Introduction of Products

Overview of the Automated Coagulation Analyzer CS-5100

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INTRODUCTION

Sysmex Corporation has been working to develop blood coagulation analyzers for the past 30 years. During this period, the company brought out several analyzers to meet the different needs of customers, as the CA series analyzers, more than 20,000 of which are presently in use the world over. In 2006 Sysmex launched the fully automated blood coagulation analyzers CS-2000*i*/2100*i* (hereinafter CS-2000*i*/2100*i*) as successors to the CA series[1]. These analyzers were equipped with new functions, such as an expanded list of analysis parameters and pre-analysis sample quality checking, which were enabled by the adoption of multi-wavelength detection system.

In recent years, the demand for shorter turnaround times (TAT) and the ability to carry out thrombosis-related tests has been increasing. The fully automated coagulation analyzer CS-5100 (hereinafter CS-5100) (***Fig. 1***) was developed to meet these demands. CS-5100 has a common platform with CS-2000*i*/2100*i*, and is capable of high throughput up to 400 tests per hour. It has both cap piercing and small volume sampling capabilities, and improved user friendliness.

BASIC SPECIFICATIONS

The major specifications of CS-5100 are listed in ***Table 1***.

This analyzer is provided with a detector that can implement 4 different methods of detection, i.e., coagulation time method, chromogenic substrate method, immunoturbidimetry and aggregation method, and can handle a wide range of analysis parameters. The measurement principles used by the analyzer and its major functions and advantages are described below.

Fig. 1 *The automated blood coagulation analyzer CS-5100*

Table 1 *Major specifications*

	Specifications	
Name	Automated coagulation analyzer CS-5100	
Dimensions and weight	Main unit: approx. 1,030 mm (W) × approx. 1,150 mm (D) × approx. 1,280 mm (H), approx. 278 kg, Floor top	
Electrical specification	Voltage: 200 ~ 240 V	
Measurement principles	Multi-wavelength detection system • Clotting Assays: Detection of transmitted light (percentage) • Chromogenic Assays: Colorimetry (kinetic method) • Immunoassays: Turbidimetry • Aggregation Assay: Turbidimetry	
Analysis parameters	• PT (Prothrombin time) • Fbg (Fibrinogen) • Intrinsic coagulation factors (VIII, IX, XI and XII) • HpT (Hepaplastin test) • Coagulation factor XIII (FXIII) • D-Dimer • VWF:Ag (von Willebrand factor antigen) • FM (Fibrin monomer)	• APTT (Activated partial thromboplastin time) • Extrinsic coagulation factors (II, V, VII and X) • TTO (Thrombotest) • AT-III, PLG, a2-PI, PC • FDP • PIC • VWF:RCo (von Willebrand factor activity)
Required sample volume	PT, APTT Fbg, HpT, intrinsic coagulation factors and FDP TTO, FXIII Extrinsic coagulation factors AT-III, PLG, a2-PI, PIC PC D-Dimer VWF:Ag VWF:RCo	50 µL 10 µL 20 µL 5 µL 16 µL 15 µL 6 µL 15 µL 4 µL
Detector	Photometric unit: 20 wells (8 equipped with stirrer function: Aggregation Assay) Heating unit: 36 wells	
Sample arms	Sample arm A: Cap piercing function / Standard mode Sample arm B: Secondary dispensing / Micro mode (Small volume mode) Number of samples taken in in the first step: 52	
Reagent arms	Reagent arm A: First reagent Reagent arm B: Second reagent Reagent arm C: Second reagent (exclusively for thrombin reagent)	
Sample tube supply unit	A maximum of 1000 sample tubes can be housed	
Throughput	Measurement of PT alone: Maximum 400 tests/h Simultaneous PT and APTT: Maximum 400 tests/h (PT: Thromborel S, APTT: FS) *The stated capacities are for the period after getting the first analysis result.	
Memory	Maximum 10,000 samples	
Display and printing	Graphic display on a touch panel Graphic printing on an external printer	
Simultaneous measurement	Maximum 60 parameters	
Detection time	Maximum 1,800 sec for any parameter	
QC data	Maximum 1,200 plots × 750 files can be stored X-bar control, L-J control	
Calibration curves	No. of points: 2-12 per curve No. of parameters that can be set: Maximum 250	
Reagent chamber	Reagent holding unit (40 wells) 10 ± 2°C (for an external environment of 20-28°C) Diluent (5 wells), room temperature	
Sample loader	10 racks (for 100 samples), room temperature loading STAT samples (for 5 samples), multi-adapter and host inquiry capabilities	
Sample transportation compatibility	Side sampling by Sample arm A Possible to use combinations of RACK and STAT	

