as qualified for qualification inspection and maintenance. It also clearly documents the qualification verification implementation details, the verification procedural protocols, and the determination criteria. One item that is easy to overlook when creating documents is clarification of the criteria used as the basis for a qualification pass/fail determination. Contrasting the verification results with the criteria is very important in the context of qualification.

At Shimadzu, document prescriptions are available that describe these criteria in detail, enabling the reliable implementation of evaluations. The procedures have also been standardized, so evaluations can be implemented efficiently in a short time.

4. Digitization of Qualification Documents

In order to save on resources and space by going paper-less, Shimadzu has been progressing toward a service to create digitized qualification documents for various models and has started a digitization service for FTIR models. Additionally, document content and structure are being revised simultaneously with the digitization of documents, based on opinions and requests received during qualifications with conventional paper documents. For example, customers have noted that the process of checking both inspection procedures and written results in order to understand them is time consuming. Also, preliminary checks of qualification documents are troublesome, as the procedures are not tailored to the system configuration for each customer. The features of the service to create digitized qualification documents are as follows.

- Document structures tailored to customer systems
- Integration of written procedures and reports
- Customized inspection items via EQP documents
- Automatic creation of summary reports
- Addition of RQ documents
- Reducing man-hours using special software, lessening human errors

A comparison with the conventional service is summarized in Table 1.

Table 1 Comparison of the Service to Create Digitized Qualification Documents and the Conventional Service

	Service to Create Digitized Qualification Documents	Conventional Service to Create Qualification Documents
Final Written Report Style	• Paper documents • PDF files	• Paper documents
Document Structure	• Customized to suit the customer system configuration • Integration of written procedures and reports	• OQP documents, in which all instrument information is noted • Structured with written procedures (IQP/OQP) and reports (IQR/OQR)
Qualification Prechecks	Confirmed with EQP documents	Confirmed with IQP/OQP documents
Customized Inspection Items	Yes	No (All by special order)
Creation of Summary Reports	Yes	No
Lineup of Qualification Documents	EQP/IQ/OQ/PM/RQ/EQR	IQ/OQ/PM

5. Document Structure Tailored to the Customer System Configuration

With conventional qualification documents, all instrument information about FTIR models handled by Shimadzu was noted in OQP documents. Therefore, unnecessary instrument information that was not related to the customer system was also provided. With digitized qualification documents, however, the structure of the documents provided is customized to suit the customer's instrument configuration, including accessories (Fig. 2).

Further, the written procedures (IQP/OQP) and reports (IQR/OQR) were provided separately, but these are now integrated. In addition, the procedures, settings values, control criteria, and results are noted separately by the OQ inspection item, making it easy to check both the inspection procedures and results.

