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# UV TALK LETTER

Vol. 19

# Data Integrity and the LabSolutions™ DB/CS Analysis Sequence

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## 1. Introduction

In the pharmaceutical industry, increasingly rigorous compliance with data integrity (DI) is required by regulatory authorities. In this context, the attention of regulatory authorities with respect to analytical instruments is turning not only to liquid chromatographs (LC), gas chromatographs (GC) and other chromatography equipment, but also to UV-Vis spectrophotometers (UV), Fourier transform infrared spectrophotometers (FTIR) and other spectroscopy equipment.

At Shimadzu, we offer multiple analysis data systems capable of accommodating DI: a database management edition (herein referred to as "LabSolutions DB") and a client server edition (herein referred to as "LabSolutions CS"). In terms of accommodating DI, systems and operations must satisfy the ALCOA principles. Both LabSolutions DB and CS (hereinafter referred to as "LabSolutions DB/CS") are equipped with functionality to support this. As one example, the Analysis Sequence application was developed to enable measurements in accordance with an analysis sequence created in advance.

With the Analysis Sequence application, the measurement parameters and report format to use in analysis are specified in advance, so settings/operational mistakes during measurements can be reduced. Additionally, combination with the report set function also makes it easier to check the logs of operations implemented for consecutive measurements.

This article provides a simple overview of DI, as well as a description of the functionality and role of LabSolutions DB/CS and the Analysis Sequence application.

## 2. DI and the LabSolutions DB/CS Functions

### • What is DI?

The draft guidance issued by the American Food and Drug Administration (FDA) reads as follows.[1)]

Q: What is "*data integrity*"?

A: For the purpose of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

In other words, accommodating DI becomes a question of how to obtain data in accordance with the ALCOA principles. Table 1 shows a simple overview of the various aspects of the ALCOA principles.[2)]

Table 1 ALCOA Principles

| Item | Meanings |
|---|---|
| Attributable | The whereabouts of attribution/responsibility are clear. It is clear who recorded the data. The individuals responsible for data measurement, recording, changes, revisions, and deletion are specified, enabling follow-up. |
| Legible | The data can be interpreted/understood. It can be read by anyone easily and without misunderstandings. |
| Contemporaneously | Measurement and recording are performed simultaneously. Any actions taken with respect to the data must also be recorded at the time they are performed. Records must not be backdated. |
| Original | The data must be the original. It must be as initially recorded and not a byproduct or transcription. All of the original documents are preserved. Data is recorded in the appropriate documents. |
| Accurate | The data is accurate. The data is complete and error free. Standard operating procedures (SOP) are followed accurately. |

## • Keywords Related to the ALCOA Principles

Regulatory authorities perform inspections to confirm whether data complies with the ALCOA principles. This section introduces four keywords that are the focus of attention in this context.

### 1. Static and Dynamic

Static refers to printed matter and other items that cannot be subjected to postrun analysis (fixed record). In contrast, dynamic refers to electronic records/data and other items that can be subjected to postrun analysis (electronic record). In inspections, the authorities check that the static and dynamic items are congruent. Additionally, if dynamic items have been subjected to a postrun analysis, a record of this information is required. The record of information is encompassed by an audit trail, the next keyword.

### 2. Audit Trail

An audit trail consists of information regarding the "who, what, when, and why" of the data, arranged in the form of a time series. If there is an audit trail, the sequence of data creation, modification, deletion, and other operations can be recovered. Even if the data has been handled inappropriately, the reporting of incorrect results can be avoided by checking the audit trail. The regulatory authorities treat the audit trail as one aspect of metadata, which is the next keyword, and consider it to be required data.

### 3. Metadata

Metadata refers to all data required in order to understand data items. The data output by the detectors in analytical instruments is simply a numerical count. For such values to be meaningful data, a series of other items are necessary, including the meaning of the horizontal/vertical axes, the instrument conditions (measurement parameters), the data analysis conditions (data processing parameters), the consecutive analyses conditions (batch file/analysis sequence file), and the operational history/log (audit trail). In inspections, it is preferable to present the metadata in a report format that can be understood at a glance.

### 4. Orphan Data

Orphan data refers to data that is recorded as is in a database without being referenced. In inspections, the authorities check whether there is any data that has not been referenced. If such data is found, it raises the suspicion that only the preferred data has been intentionally used.

## • LabSolutions DB/CS Functions

LabSolutions DB/CS is equipped with functions to support compatibility with the ALCOA principles, as described below.

In terms of attribution, the users must be appropriately managed. By using the LabSolutions user management function, accounts for LabSolutions can be configured independently of PC accounts, thereby guaranteeing data attribution. Further, using the electronic signature function clarifies who confirmed/approved the data. Additionally, the authority settings, one aspect of the user management functions, allots authority appropriately to each user, enabling only operations in accordance with SOP, and improving accuracy. Refer to Technical Report C191-E048 (scheduled to be issued in April 2020) "Practical procedure for data integrity compliance in the analytical laboratory" regarding how authority should be granted to each user.