MEASUREMENT PRINCIPLES

The CS series analyzers detect transmitted light unlike the CA series analyzers, which detect scattered light. The light from the source is spectrally split into 5 beams, of wavelength 340, 405, 575, 660 and 800nm, which are shone on the reagent-sample mixture. The transmitted light of each wavelength is detected every 0.1sec (***Fig. 2***). The transmitted light is then converted into an electrical signal and the coagulation time or concentration is calculated by a microprocessor. This is called multi-wavelength detection system as light of 5 different wavelengths are used for analysis. A 340 nm interference filter, which is in the ultraviolet range, is provided as a standard component. This enabled measurement of the coagulation factor XIII from the reduction in absorbance by NADH, which could not be handled by conventional coagulation analyzers.

Table 2 shows the within-run reproducibility of values of different parameters measured by the clotting assays, chromogenic assays, and immunoassays. Good reproducibility was seen with all the parameters.

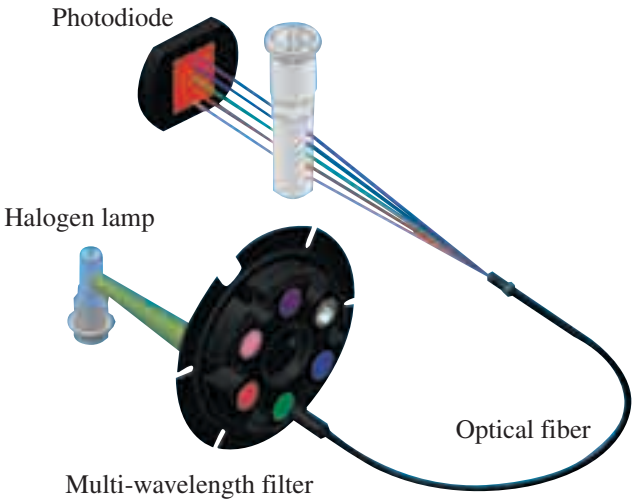


Fig. 2 *Multi-wavelength detection*

Table 2 *Within-run reproducibility*

n = 20	Clotting Assays								Chromogenic Assays				Immunoassays		
	PT			APTT	Fbg		TTO	HpT	ATIII	α2PI	PLG	PC	DD	FDP	PIC
	sec	%	INR	sec	sec	mg/dL	%	%	%	%	%	%	μg/mL	μg/mL	μg/mL
Mean	12.11	91.56	1.051	27.74	6.75	263.07	137.49	107.02	102.34	108.56	106.11	109.69	1.88	6.68	2.32
SD	0.07	0.92	0.007	0.10	0.14	6.39	2.23	1.16	0.39	0.89	1.61	1.89	0.05	0.18	0.07
CV	0.57%	1.01%	0.65%	0.36%	2.07%	2.43%	1.62%	1.08%	0.38%	0.82%	1.52%	1.72%	2.78%	2.70%	3.00%
Max	12.2	93.0	1.06	27.9	7.0	279.6	141.9	110.0	103.0	110.3	109.1	115.2	2.0	7.0	2.5
Min	12.0	90.3	1.04	27.6	6.4	252.1	134.6	105.0	101.7	106.5	102.6	106.5	1.8	6.3	2.2
Range	0.2	2.7	0.02	0.3	0.6	27.5	7.3	5.0	1.3	3.8	6.5	8.7	0.2	0.7	0.3

Reagents: Thromborel S, Thrombocheck APTT-SLA, Datafi Fibrinogen, Complex Factor T blue, Complex Factor H, Berichrom antithrombin III auto B, Berichrom α2-antiplasmin, Berichrom plasminogen, Berichrom protein C, BL-2 P-FDP and Lias Auto PIC

The advantage of this method of detection is that the influence of physiological interfering factors such as lipemia, which could not be handled by conventional optical analyzers, is reduced by selecting the optimum wavelength for each sample analyzed by the clotting assays (***Table 3***). For example in PT measurement, when an error occurs with a lipemic sample at the main measurement wavelength of 660 nm, data obtained at the sub wavelength of 800 nm, which is less affected by lipemia, is used to calculate the clotting time (***Fig. 3***). There is also a report that samples with low fibrinogen concentration, which showed analysis error in PT and APTT measurement because the change (dH) in the coagulation reaction curve was insufficient, could be successfully analyzed by a CS series analyzer as the measurement was switched over to the sub wavelength which gave a sufficiently large dH[2]. It has been confirmed for fibrinogen measurement also that the measurement range could be expanded by selecting main and sub wavelengths of 405 and 660 nm respectively[3, 4] (***Fig. 4***).