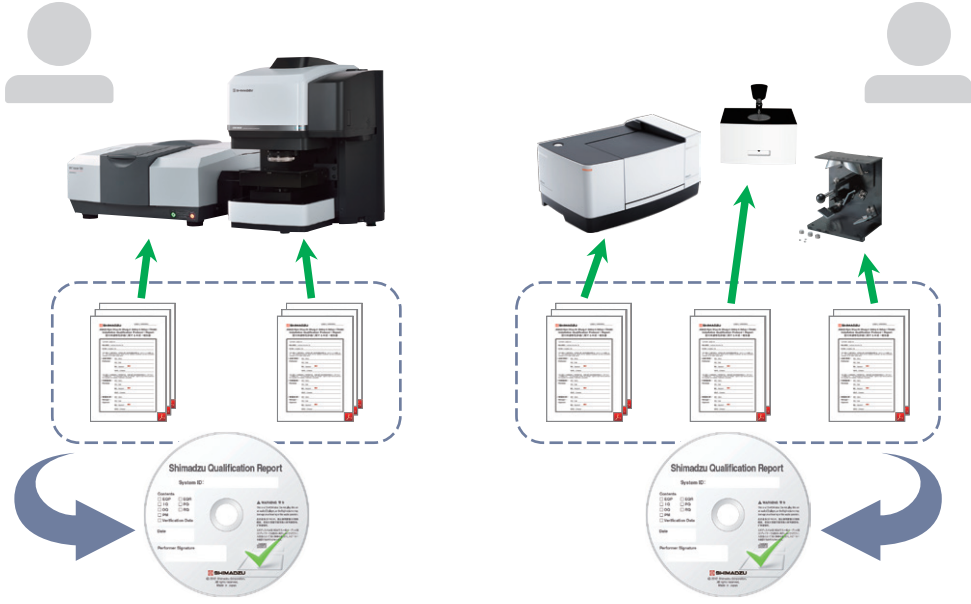

Fig. 2 Documents Customized to Suit the Customer's System Configuration

6. Prechecking Evaluations via EQP Documents

In the new format, equipment qualification plan (EQP) documents are now provided for the preliminary plan and check of IQ/OQ implementation items by the customer. In the EQP documents, inspection items and control criteria can be easily checked in a tabular format. Further, whether or not inspection is implemented, changes (edits) to control criteria values can be noted for each inspection item, and even the inspection details can now be customized. During the actual qualification procedures, special software is used, and the inspection items customized in the EQP are automatically reflected in the IQ/OQ documents, so human transcription errors do not occur.

7. Summary Reports (EQR)

In the new format, a summary report on the inspection results (equipment qualification record (EQR)) is provided separately from the IQ and OQ inspection results reports. The summary report shows the page numbers from the original IQ and OQ documents, making it easy to reference the original documents, and greatly simplifying document searches during audits. The summary report is automatically created after the IQ/OQ documents are created by special qualification software, so no human labor is required, and transcription mistakes do not occur.

8. Qualification During Repairs via RQ Documents

When a field engineer repairs an instrument, in the conventional format, post-repair performance checks were implemented using OQ documents. However, in the new format, a new post-repair re-qualification (RQ) document is now available. This is because with post-repair performance checks, it is preferable to implement qualification on inspection items for which there is believed to be a risk that the instrument repairs will have an impact on the analysis results, rather than from the position of OQ.

9. Function to Automatically Load Pharmacopeia Validation Results

With Shimadzu FTIR systems, the control software is equipped with pharmacopeia validation programs. These pharmacopeia-based inspection items are adopted in OQ inspections, so a function has been added to load the examination results from the pharmacopeia validation program into the special software for creating the qualification documents, thereby automatically transcribing the examination values. Conventionally, an inspector checked the validation results and entered the values. With this new transcription function, human labor is reduced, and transcription omissions and mistakes, and other human errors do not occur.

References

- Ministerial Ordinances on GMP (Ministerial Ordinance 179 from The Ministry of Health, Labour and Welfare)
- ICH Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (Pharmaceutical and Food Safety Bureau Notice No. 1200)
- GAMP Guide: Validation of Automated Systems (GAMP4)

Reference Materials

- GAMP JAPAN FORUM
  https://www.ispe.gr.jp/ISPE/english/index.htm

Introduction of Various ATR Measurement Attachments (1)

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A feature of the ATR method is that unlike the transmission method, pretreatment is not required, so analysis is easier. Solid and powder samples are placed on the prism and then pressed tightly against it using a compression clamp, while liquid samples are simply placed on the prism and the spectrum is then obtained. In recent years, it has become possible to use synthetic diamonds as prisms, and a number of user-friendly ATR attachments have been developed, so they are actively in use[1]. In the midst of such circumstances, the ATR method, which was only listed as a general test method, is now listed as an identification test for official monographs in the 17th edition of the Japanese Pharmacopoeia, so applications for the ATR method have expanded. For example, hypromellose acetate succinate is one of the pharmaceuticals for which the ATR method is specified. It prescribes the "identification—determine the infrared absorption spectrum of hypromellose acetate succinate as directed in the ATR method under infrared spectrophotometry: it exhibits absorption at the wave numbers of 2840 cm^{-1}, 1737 cm^{-1}, 1371 cm^{-1}, 1231 cm^{-1}, and 1049 cm^{-1}."[2]

For ATR measurement attachments, the single-reflection ATR attachment is the most common type, and a lineup of various models is available to suit the objective. Here, in addition to general ATR prism selection methods, I introduce ATR measurement attachments capable of multiple-reflection ATR and temperature control.