Report editing functions are effective with respect to legibility because they enable not only the data but also the logs, measurement parameters and other required metadata to be arranged freely.

The general functions provided by LabSolutions can be used to satisfy the requirements for simultaneity and authenticity. The data file is registered in the database together with the time stamp created after measurement. The editions of the data file are tracked, so it is not possible to overwrite the original with a data file from a postrun analysis. Postrun analysis is also logged.

In terms of accuracy, it is important to confirm whether or not the analysis was performed correctly in accordance with the required SOP. However, searching for only those logs related to the required data in the midst of voluminous log records can be difficult. In such cases, if the LabSolutions DB/CS report set function is used, a single PDF file can be created that aggregates not only a ledger listing the sample information for the user-selected data file as well as the analysis results report, but also the associated operational logs. This makes it easy to confirm the accuracy of the data.

## 3. Description of the Analysis Sequence Application

The Analysis Sequence application manages an analysis series as a sequence file, and functions to implement only the measurements specified in this context. In other words, if an analysis sequence created in accordance with an SOP is implemented, it is not possible to implement operations or settings not prescribed by the SOP, thereby heightening the accuracy of the ALCOA principles. This section provides an overview of the Analysis Sequence application functions, based on operations/operational procedures that could be realistically anticipated.

Fig. 1 shows the operations/operational sequence when the Analysis Sequence application is not used. The operations vary considerably depending on the operator, and it can be anticipated that mistakes will occur with respect to the settings/operations. Additionally, if the report set function is used to create reports containing the required information, orphan data is likely to be produced due to selection omissions when operators are selecting the individual data items. As a result, the test manager will have the task of checking the logs to see whether mistakes have occurred due to measurements/operations by the operator and, at the same time, will need to check for orphan data in Data Manager. The Analysis Sequence application provides functions developed to resolve such issues.

Fig. 2 shows the operations/operational procedures when the Analysis Sequence application is used. With the Analysis Sequence application, the test manager registers the measurement parameters and report format in advance as a consecutive analysis (analysis sequence file). As a result, settings/operational mistakes by the operators are reduced. When the analysis sequence file is started, the specified application starts up automatically. Analysis can then be completed simply by positioning the samples as per the messages displayed, and clicking the measurement start button. Additionally, the obtained measurement results are linked as a batch data set, so a report set can be created without selecting the individual data items. As a result, orphan data is no longer produced due to selection mistakes.

In this way, the Analysis Sequence application prevents settings/operational mistakes by the operators. At the same time, it heightens the efficiency of the test manager and reduces orphan data.

**Test manager**
- 1. Preparation
  - • Creation of parameters
  - • Creation of a report format
  - • Creation of Standard Operating Procedure (SOP)

**Operator**
- 2. Analysis in Accordance with SOP
  - • Call up of parameters
  - • Background/baseline measurement
  - • Standard sample measurement
  - • Sample measurement
  - • Call up of the report format
- 3. Creation of Reports
  - • Creation of a report by selecting individual data items

**Test manager**
- 4. Approval
  - • Checking of reports
  - • Checking of logs
  - • Checking for orphan data

Fig. 1 Operations/Operational Procedures when the Analysis Sequence Application is not Used

**Test manager**
- 1. Preparation
  - • Creation of parameters
  - • Creation of a report format
  - • Registration of the analysis sequence

**Operator**
- 2. Implementation of the Analysis Sequence
  - • Various measurements
  - (Simply position the samples, and click the OK button)
- 3. Creation of Reports
  - • Created from the batch data set with a single click

**Test manager**
- 4. Approval
  - • Checking of reports

Fig. 2 Operations/Operational Procedures when the Analysis Sequence Application is Used

## 4. Operation of the Analysis Sequence Application

This section provides an actual example of the use of a UV spectrophotometer while operating the Analysis Sequence application. The Analysis Sequence application is optionally available for LabSolutions DB/CS, and can be used by authenticating the digital license.

Following authentication, an [Analysis Sequence] icon is added to the analysis tool tab in the main LabSolutions window, as shown in Fig. 3.

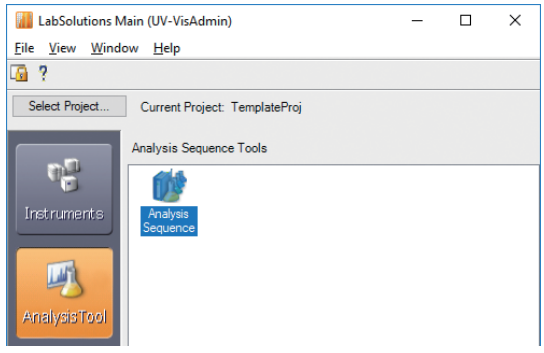


Fig. 3 LabSolutions Main Window

In the detailed Analysis Sequence window shown in Fig. 4, each row corresponds to one measurement. The sample information as well as the measurement parameters and report formats can be configured for each measurement.*1 The items that can be configured differ depending on the model and measurement mode.*2 For example, when used for UV spectral measurements, the spectral file readout settings can also be configured in order to display a comparison with the standard substance in the report.*3

The analysis sequence file is saved and used as a template file separately for each SOP, so the analysis sequence files can also be registered efficiently.

