Featured Articles

Improving Laboratory Reliability through Visualization of Medical Testing Process

Masaharu Nishida
Kiyotaka Umino
Kumiko Kamihara
Tomonori Mimura

OVERVIEW: Recent years have seen demand for a higher level of quality management in the field of in vitro diagnostics for medical testing. Among the requirements for certification under the latest ISO 15189 standard is the collection and management of records for all testing processes. When Hitachi High-Technologies Corporation conducted a survey of all processes that take place at a testing laboratory, it found that management of the materials used with test equipment and management of measurement processes were of particular importance to laboratory-wide management. To achieve this, Hitachi High-Technologies developed a laboratory automation system, which uses single holders with RFID tags, and the reaction curve fitting method, a technique for determining the characteristics of the chemical reactions that take place during sample analysis.

INTRODUCTION

MEDICAL testing, the analysis of blood or other samples from a patient, plays an important role in diagnosing disease and in deciding how best to treat it. Along with performing large numbers of analyses in a short timeframe to cope with the increasing number of tests and samples, medical laboratories also need to provide doctors with accurate and highly reliable data. To achieve this, laboratories have installed automated sample transportation lines and a variety of automatic analyzers. Along with progress in the automation of medical testing comes a strong demand for reliability, with a variety of practices having been developed for this purpose.

Meanwhile, the ISO 15189:2003 standard has been published for quality management in medical laboratories, with implementation starting in Japan in 2005. The main method used in the past for the management of laboratory accuracy has been to conduct quality control using regular measurements of selected patient samples (quality control samples). This was also augmented by quality control of equipment and materials, including patient sample handling, reagents and other consumables, and devices.

The ISO 15189 standard certifies laboratory quality in terms of the results of the information required for laboratory-wide quality control, techniques for quality control of equipment and materials, testing accuracy control data, and the verification of reliability improvements.

This article describes techniques for the quality control of laboratory automation systems and analyzers.

MOVEMENT OF SAMPLES THROUGH A MEDICAL LABORATORY

After patient interview and the collection of samples in an examining room, samples are taken to a medical laboratory for testing. The route followed by a sample depends on its type (blood serum, plasma, urine, etc.) and the tests to be performed (biochemistry, immune serum, hematology, etc.). It may pass through preparatory processes such a centrifugation, etc. via laboratory automation equipment and a variety of analyzers (biochemistry and immunoassay analyzers, blood analyzers, etc.) in order to generate the output results as data that help facilitate patient treatment back in the examining room (see Fig. 1).

Laboratories collate and combine results from a variety of measurements that are passed back to the doctor in a patient examination report. The Information & Telecommunication Systems Company of Hitachi, Ltd. markets an information system for managing multiple analyzers and supporting operations from ordering tests to performing them and reporting the results.

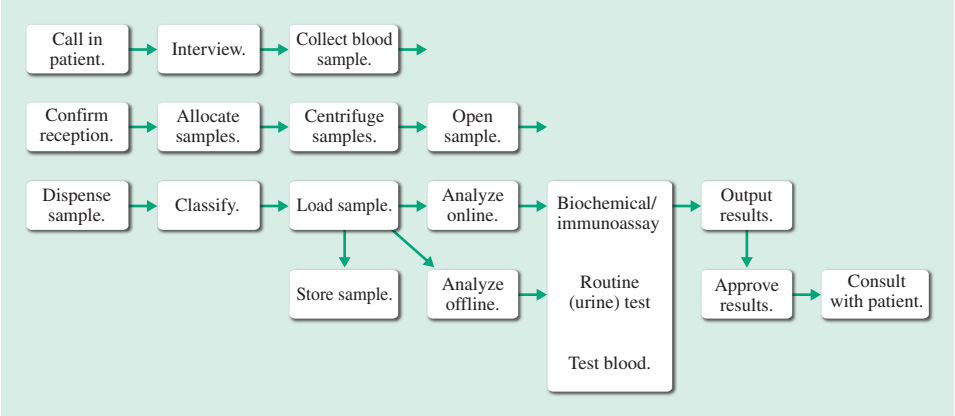

Fig. 1—Laboratory Sample Flowchart.
After sample preparation, which depending on the sample type may include centrifugation, labeling, and dispensing, a blood sample is transported to the analyzer where the specified measurements are performed.