1. Prism and Plate Selection

In recent years, diamond prisms have become commonplace, as they can accommodate hard samples and offer a wider measurement wave number range. However, the use of Ge prisms with their high refractive index and shallow penetration depth is effective when measuring nano-order thin films and black rubber containing a lot of carbon black. Additionally, when samples containing the nitrile group are measured with a diamond prism, peak confirmation can become difficult due to absorption by the diamond at about 2000 cm^{-1}. In such cases, peak confirmation can be made easier by using a Ge or ZnSe prism that does not feature absorption at about 2000 cm^{-1}. Selecting the optimal prism for the objective will simplify subsequent analysis. For details on the ATR spectrum for each type of prism, refer to Shimadzu Application News No. A485 "Spectral Characteristics Dependent on ATR Crystal Selection —Differences in Properties (Shape, Hardness, Refractive Index) According to Sample—."

The lineup of QATR-S single-reflection ATR measurement attachments, shown in Fig. 1, includes diamond as well as Ge and ZnSe prisms, and the prism plate is easy to replace without using a screwdriver. Additionally, the clamps are equipped with torque limiters to protect the prism when the sample is pressed against it, so they can be used with confidence. The hypromellose acetate succinate noted in the Japanese Pharmacopoeia and introduced at the start of this article was measured using a QATR-S diamond prism.

The ATR spectrum is shown in Fig. 2. As prescribed in the Japanese Pharmacopoeia, peaks were confirmed in the vicinity of wave numbers 2837 cm^{-1}, 1736 cm^{-1}, 1371 cm^{-1}, 1231 cm^{-1}, and 1048 cm^{-1}.

Fig. 1 QATR-S Single-Reflection ATR Measurement Attachment

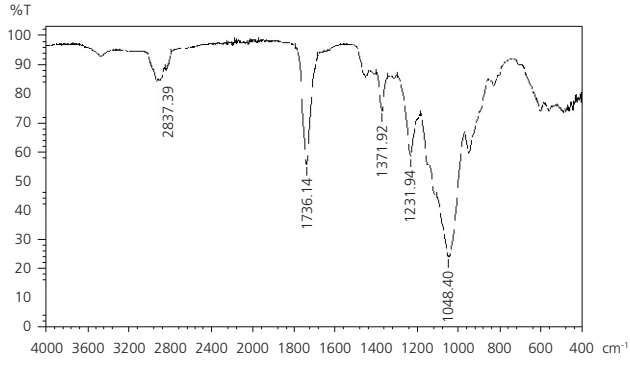


Fig. 2 ATR Spectrum for Hypromellose Acetate Succinate

When measuring corrosive samples, it is necessary to consider not only the prism but also the surrounding metal plate. Generally, stainless steel is used for the surrounding plate, so it is necessary to be careful of plate corrosion. When measuring strong acid samples, select a material such as hastelloy that is resistant to acids.

2. Single-Reflection/Multiple-Reflection ATR Measurements

The intensity of the spectrum obtained from a single-reflection ATR method tends to be weaker in comparison to the transmission method, because of the shallow penetration depth. In such cases, using a multiple-reflection ATR measurement attachment can increase the sensitivity. (The sensitivity could decrease, however, for powders, solids, and other samples with poor adherence.) In FTIR TALK LETTER vol. 19, the multiple-reflection ATR method was introduced in Measurement Method ABCs: Multiple Reflection ATR Method. The multiple-reflection ATR method is effective for low-concentration samples and is particularly good for liquid samples with good adherence.