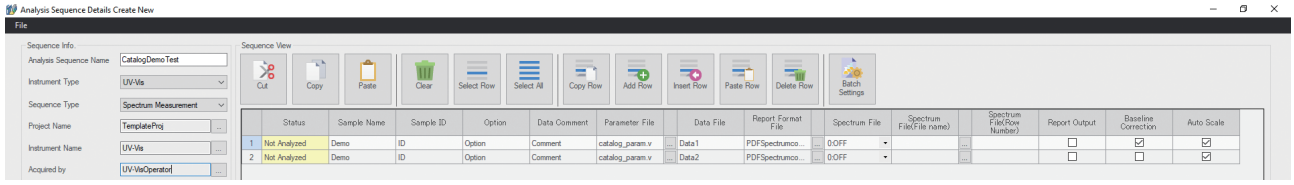


Fig. 4 Detailed Analysis Sequence Window

*1 With quantitative and photometric measurements, the parameters and report formats cannot be configured separately for each measurement. Only one type can be configured for one sequence.

*2 With FTIR, only the spectral measurements can be selected.

*3 The parameters and other settings items differ for each sequence type. In the spectrophotometer(RF), the spectral, quantitative and photometric measurements can be selected as with UV.

The analysis sequence file created is managed and registered in Analysis Sequence Manager. The Analysis Sequence Manager window shown in Fig. 5 displays the status of the registered analysis sequence files (before analysis, during analysis, etc). The user can implement any analysis sequence from this window.

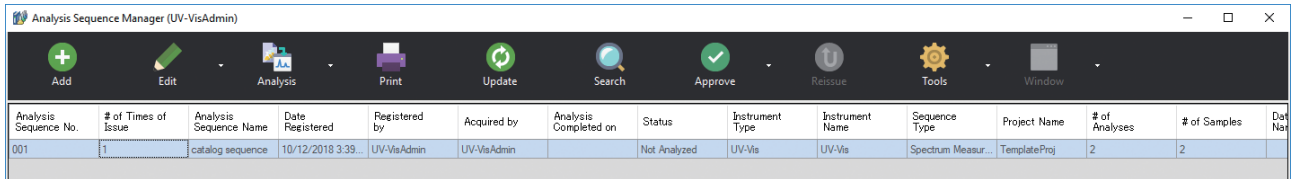


Fig. 5 Analysis Sequence Manager Window

When an analysis sequence is implemented, the target application starts up and a dialog box is displayed, as in Fig. 6. The operator positions the samples and proceeds with the measurements in accordance with the messages displayed in this dialog box. Preset conditions and files are used for the measurement parameters and report format. The operator simply follows the instructions in the dialog box, so settings/operational mistakes are reduced.

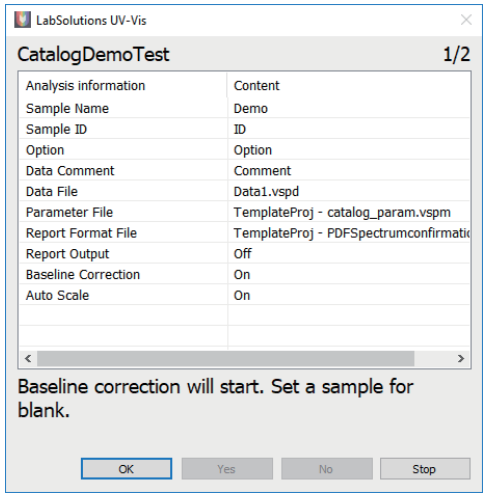


Fig. 6 Dialog Box

When finished, a batch data set is created, which is linked to the data obtained within the same analysis sequence. As shown in Fig. 7, click the batch data set in the Data Manager window to display a list of the data files obtained. Using this batch data set, a report set can be created in which all the associated data file-related sample information, operational logs, and analysis results reports are collated in a single PDF.*4

*4 A digital link can be created between the data and the report set. At the same time, the data can be locked (rendered incapable of being edited) automatically. In this way, it is possible to prevent editing and other tampering with the data after the report has been created.