A subject attracting considerable interest at present is the digitization of clinical data and the use of electronic medical records and big data analytics for purposes such as preventive medicine.

At the same time, there has been less progress on systematizing the handling of materials in the laboratory, such as quality control samples and reagents. While identification barcodes are attached to patient samples at the time of collection, and the collected samples then move through the sample preparation steps prior to loading into the analyzer and performing measurements, because the number and type of samples and the tests to be performed vary from patient to patient, difficulties have included the efficient tracking of multiple samples in realtime and backtracking the actual route that samples have taken.

LABORATORY MANAGEMENT

Comprehensive management techniques are important for laboratory-wide quality control, including not only sample test results but also the management of equipment (analyzer operation, maintenance and inspection, etc.) and materials (samples, reagents, etc.).
(1) The interconnection and operation of preparation and analysis processes in the laboratory must be managed.
(2) Practices are needed for the monitoring and quality control of analytical testing processes of patient samples in the various types of analyzers.
(3) It is necessary to manage equipment and materials, such as reagents, quality control materials, and maintenance.

When a fishbone diagram (cause and effect diagram) is used to represent the requirements of laboratory management, these can be broadly divided into requirements that relate to equipment and requirements that relate to the people who use the equipment and their operating practices (see Fig. 2).

The equipment-related requirements can be further divided into managing equipment condition, managing consumables, and managing equipment operation.

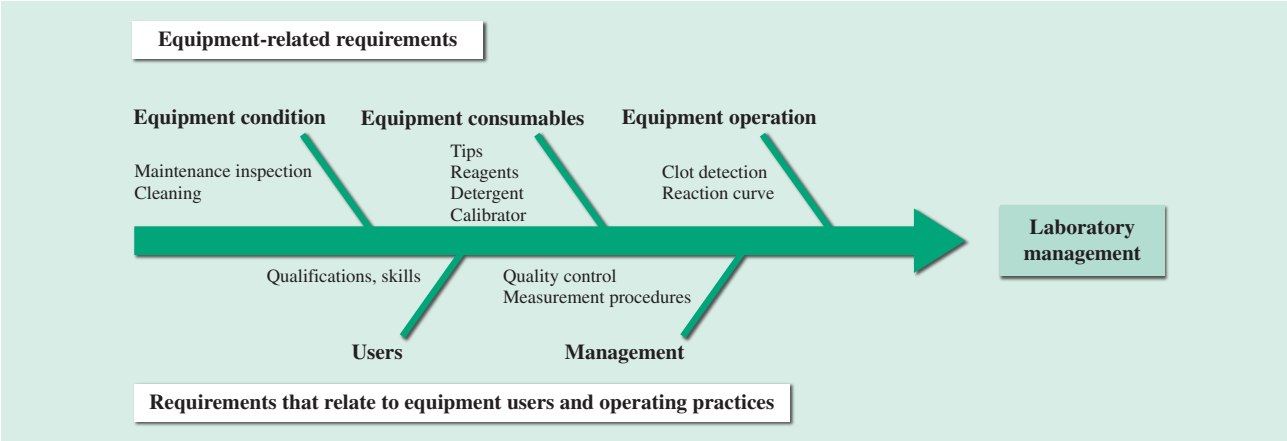

Fig. 2—Laboratory Management.
Laboratory management can be broadly divided into requirements that relate to equipment and requirements that relate to the people who use the equipment and their operating practices.