With the MicromATR™ (micrometer) shown in Fig. 3, the user can select a single-reflection, 3-reflection, or 9-reflection ATR prism. The ATR spectra for water measured with a single-reflection, 3-reflection, and 9-reflection ATR prism are shown in Fig. 4. In comparison to single-reflection ATR, approximately 3× and 9× the peak intensity were obtained in the 3-reflection and 9-reflection ATR spectra, respectively. Note that with the 9-reflection ATR prism, the prism diameter is 5 mm or less and the sample volume required for measurement is only 30 µL.

Fig. 5 shows a schematic diagram of the MicromATR multiple-reflection ATR prism. There is a gap between the diamond prism and the supporting ZnSe lens, so if too much force is applied, the prism could be damaged. Accordingly, the 9-reflection ATR measurement attachment is exclusively for liquid samples. The 3-reflection ATR measurement attachment can measure either liquids or solids, but for the measurement of hard samples, the single-reflection ATR measurement attachment is recommended.

Fig. 3 MicromATR

As indicated in Figs. 5 and 6, the 3-reflection ATR prism is in the same plane as the plate, just like with the single-reflection ATR prism. With the 9-reflection ATR prism, however, the prism is structured so as to retain the sample in an indentation, so it must be cleaned carefully after measurement.

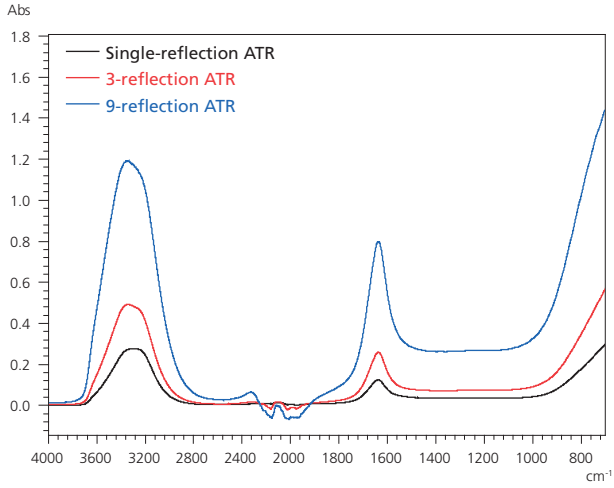


Fig. 4 ATR Spectra for Water (Single-Reflection, 3-Reflection, and 9-Reflection ATR Prisms)

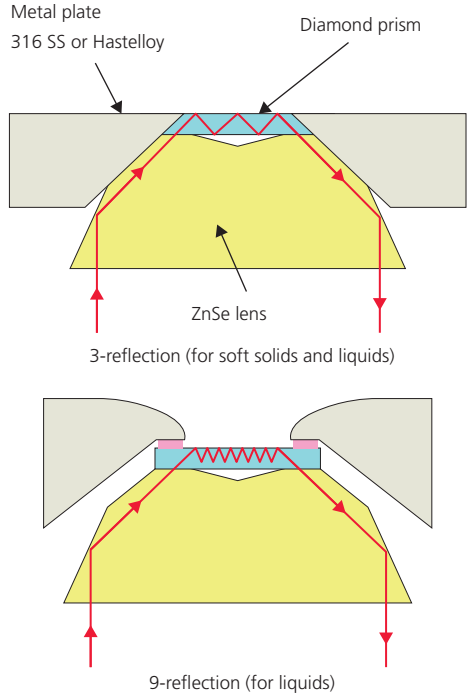


Fig. 5 Schematic Diagram of the Multiple-Reflection ATR Prism

Fig. 6 3-Reflection (Left) and 9-Reflection (Right) ATR Prisms

3. Heated ATR Measurements

Normally, measurements are performed at room temperature. By using the ATR accessories introduced in this section, however, it is possible to heat the prism plate using a temperature controller.