From these results, it is believed that the multi-wavelength detection system adopted in the CS series not only expands the list of analysis parameters but also reduces the influence of physiological interfering factors, lipemia in particular, which in turn contributes to reduction of the retesting rate.

Table 3 *Wavelength used for measurement*

Parameter	Main wavelength	Sub wavelength
PT, APTT	660	800
Fbg	405	660

(nm)

When a suitable transmitted light intensity or reaction intensity is not obtained with the main wavelength, the result obtained at the sub wavelength is displayed.
When one of the errors listed below is detected at the main wavelength, the analyzer uses the result obtained at the sub wavelength.

- Trans Light High
- Turbidity Level Over
- Slight Coagulation
- No Coagulation

However, if a suitable transmitted light intensity or reaction intensity is not obtained with either of the wavelengths, the result obtained at the main wavelength is displayed.

* This function is used with the clotting assays only because the wavelengths that can detect the reaction in the chromogenic assays and immunoassays are limited.

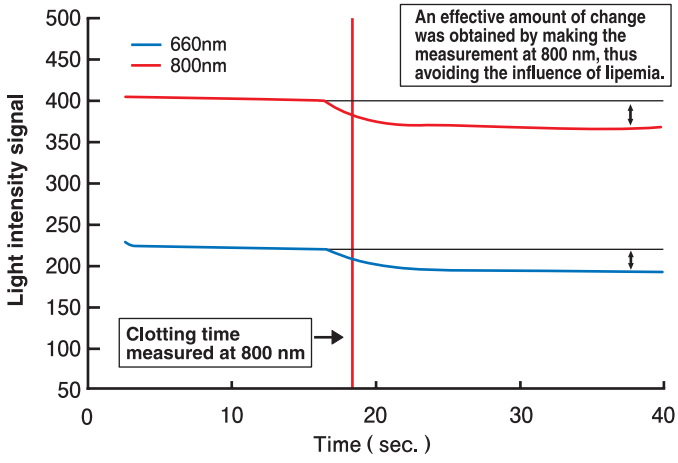


Fig. 3 *Wavelength used for measurement*

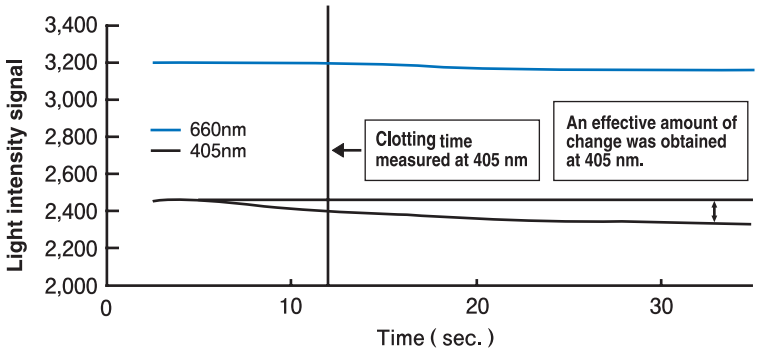


Fig. 4 *Measurement of Fbg of a low fibrinogen sample*

MAIN FUNCTIONS AND FEATURES

1. High throughput

The CS series analyzers detect transmitted light. The detector part of the analysis unit is independent of the parameter being analyzed. All are general use detection channels that can handle clotting assays, chromogenic assays, and immunoassays. CS-5100 is equipped with a 20 channel (20ch) detector, and is capable of high throughput analysis of maximum of 400 tests per hour for PT alone or simultaneous PT and APTT. The problem with conventional models, of reduction in throughput when parameters that require the chromogenic assays or immunoassays are added, has been eliminated.

There are 3 reagent probes used exclusively for the first reagent, second reagent and thrombin reagent. The exclusive use of one probe for the thrombin reagent prevents contamination of the reagents, apart from reducing the number of probe washings needed. The sample rack in the measurement line can move faster and more smoothly than in earlier analyzer models. High throughput processing has been realized by the combined effect of these mechanisms.