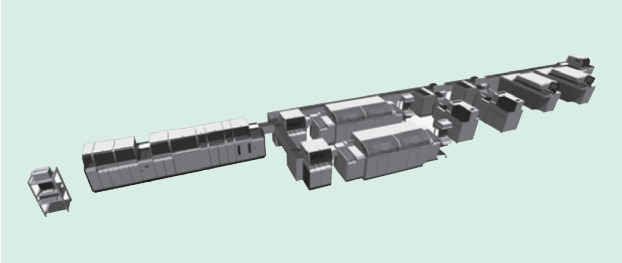

Fig. 3—Example Layout of Laboratory Automation System.
Efficiency improvements and the elimination of errors can be achieved by combining Hitachi High-Technologies' laboratory automation system with its automatic biochemical analyzers.

(a) Managing equipment condition
This includes maintenance inspections, parts replacement, cleaning, and so on.
(b) Managing consumables
These include cuvettes, lamps, reagents and calibrators (lot, expiry date), electrodes, detergents, sample tubes (test tubes), and tips.
(c) Managing equipment operation
This includes detecting shortages of samples or shortages of reagents, detecting fibrin clots, calibration curve sensitivity, and reaction curve management.

In regard to requirements that relate to the people who use the equipment and their operating practices, quality control and measurement procedures can be improved by enhancing the user interfaces of equipment and systems to make it easier for staff to perform checks quickly and determine equipment status prior to use. Similarly, the more that the screens used on sample preparation equipment and analyzers are based on similar concepts, the less time it takes for medical testing technicians to check the status of sample preparation equipment or learn how to operate the analyzers.

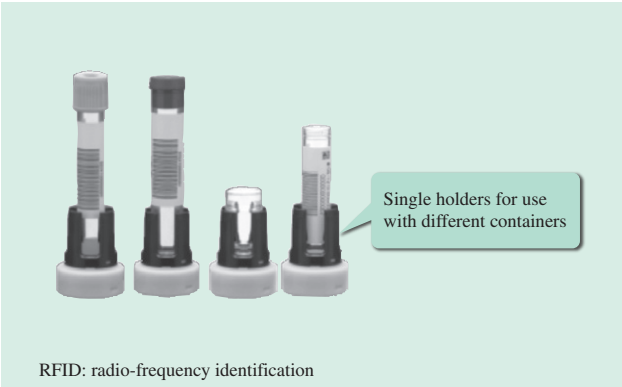

Fig. 4—Single Holder with RFID Tag.
High-speed transportation is achieved by taking advantage of the faster reading time possible when using RFID. This facilitates the tracking of samples to ensure that each one is transported to the required analyzers.

SAMPLE MANAGEMENT IN LABORATORY AUTOMATION SYSTEMS

Single sample carriers are a useful way to speed up the transportation of samples in the laboratory and to make this process more efficient. Similarly, the double identification of samples is necessary to verify that the controlled laboratory has performed measurements on all of the collected samples. This means attaching radio-frequency identification (RFID) tags to new single holders, and sample barcodes to test tubes that contain samples. Hitachi High-Technologies Corporation has developed a laboratory automation system that tracks the location of samples on the transportation line and prevents misidentification (see Fig. 3).

The laboratory automation system uses single holders with RFID tags to identify samples on the transportation line (see Fig. 4).

Because of the need to halt and rotate samples to read the sample information when using barcode labels, this takes approximately 5 s. RFID tags, in contrast, do not require this halt and rotate step and can be read in just 0.2 s. Accordingly, the use of RFID has increased transportation speed.

Furthermore, enhancements to user interfaces have made it easy to determine where individual samples

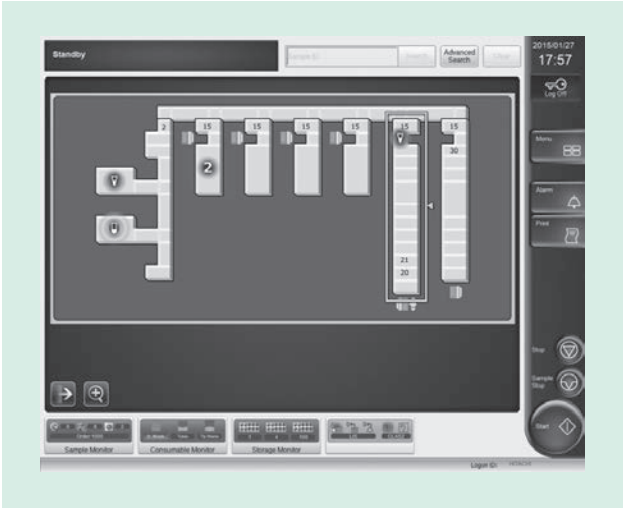

Fig. 5—The Laboratory Automation System Sample Monitor Screen.
The screen is used to check the location and progress of specific samples.