The following is an example of the analysis of changes in the secondary protein structure of albumen due to thermal denaturation. A heated 3-reflection ATR prism was installed in the MicromATR (Fig. 3), and albumen from a hen's egg was analyzed. The MicromATR can heat up to 130 °C using the temperature controller shown in Fig. 7. Here, the prism temperature was raised from 40 °C to 100 °C in 10 °C increments, and the spectrum was obtained at each temperature. Note that albumen contains moisture, so during analysis, it is necessary to subtract the water spectrum from the albumen spectrum. The hydrogen bonds in water depend on the temperature, so the water spectrum was also obtained at each temperature.

Fig. 7 MicroATR Temperature Controller and Heated 3-Reflection ATR Prism

Fig. 8 shows the infrared spectra in the amide I band for albumen at each temperature. An expanded view of the 1700 to 1600 cm^{-1} region comprising the amide I band is shown after subtracting the water spectrum from the albumen spectrum. It is reported that denaturation of albumen starts when it is heated to 60 °C.[3] As in Fig. 8, changes in the spectrum start to appear at 60 °C. Peaks in the vicinity of 1625 cm^{-1} and 1675 cm^{-1} increase markedly, and a relationship to thermal denaturation can be confirmed.

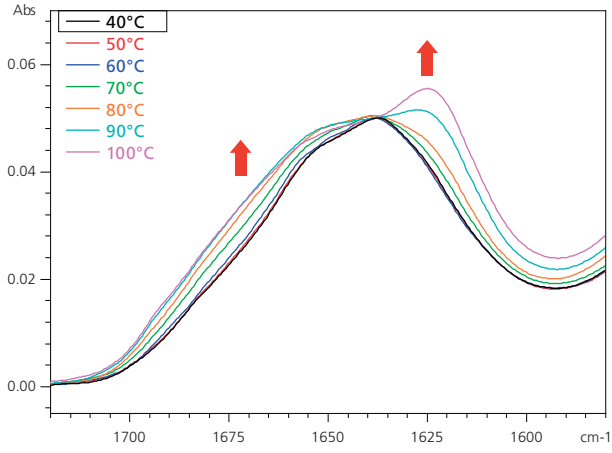


Fig. 8 Infrared Spectra for the Albumen Amide I Band

The heating temperature differs depending on the accessories and the prism type. The GladiATR™ shown in Fig. 9 has a heating plate capable of heated measurements at 210 °C, 300 °C, and 350 °C. Attaching the cooling option makes it possible to use it as a low-temperature ATR measurement attachment as well. For details, contact S.T. Japan.

Fig. 9 GladiATR and Temperature Controller

4. Conclusion

The ATR method makes it easy to measure samples whether in liquid, solid, or powdered form, without pretreatment, so this is a very convenient attachment. Solid samples rely on adherence but liquid samples can be measured just by dripping the sample onto the prism, making these instruments also suitable for quantitative analysis. In this case, a multiple-reflection ATR measurement is adopted, which can detect even trace peaks. Additionally, heated ATR measurements make it easy to track reactions due to heat changes in substances.

Next I will continue with an introduction to various ATR measurement attachments and observation-capable ATR measurement attachments.

References

1) "Foundations and New Methods of Infrared Spectrometry" written and edited by Mitsuo Tasumi, S.T. Japan
2) The Ministry of Health, Labour and Welfare "Japanese Pharmacopoeia, 17th Edition"
3) Yoshinori Mine, Tatsushi Noutomi, and Noriyuki Haga Thermally induced changes in egg white proteins. J. Agric. Food Chem., 1990, 38 (12), pp 2122–2125

Q&A

Where does a small peak in the vicinity of 1720 cm^{-1} arise from?

The peak that appears in the vicinity of 1720 cm^{-1} arises from the carbonyl group (C=0). It is generally quite a prominent peak. If the peak is small, there are likely two reasons.