2. Cooling function for reagent table

The inside of the reagent table is held at the low temperature of about 10°C, and the temperature is made thoroughly uniform by circulating the air with an inbuilt fan (***Fig. 5***). A heater-equipped cover is placed at the top and the cooling source is at the bottom. This configuration concentrates dew formation below the reagent table and prevents dew from forming on the reagent table, rack or vials. Furthermore, air exchange between the reagent table and the outside is minimized to prevent evaporation of reagents.

Thus, the design is such that the temperature and humidity around the reagent table are little affected by the external environment, which improves the onboard stability of reagents and makes 24-hour testing service available. ***Fig. 6*** shows data on stability of reagents maintained for 24 hours in the seal opened condition.

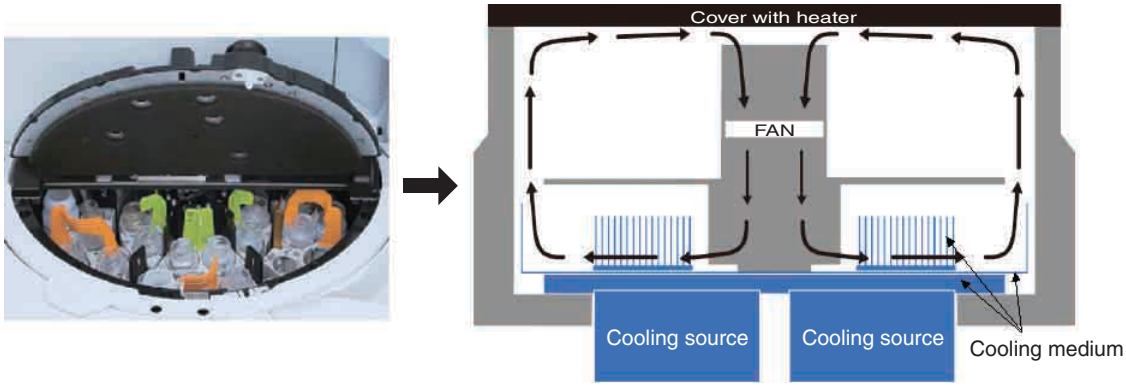
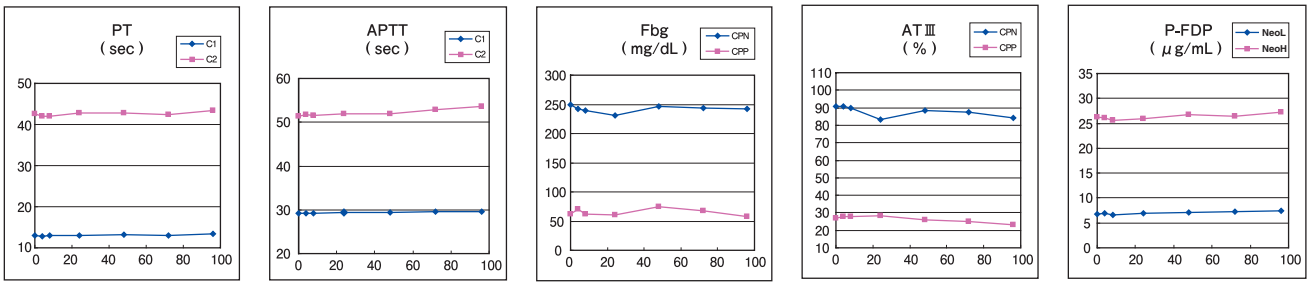


Fig. 5 *Cooling function for the reagent table*



Reagents: Thromborel S, Actin FSL, Datafi fibrinogen, Berichrom antithrombin III Auto B, Latex test BL-2 P-FDP
Samples: Citrol level 1 (C1), Citrol level 2 (C2), Control plasma N (CPN), Control plasma P (CPP), FDP control neo (Neo)
Environment: Room temperature 23_C, relative humidity 50%
Conditions: Reagents were set in the seal opened condition for 24 hours on the reagent table.