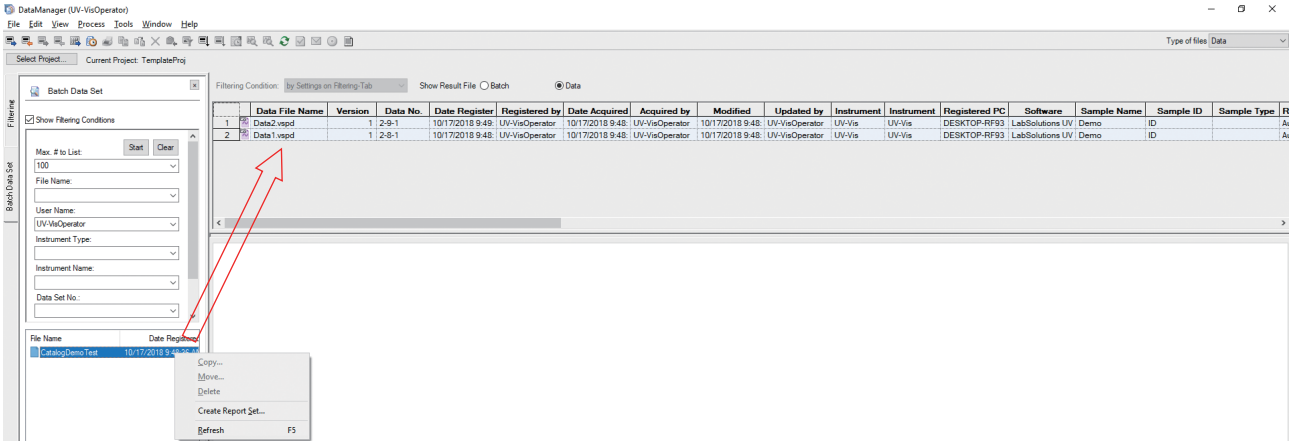


Fig. 7 Selecting an Analysis Sequence File in the Data Manager Window

If electronic signatures are used when examining and approving the report set created, these can be implemented in conjunction with examination and approval of the original data for the report set. As shown in Fig. 8, the color of the data information table row differs depending on the signature stage, so the progress with respect to the signatures can be checked at a glance.

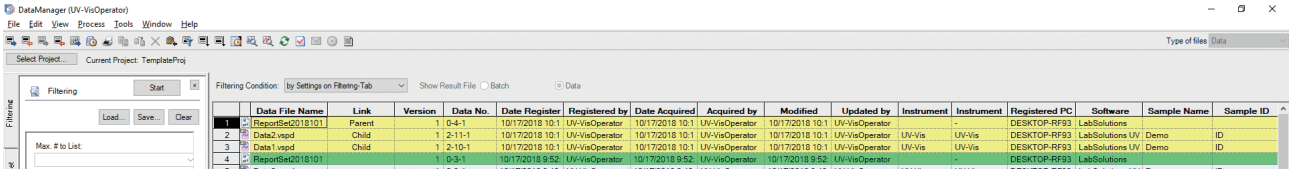


Fig. 8 Example of the Display in Data Manager

## 5. Summary

This article has provided a simple overview of data integrity, and has described LabSolutions DB/CS and the Analysis Sequence application. A variety of adjustments are now required with respect to systems, operational methods, and management structures related to compliance with DI and various regulations. In this context, Shimadzu offers an analysis data system combined with functions to support DI compliance. At the same time, we will continue to pursue functional improvements and new functionality in order to respond to the needs of our customers.

### References


1) FDA (2018) "Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry" <https://www.fda.gov/-regulatory-information/search-fda- guid-ance-documents/data-integrity-and-compliance-drug-cgmp-questions- and-answers-guidance-industry>. Accessed in May 2019
2) Japan Pharmaceutical Manufacturers Association (JPMA) (2012) "Proposal Related to a Quality Management Process Aimed at the Efficient Implementation of Clinical Trials" <http://www.jpma.or.jp/medicine/shinyaku/tiken/allotment/chiken_process.html>. Accessed in May 2019

*Application*

# Automatic Analysis with a UV-Vis Spectrophotometer

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Sippers and syringe sippers are accessories used to measure solutions with a UV-Vis spectrophotometer. These accessories transfer a solution directly from a test tube or beaker to the sample chamber. This avoids the work of placing the solution into the cells, enabling samples to be provided consecutively. Multiple samples can also be measured automatically through combination with an autosampler. However, there are a variety of concerns when a sipper or syringe sipper is used in comparison to the use of a typical 10 mm quartz cell. In addition to an introduction to automatic analysis using the combination of an autosampler with a sipper or syringe sipper, this article will focus on carryover, which is one such concern, and will describe the optimal suction volume.

## 1. Introduction to the CETAC Autosampler and Special Control Software

With Shimadzu UV-Vis spectrophotometers, the CETAC ASX-560/ASX-280 autosampler can be connected in combination with a sipper or syringe sipper. Fig. 1 shows the ASX-560. These autosamplers can be controlled using LabSolutions UV-Vis software. Fig. 2 shows the settings window for the software. At the top right of the settings window, the rack on the autosampler can be selected. Selection is easy regardless of where the sample is positioned.