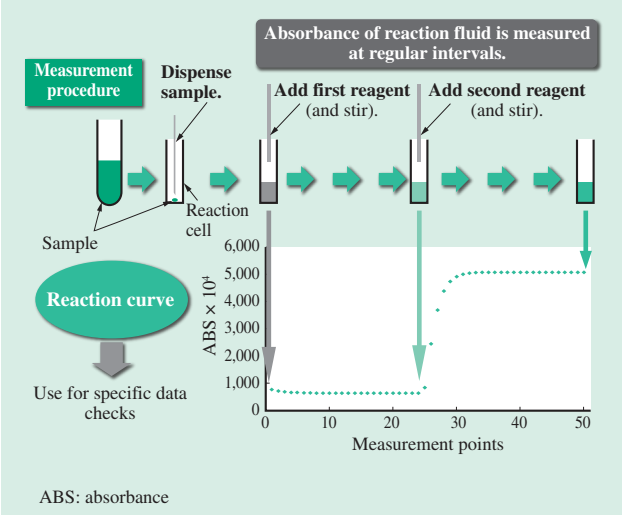

Fig. 6—Measurement Processes for Automatic Biochemical Analyzers.
Reagents are added to the blood serum, urine, or other sample and the sample is stirred to promote a reaction causing the optical absorbance to change. This changing absorbance value is measured at regular intervals.

are located in a large laboratory, making it possible to respond quickly to doctor inquiries about testing progress or conduct prompt retesting (see Fig. 5).

MANAGEMENT OF MEASUREMENT PROCESS FOR ANALYZERS

The sequence of operations performed by analyzers also needs to be managed. The following are some examples of such checks.

(1) Before measurement
Is the cuvette clean?

(2) Sample dispensing
Has the correct quantity of sample been pipetted?
Was any fibrin or other contaminating material pipetted along with the sample?

(3) Reagent dispensing
Has the correct quantity of reagent been pipetted?

Furthermore, management of the measurement process can ensure the reliability of measurement through the combined control of both the reaction process and equipment operation. In recent years, analyzers have also been fitted with mechanisms for detecting abnormal conditions during the analysis reaction, such as the use of a photometer to check for excess absorbance or clot detection in the sampling mechanism. The requirement is to achieve a higher level of reliability by trying to detect abnormalities not just in the measurement results but also during the reaction.

In an automatic biochemical analyzer, this is achieved by taking periodic photometer absorbance measurements after the sample and reagent have been added to the cuvette (see Fig. 6).

The sequence of absorbance values obtained by these measurements is called the "reaction curve." The end-point assay and rate assay are two types of reaction curves. In an end-point assay, the reaction reaches equilibrium during the measurement period, whereas a rate assay measures how the reaction changes.

Hitachi High-Technologies is working on use of the reaction curve fitting method to monitor ("visualize") the reaction process as a check.

The reaction curve fitting method is a technique for producing numeric indicators (parameters) for the measured reaction curve by using a model function derived from chemical kinetics to approximate it in accordance with the reaction pattern based on factors such as lipid quantity or enzyme activity.