Fig. 6 *Onboard stability of reagents*

3. Improved reagent management

There are 2 reagent tables, an inner one and an outer one. Exclusive reagent racks in which the reagents, control standards, and calibrators can be randomly set up at a total of 40 locations, i.e., 10 locations (2 vial racks × 5) on the inner table and 30 (6 vial racks × 5) on the outer table, and used flexibly according to the type of analyzer operation desired (***Fig. 7***). The reagent holders (base) in the reagent rack have a slanted design. This has been done to reduce the dead volume of the reagent. The diluent holders are provided at 5 locations (room temperature) separately from the reagent table. The reagents and diluents can be set randomly within their respective units. The analyzer automatically reads the barcodes of the vials and recognizes the reagent information (name of the reagent, lot number and vial size) and position of the reagent vial. Also, the liquid surface sensor of the reagent probe monitors the residual amount of reagent, calculates the number of tests that can be done with it, and displays the information on the reagent management screen together with the time of initially setting the reagent in the rack (***Fig. 8***). More than one vial of the same reagent can be set, as the analyzer automatically uses the reagent vials in sequence according to the order of the time elapsed after setting each vial in the rack so that the operator can simply use the analyzer without having to pay attention to such aspects.

4. Monitoring the progress of analysis

In CS-5100, when an order is input into the analyzer, the expected time of completion of the analysis will be displayed on the job list. Therefore, the operator can promptly respond to queries from the clinical side about the progress of tests on STAT specimens, etc. For the individual samples also, as in the conventional analyzers,

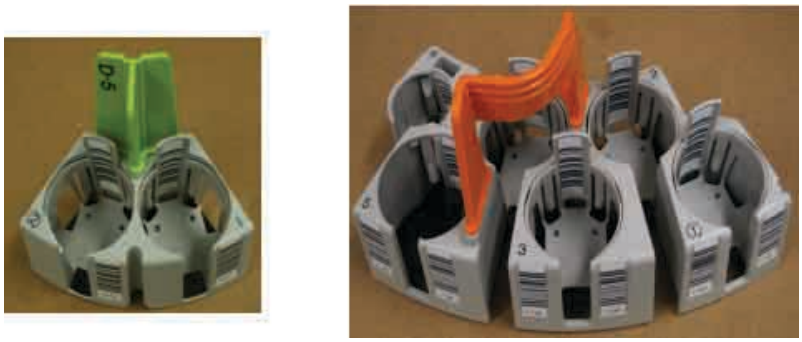


Fig. 7 *Reagent racks*

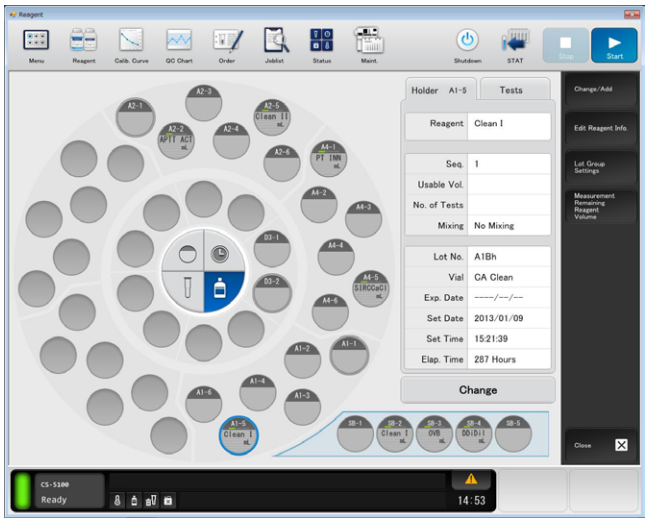


Fig. 8 *Reagent management screen*

the operator can find out the status, such as whether the sample is being dispensed, incubated, or under detection, from the marks that indicate the progress. Further, the time required for resumption of a paused analysis is also displayed (***Fig. 9***). These features contribute to reducing operator stress and improving efficiency.

5. Sample quality check function

1) HIL check

This is a function that checks for physiological interfering factors in the sample, such as hemolysis, bilirubin (icterus) and lipemia [5, 6]. In this function, a photometric device (HIL detector), which uses the same light source as for the multi-wavelength detection, is provided in the primary sample loading unit, and the absorbance at 405, 575 and 660 nm is calculated to estimate the level of interfering substance in the sample (***Fig. 10***). When this level is above a certain threshold, a flag is displayed with the analysis result (***Fig. 11***). On-off status of the HIL check and the threshold level for flag display can be set independently for each interfering factor, making it possible to customize this function.