Additionally, measurement conditions can be configured separately for each sample, so samples with different measurement conditions can be configured at the same time. Further, pass/fail determinations about the measurement results can be made using the spectral evaluation function in LabSolutions UV-Vis. Pass/fail determinations about each sample are evident at a glance as soon as the measurements are finished.

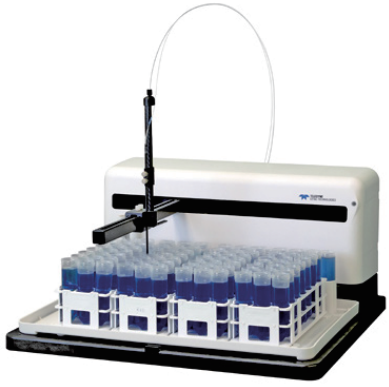


Fig. 1 CETAC ASX-560 Autosampler

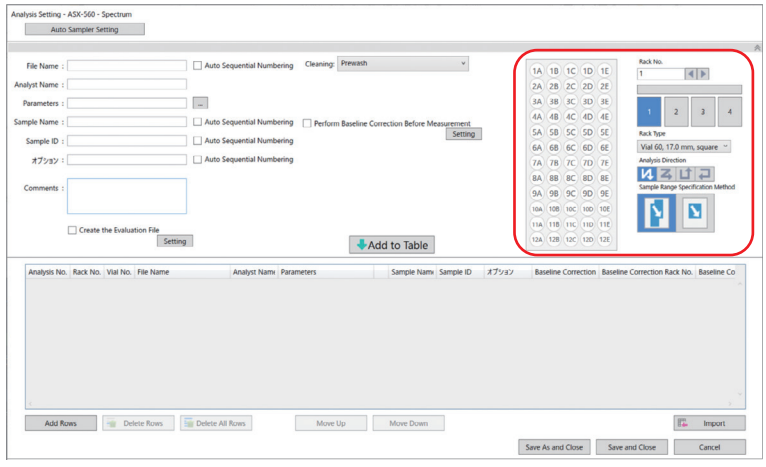



Fig. 2 Settings Window for the Autosampler Control Software

## 2. Introduction to Sippers and Syringe Sippers

The sipper and syringe sipper shown in Figs. 3 and 4 are distinguished by the method of drawing in the sample solution. Sippers use a peristaltic pump, while syringe sippers use a syringe pump. They are further classified by the presence or absence of a thermostatic function and by the flow cell type. The features of each sipper and syringe sipper are shown in Tables 1 and 2. The standard required sample volume noted here refers to the sample volume that can be measured with no impact from the sample that passed through the flow line just before. ("With no impact" is defined as carryover of 1.0 % or less. Note that in the case of consecutive sample measurements, carryover refers to a situation in which the previous sample remains in the flow cell, thereby affecting the measurement of the next sample. With a sipper, a sample suction volume resulting in carryover of 1.0 % or less is configured as the standard required sample volume.)

Table 1 List of Sippers

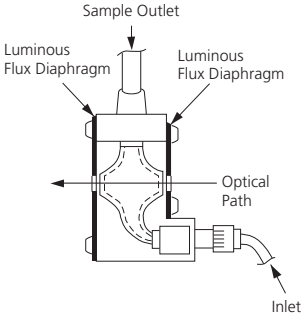
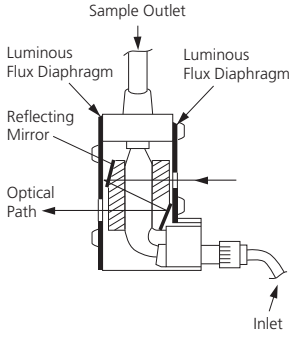
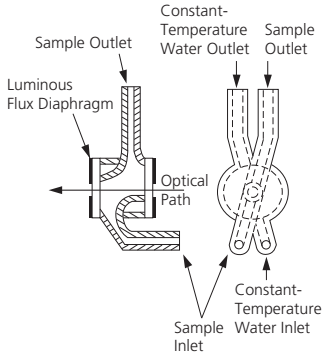
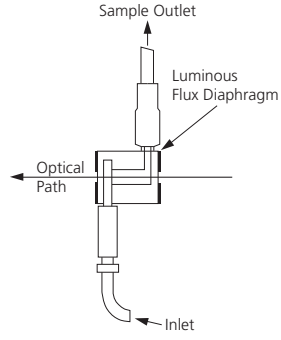
| Peristaltic Pump Type | | | |
|---|---|---|---|
| 160L | 160T | 160C | 160U |
|  |  |  |  |
| Cross-Section of a L-Type Flow Cell<br>Standard Type<br>(Required Sample Volume: 2.0 mL) | Cross-Section of a T-Type Flow Cell<br>Triple-Pass Type<br>(Required Sample Volume: 1.5 mL) | Cross-Section of a C-Type Flow Cell<br>Constant-Temperature Type<br>(Required Sample Volume: 2.5 mL) | Cross-Section of a U-Type Flow Cell<br>Super-Micro Type<br>(Required Sample Volume: 0.5 mL) |