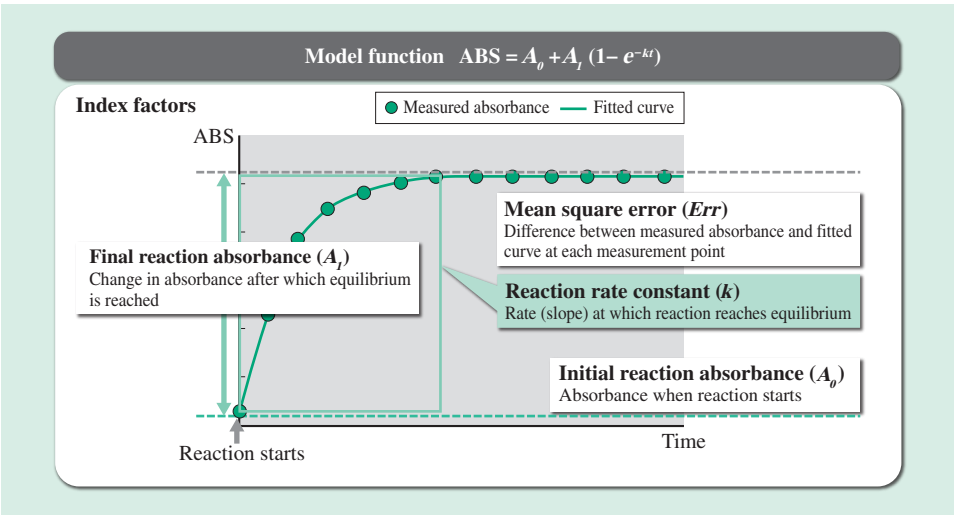

Fig. 7—Reaction Curve Fitting for End-point Analysis.
Four "index factors" that characterize the pattern are calculated using a model function derived from chemical kinetics.

The approximation function is calculated as follows.

In the case of an end-point assay, the absorbance starts changing when the reaction is initiated then settles to a constant value after a certain period of time. Accordingly, the reaction is approximated by a model function that replicates the start of the reaction and its final level of absorbance (see Fig. 7).

In the case of a rate assay, the approximation uses a model function that replicates the lag phase immediately after the reaction is initiated during which it has yet to reach a steady rate (see Fig. 8).

Hitachi High-Technologies has used the reaction curve fitting method to obtain numeric parameters for a variety of reaction curve patterns so that abnormalities caused by the sample, reagent, or equipment during the reaction process can be detected by monitoring the value of these parameters.

FUTURE MEDICAL LABORATORIES

In the future, the development of the Internet of things (IoT) will increasingly change the laboratory, including an increase in the number of sensors fitted in analyzers to help determine the location of patient samples, and the embedding of integrated circuit (IC) chips in consumables to enable the realtime management of equipment and materials where required. Amid this flood of information, laboratory administrators will be called on to respond appropriately depending on the circumstances, whether it is the morning rush during the day or emergencies during the night. This requires the collation and interpretation of a variety of information and the provision of information that is appropriate.

Continuous Improvement of Laboratories

Laboratories are continually changing in step with advances in medicine. The use of experience design for analysis is an effective way to make ongoing improvements in the laboratory, such as further shortening the time taken to provide test reports, analyzer integration, and changes to testing routes along with the expanding range of measurements to be performed due to advances in personalized medicine such as genetic diagnosis and the addition of new biomarkers. Also of importance will be integrated management systems that enable the incorporation of new analyzers and flexible changes to laboratory layout through the use of IoT technology with various sensors.

Innovation in Information Delivery —Greater Use of Mobile Devices—

Systems have already been implemented for sending things like equipment alarms or emergency test results to mobile devices. These devices are a useful way of monitoring and checking information in realtime. In the future, bidirectional practices such as the issuing of instructions to laboratory staff by administrators and communicating with equipment maintenance companies to share information will lead to quicker responses. In addition to their use in laboratories, the standardization of mobile devices as part of hospital infrastructure is also anticipated.