Firstly, the sample is a mixture. Fig. 1 shows the ATR spectra for rubber packing material and phthalate esters. In rubber packing material, the acrylonitrile butadiene rubber (NBR) likely contains calcium carbonate and phthalate esters. Of these, the phthalate esters include the carbonyl group, and a large peak is evident in the vicinity of 1720 cm^{-1} (Fig. 1: Black spectrum). On the other hand, when phthalate esters are included in rubber packing as an additive, the peak in the vicinity of 1720 cm^{-1} becomes relatively small (Fig. 1: Red spectrum).

Secondly, sample deterioration could be a reason. Fig. 2 shows an example of the measurement of the UV deterioration of an acrylonitrile butadiene styrene (ABS) resin. Normally, ABS resin does not have a carbonyl group. However, as oxidative deterioration due to UV irradiation progresses, a carbonyl group in the vicinity of 1720 cm^{-1} appears. Additionally, with extended irradiation, the carbonyl group peak becomes larger. In addition, oxidative deterioration causes the hydroxyl group (OH: in the vicinity of 3400 cm^{-1}) to increase and the trans vinylene group (=C-H out-of-plane deformation vibration: in the vicinity of 966 cm^{-1}) to decrease.

As noted above, if there is a small peak in the vicinity of 1720 cm^{-1}, check whether the sample is a mixture, or whether there has been oxidative deterioration.

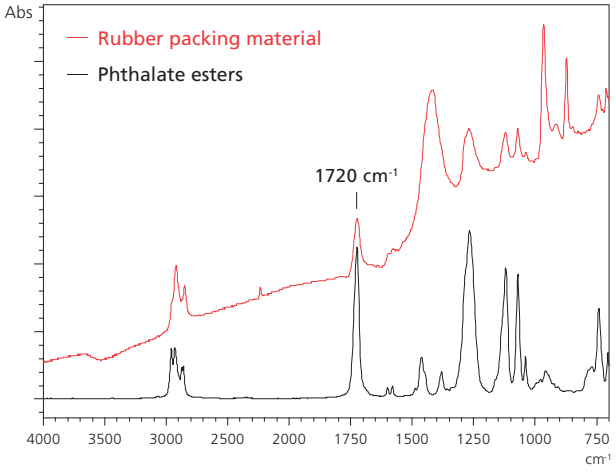


Fig. 1 ATR Spectra for Rubber Packing Material and Phthalate Esters

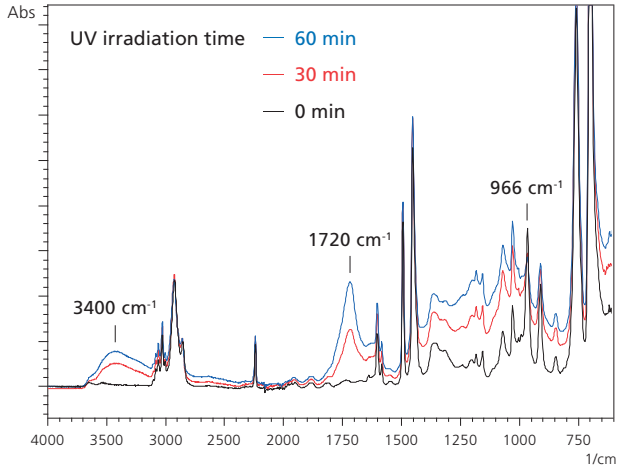
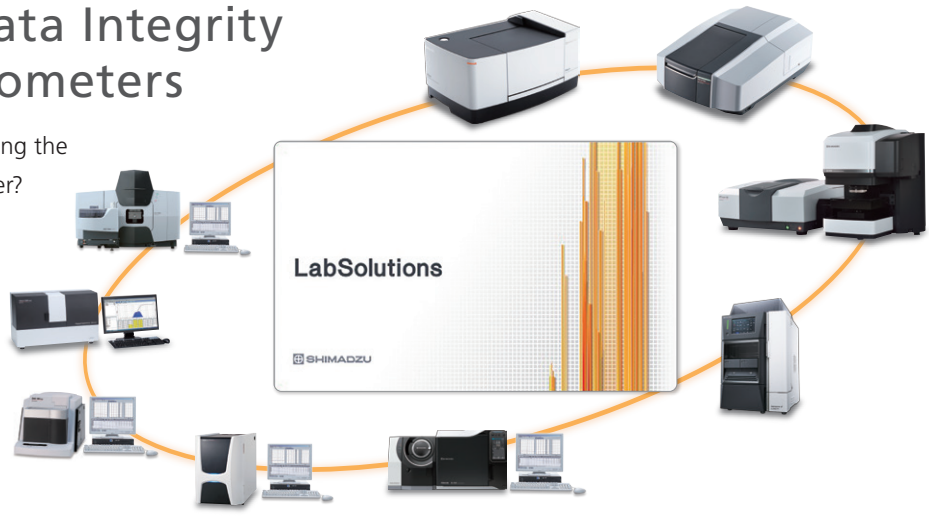