Table 2 List of Syringe Sippers

| | Accessories | Cell/Thermostatic Function | Required Sample Volume |
|---|---|---|---|
| Syringe Type<br>(Sold Separately) | Syringe Sipper N Type | Normal Temperature Type | 0.9 / 1.0 / 5.0 mL<br>(by Flow Cell) |
| | Syringe Sipper CN Type | Constant-Temperature Circulated Type | |

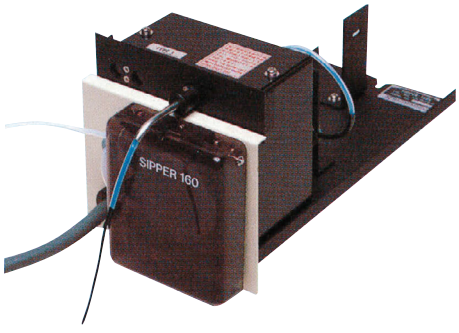



Fig. 3 Sipper 160


Fig. 4 Syringe Sipper

The Sipper 160 is very compact and can be placed within a sample chamber for use. By contrast, the connecting parts of the syringe sipper are made of fluoropolymer, glass, and quartz, and are highly resistant to chemicals. Additionally, since a syringe is used for suction, the suction volume repeatability is very high (repeatability: ±0.03 mL). For details on each sipper, refer to UV TALK LETTER Vol. 8.

With sippers and syringe sippers, the software can be used to configure the (1) suction speed, (2) suction time/suction volume, (3) discharge time/discharge volume, (4) stabilization time, and (5) number of rinses. The optimal settings must be configured to suit the state of the sample being measured.

## 3. Relationship between Tube Length and Suction Time

With a sipper, the solution is drawn in by placing a suction tube in the test tube. However, the length of the suction tube must be extended when drawing in solution from tall test tubes and when connecting to an autosampler, which can lead to carryover.

Here, the impact due to carryover caused by the suction tube length was verified when a suction tube was used manually, and when measurements were performed with the previously mentioned ASX-560 and the UV-1900 series connected. (An aqueous solution of potassium permanganate was measured.) The tube lengths for both systems are shown in Table 3, and a photograph showing the manual use of the suction tube is shown in Fig. 5.

The measurement sequence is shown in Fig. 6, and the measurement results are shown in Figs. 7 and 8. For the carryover measurement method, refer to UV TALK LETTER Vol. 8.

Table 3 Both Systems

| System | Suction Tube | ASX-560 |
|---|---|---|
| Tube Length[1)] | 50 cm | 150 cm |

1) The length of the suction tube is measured from the base of the tube where it emerges from the sipper to the tip.

Fig. 5 Schematic Showing Manual Use of the Suction Tube

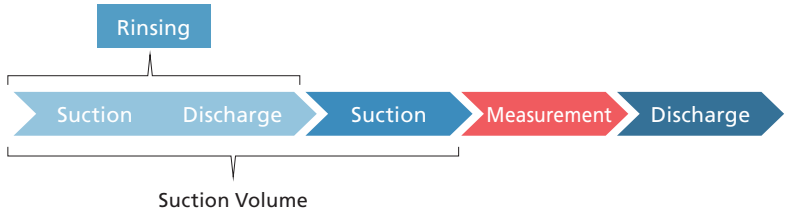



Fig. 6 Sipper and Syringe Sipper Measurement Sequence

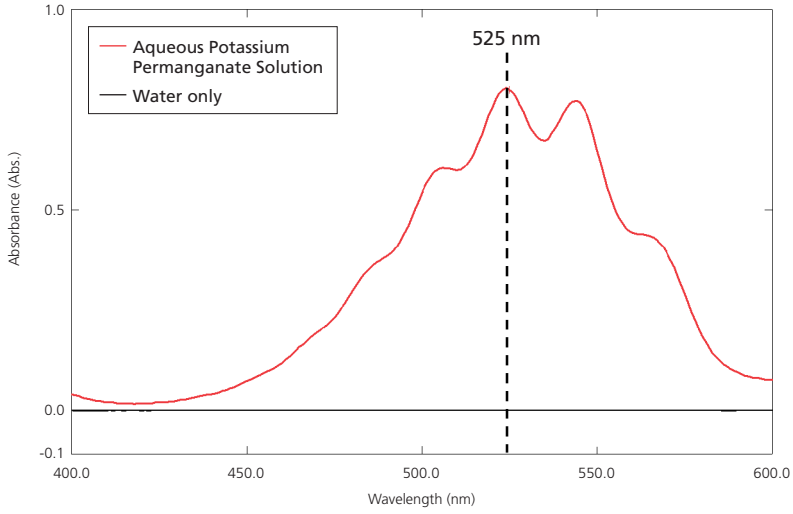



Fig. 7 Absorption Spectrum of an Aqueous Potassium Permanganate Solution

Suction Tube

| | Samples | Type | Ex | WL525.00 |
|---|---|---|---|---|
| 1 | Water 1 | UNK | | 0.000 |
| 2 | Water 2 | UNK | | −0.000 |
| 3 | Water 3 | UNK | | 0.000 |
| 4 | Sample 1 | UNK | | 0.811 |
| 5 | Sample 2 | UNK | | 0.815 |
| 6 | Sample 3 | UNK | | 0.814 |
| 7 | | UNK | | |