It is extremely important for staff that the screens used by mobile and other IT devices, sample preparation systems, and the different types of analyzers be based on the same concepts so that anyone can intuitively know how to use them, thereby helping shorten the time it takes to learn how to

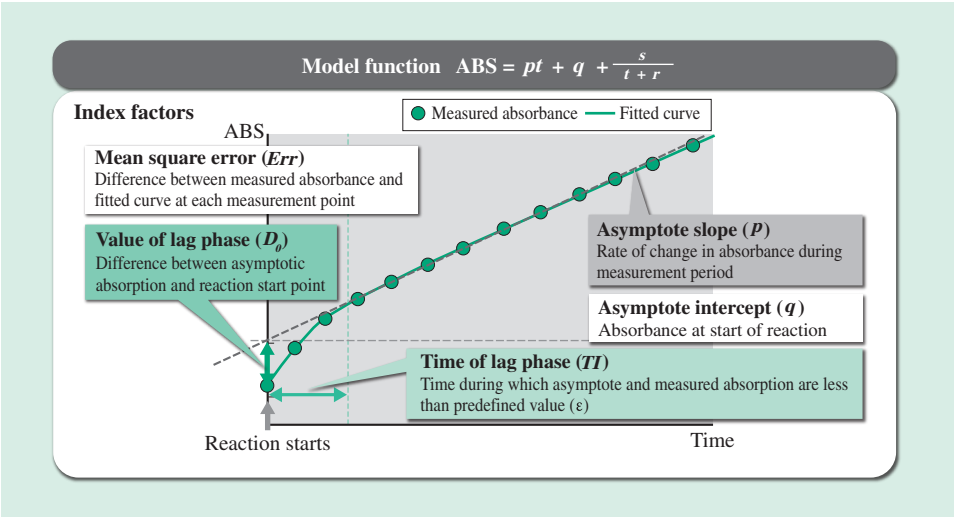

Fig. 8—Reaction Curve Fitting for Rate Analysis.
Five characteristic "index factors" are calculated using a model function that replicates the lag phase.

operate these systems. It is also essential that staff members are provided with appropriate instructions.

CONCLUSIONS

Thanks to user interface enhancements, the use of single sample carriers with RFID tags, and the reaction curve fitting technique, it is now possible to visualize the complex processes that take place at medical laboratories, which combine medical testing information with such equipment and materials as analyzers, samples, and reagents. In addition to improving productivity, this visualization of the medical testing process is also leading to improved laboratory reliability through process management. In the future, Hitachi High-Technologies intends to provide appropriate operational information in realtime and support the adoption of IoT technologies.

REFERENCES

(1) M. Iijima, M. Hanawa, and M. Nishida, "The LABOSPECT Series: Hitachi's Automatic Clinical Chemistry Analyzer to Realize the High Quality Laboratory Testing," Hitachi Hyoron **88**, pp. 702–707 (Sep. 2006) in Japanese.
(2) T. Kawai, "ISO 15189:2007 for Medical Laboratories, Explanations of Requirements and Terminology, Certification Case Studies" (Mar. 2008) in Japanese.
(3) Hitachi Solutions, Ltd. News Release, "Launch of Lavolute 8 Clinical Testing System for Medical Institutions, Accurate and Fast Medical Testing" (Apr. 2014) http://www.hitachi-solutions.co.jp/company/press/news/2014/0416.html in Japanese.
(4) A. Katayama et al., "Trends in Design and Associated IP Management," Hitachi Review **64**, pp. 346–351 (Jul. 2015).

ABOUT THE AUTHORS

Masaharu Nishida
Medical Systems Design 1st Department, Science & Medical Systems Business Group, Hitachi High-Technologies Corporation. He is currently engaged in the development of medical systems. Mr. Nishida is a member of the Japan Society of Clinical Chemistry (JSCC) and The Japan Society for Clinical Laboratory Automation (JSCLA).

Kiyotaka Umino
Medical Systems Design 2nd Department, Science & Medical Systems Business Group, Hitachi High-Technologies Corporation. He is currently engaged in the development of medical systems.

Kumiko Kamihara
Medical Systems Design 1st Department, Science & Medical Systems Business Group, Hitachi High-Technologies Corporation. She is currently engaged in the development of medical systems. Ms. Kamihara is a member of the JSCLA.

Tomonori Mimura
Medical Systems Center, Science & Medical Systems Business Group, Hitachi High-Technologies Corporation. He is currently engaged in the development of medical systems. Mr. Mimura is a member of the JSCC, JSCLA, and Japanese Society of Laboratory Medicine (JSLM).