Fig. 9 *Time display*

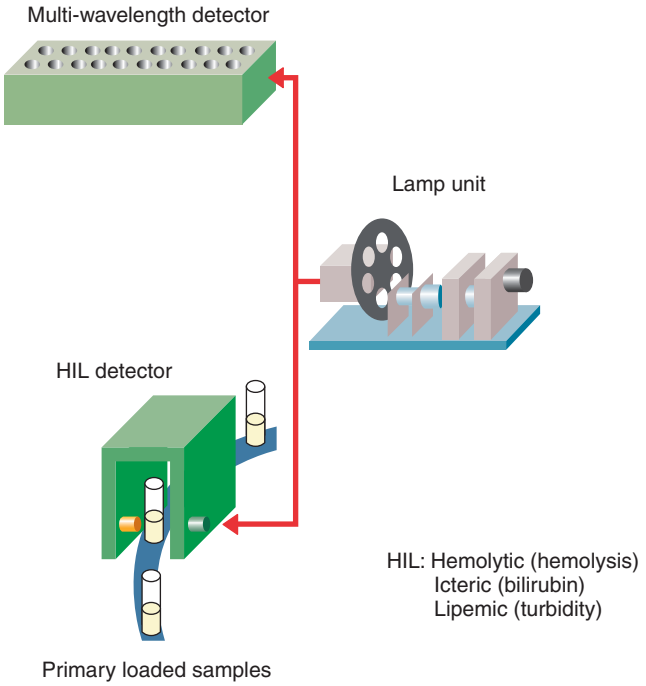


Fig. 10 *HIL detector*

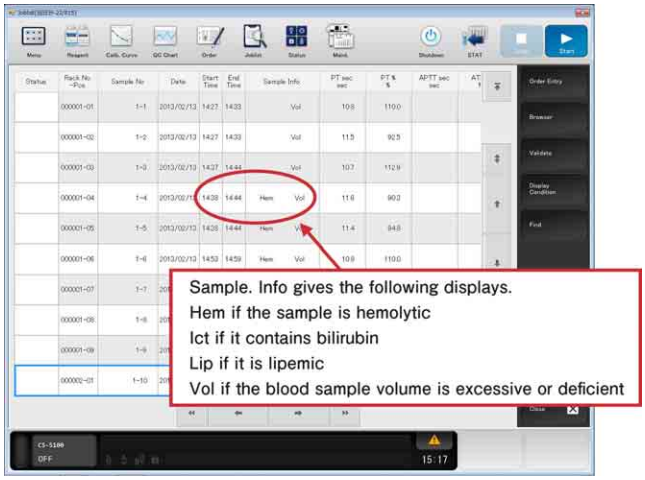


Fig. 11 *Results of sample quality check*

2) Sample volume check
This function checks whether the sample volume in the blood sample tube is appropriate. A specimen used for hemostatic and fibrinolytic testing needs to be sampled at the 9:1 ratio of blood and sodium citrate. PT-INR increases when the volume of blood sample is less than 90% of the specified volume[7]. To eliminate such problems, in CS-5100 the height of the liquid surface is detected by a probe at the time of sample aspiration, to verify the sample volume (***Fig. 12***). If the volume is excessive or deficient relative to the specified range, a flag is displayed with the analysis result (***Fig. 11***). If an unexpected analysis result is obtained or an error is displayed with a result, the cause must be identified taking into account the sample side factors like the influence of hemolysis or lipemia, excess or deficient sample volume, etc. Therefore, the flags displayed by the sample quality check function may be used as additional information for determining the reasons for such results.

6. External appearance

In CS-5100, the floor top main unit and the information processing unit (IPU) are separate as shown in ***Fig. 1***. The washing water and effluent tanks can be housed in a dedicated cart (optional), which makes the general appearance sleek.
The design of this analyzer is according to the so called "Silent Design", a new concept of Sysmex. It is worker centric designing where the movements of the operator are taken into account in order to provide a better environment for those engaged in laboratory testing.

7. User interface

The IPU monitor has a large (17 inch) touch-operated LCD screen to improve user friendliness. The touch panel may be used for ordinary analysis operations and a keyboard and mouse for detailed analysis setting (***Fig. 13***).

8. Others

CS-5100 has two sample probes. One of them has cap piercing capability and therefore can reduce the biohazard risk. It can carry out sampling from randomly loaded combinations of sealed and open sampling tubes and cups. The other probe is for small volume samples, and is capable of sampling to a much smaller dead volume (***Fig. 14***).