ASX-560

| | Samples | Type | Ex | WL525.00 |
|---|---|---|---|---|
| 1 | Water 1 | UNK | | 0.000 |
| 2 | Water 2 | UNK | | 0.000 |
| 3 | Water 3 | UNK | | −0.000 |
| 4 | Sample 1 | UNK | | 0.814 |
| 5 | Sample 2 | UNK | | 0.818 |
| 6 | Sample 3 | UNK | | 0.817 |
| 7 | | UNK | | |

Fig. 8 Absorbance Value at 525 nm for Both Systems

The carryover for both systems was calculated from the results in Fig. 8 using the following formula (1). The calculation results are shown in Table 4.

Carryover (%) = (Absorbance for Sample 2 - Absorbance for Sample 1) / Absorbance for Sample 2 or Absorbance for Sample 3 x 100 (1)

Table 4 Carryover for Both Systems

| System | Suction Tube | ASX-560 |
|---|---|---|
| Carryover (%) | 0.0 | 0.5 |

From Table 4, it was demonstrated that the shorter the tube, the more difficult it was for carryover to occur. However, it was evident for both systems that carryover was 0.5 % or less. Additionally, while performing this verification, an investigation of the measurement conditions that minimize carryover was also implemented.

From the results it was evident that for both systems, the measurement conditions shown in Table 5 minimize carryover. (The carryover with these measurement conditions is as shown in Table 4.)

Table 5 Measurement Conditions for Both Systems

| Settings Items | Suction Tube [2)] | ASX-560 [2)] |
|---|---|---|
| Suction Speed | High-Speed | High-Speed |
| Suction Time | 6 sec | 8 sec |
| Discharge Time | 2 sec | 2 sec |
| Stabilization Time | 2 sec | 2 sec |
| Number of Rinses | 0 | 1 |
| Suction Volume [3)] | Approx. 3.6 mL | Approx. 6.0 mL |

2) The inner diameter of the tube is $\varphi$ 1 mm for manual operation using a suction tube and $\varphi$ 0.5 mm for ASX -560. The smaller the diameter of the tube, the less suction is required for the same suction time.

3) The amount of solution used in aspiration and cleaning.

Note that with the ASX-560, the tube length is a rather long 150 cm, so the suction time was lengthened because a lot of solution is required to replace the solution within the tube. The carryover is sufficiently small with the measurement conditions here. However, carryover can be further reduced by further extending the suction time. Additionally, with the ASX-560, rinsing was performed before sample measurement. When the suction tube is lengthened as with the ASX-560, carryover can be minimized by performing rinsing.

## 4. Summary

Here, we summarize the points for reducing carryover with a sipper.

- Keep the suction tube as short as possible. If an autosampler is used, keep the tube short enough that there is no impact on its operation.
- If the length of the suction tube is changed because an autosampler is installed, optimize the conditions to reduce carryover by reinvestigating the suction volume and other conditions.
- If the suction tube cannot be shortened, perform rinsing.

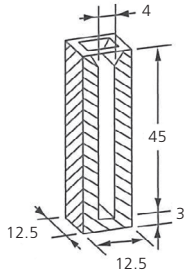
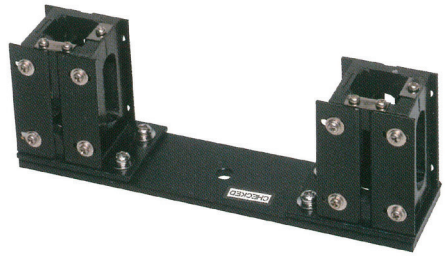
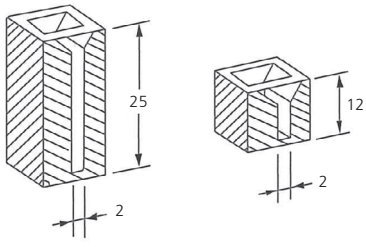
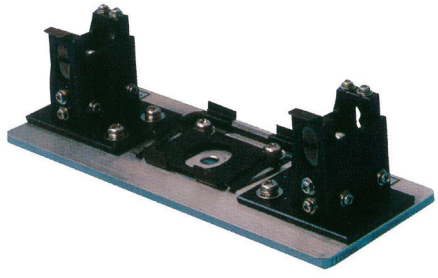
When a sipper is used in this way, the measurement conditions must be optimized to suit the features of the sample and instrument. Before performing measurements, optimize the conditions.