Fig. 2 UV Deterioration of ABS Resin

Solutions Provided by Shimadzu

Strengthened Data Integrity for Spectrophotometers

Are you having difficulty strengthening the data integrity of a spectrophotometer? Shimadzu can strengthen the data integrity of not only HPLC, GC, and other chromatography systems, but also FTIR, UV, RF, and other spectrophotometers, as well as other analytical instruments.

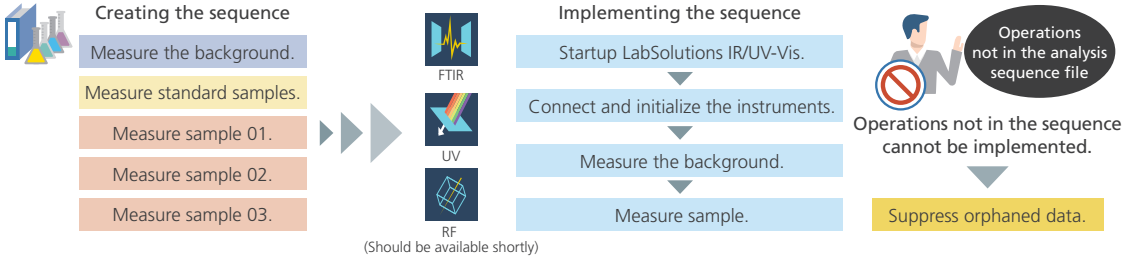


Networked Control of FTIR, UV, and RF Data

You can construct a system for obtaining highly reliable data, including measures to prevent data tampering through integrated control of the data from various analytical laboratory instruments in a database of the LabSolutions DB/CS analysis data system.

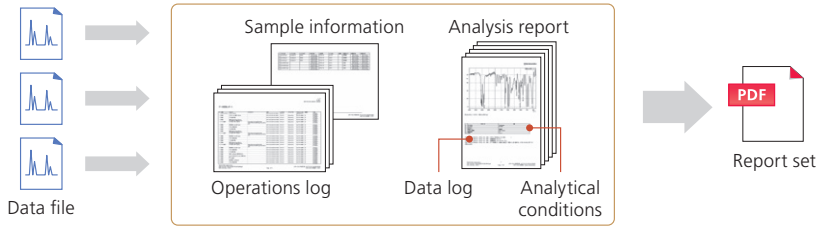
Suppressing Orphaned Data by Using an Analysis Sequence

For compliance with data integrity, a system is needed that can indicate that no incorrect operations were performed. Shimadzu has introduced the concept of an analysis sequence for spectrophotometers. This makes it possible to confirm that the sequence of analyses was implemented in accordance with the testing instructions (or standard operating procedures (SOP)).



Visualization of the Sequence of Analysis Operations

A report set can be created to enable the sequence of analysis operations to be visualized. It becomes easy to check for incorrect operations, which contributes to more efficient checking of procedures and ensures reliability.



For details on strengthening the data integrity for spectrophotometers, check the following website:
https://www.shimadzu.com/an/industry/pharmaceuticallifescience/fda.html

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