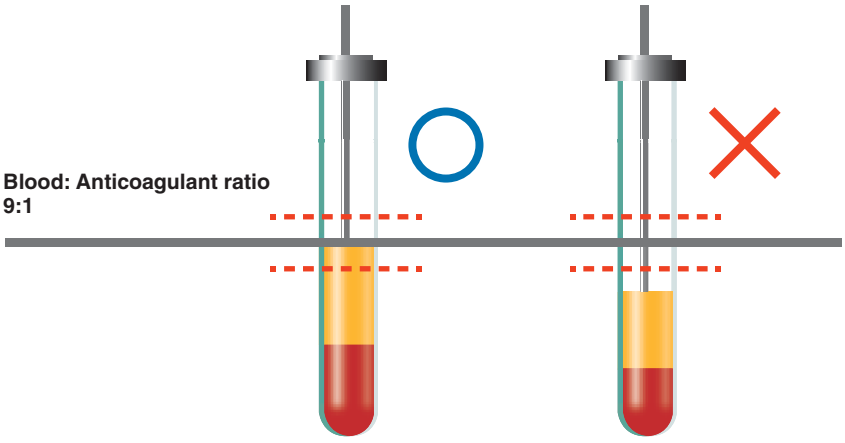


Fig. 12 *Sample volume check*

In addition, the analyzer is equipped with numerous other functions such as Auto QC, which performs automatic quality control at certain time intervals, STAT sample holder (for 5 samples) in which samples can be placed on the STAT table any time, multi-dilution assay (MDA), and reflective assay.
Furthermore, the analyzer is compatible with Sysmex Network Communication Systems (SNCS) through which the customer's analyzer can be connected online to the company's Customer Support Center to provide real-time QC, online support, web information service, analyzer breakdown prediction*, and prevention and correction of breakdowns* (*These are currently under development). This can contribute to the creation of a reliable and easy-to-use environment for users.
Finally the analyzer enable connectivity to major sample transportation lines through side sampling by the sample probe and then is able to more flexibly cope with laboratory setups of ever increasing diversity.

Fig. 13 *Main screen and calibration curve screen*

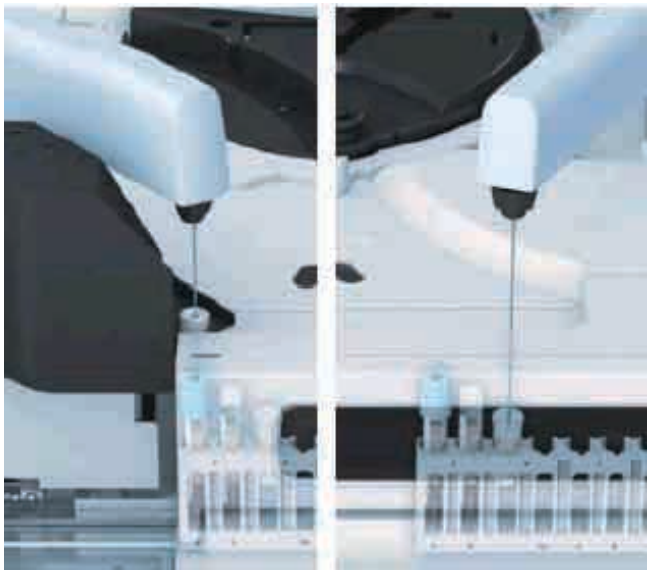


Fig. 14 *Cap piercing and small volume sampling*

CONCLUSION

In the field of thrombosis and hemostasis, importance in diagnosis and treatment was earlier given to hemorrhagic diseases such as hemophilia. However, currently thrombotic diseases like myocardial infarction, cerebral infarction, pulmonary embolism, etc. account for about 1/3rd of the fatalities in Japan, and active research is underway on their diagnosis and prevention. Orders for thrombosis and hemostasis testing are increasing in fields of critical care, such as pre- and post-operative care, emergency medical care, and organ transplants, and there is an increasing demand for rapid testing with 24-hour service availability.

CS-5100 is an analyzer developed to meet this increasing need for thrombosis and hemostasis testing. I believe that CS-5100 described here, with its various functions and advantageous features which include the high throughput processing, would be able to contribute to making testing at the point of care speedier, more reliable and efficient.

References

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