## *Q&A*

# The volume of the sample is limited. What is the best way to measure as small a volume as possible?

Generally, the volume of a cell with an optical path length of 10 mm, which is commonly used, is 4.5 mL. When measuring samples, measurements can be performed if about 3 mL of sample is placed in the cell. If there is not much sample, a small-volume cell can be selected.

Small-volume cells with an optical path length of 10 mm include semimicro cells, micro cells, and supermicro cells (see the figure below). A semimicro cell requires 1 mL of sample, a micro cell requires 400 µL, and a supermicro cell requires 50 µL. Measurements can be performed with even smaller volumes by selecting a cell with an optical path length of 5 mm. When using small-volume cells, a cell holder with a mask to accommodate the respective cells or a supermicro cell holder will be required. The compatible cell holder ensures that the light used in the measurement irradiates only the sample region of the cell. Accordingly, part of the light beam is cut, which tends to increase the noise level compared to when a general-purpose cell is used.

| Small-Volume Cells | Compatible Cell Holders |
|---|---|
|  Semi-Micro Cell |  Micro Cell Holder with Mask |
|  Micro Cell Super-Micro Cell |  Super-Micro Cell Holder |

In addition to these cells, other small-volume cells are commercially available from cell manufacturers. When purchasing a commercially available cell, select a cell compatible with the position of the light beam for the instrument used. In the case of Shimadzu spectrophotometers, select a cell compatible with a light beam height of 15 mm.

# Enables More Efficient Analysis

Analytical Data System for UV-Vis Spectrophotometers

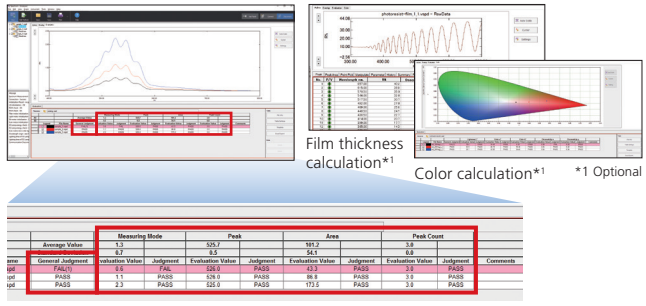
# LabSolutions™ UV-Vis

Enables faster and easier use of spectrophotometers.
Frees the operator from manual operations.

## Smart Quality Control

Operations from analysis of spectra to judgment are automated.
Supports all users to maintain product quality.

A comprehensive 'pass' determination is made if all evaluation items pass in accordance with a customized evaluation method. Multiple evaluation items can be created.

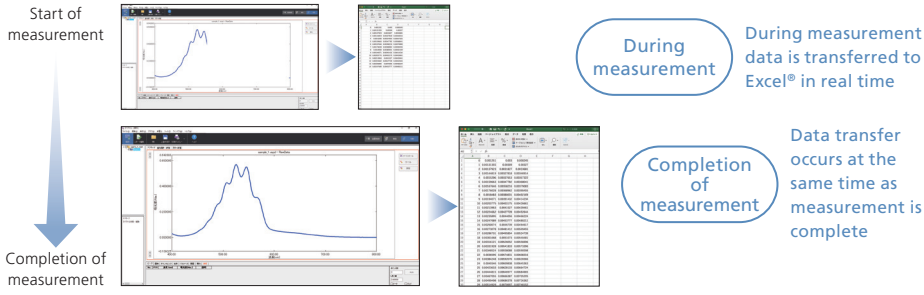



The results of pass/fail judgments with respect to evaluation conditions for all samples can be produced as a list.

## Seamless Data Transfer

Data transfer to an Excel® sheet or saving in a text file can be automatically performed.

During measurement, the spectrum and the time course waveform can be transferred to Excel® in real time. The data can be analyzed without having to save it in text format.



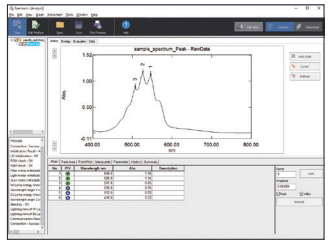

Excel® real-time transfer function

## Simple Window Format

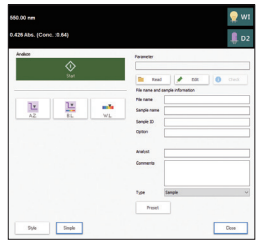
Combines convenient, everyday functions with a user-friendly interface.

On the main window only the frequently used functions and information are laid out. Operations such as measurement, viewing of data, analysis, etc. can be performed by anyone using the large buttons and icons.

Functions for instrument control are gathered on a dedicated panel, enabling operations ranging from setting sample information to analysis to be performed with ease.



Main Window



Instrument Control Panel



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