Introduction of Products

Overview of the Automated Blood Coagulation Analyzer

CS-2000*i*

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INTRODUCTION

Every year, the rate of occurrence of thrombotic events is showing an upward trend throughout the entire world. Therefore, not only the number of global coagulation tests such as PT, aPTT and TT is increasing but also the number of screening tests for thrombosis, such as D-Dimer, Protein C and Protein S, show an increase. In response to this, coagulation analyzers equipped with multiple measurement principles such as Clotting, Chromogenic and Immunoturbidmetric are becoming mainstream in the market[1, 2].

Recently, we have developed an Automated Blood Coagulation Analyzer, the CS-2000*i*/2100*i* (CS-2100*i*: Cap piercing model), as a next-generation successor to the CA series of instruments (***Fig. 1***). The system is a fully automated analyzer, for in vitro diagnostic use, that can quickly analyze a large number of samples with a high degree of accuracy. It incorporates the latest technologies and has achieved improvements in usability.

In this article, we will give an outline of the instrument and explain its new functions as well as provide some basic data.

Fig. 1 *CS-2000i overview*

DEVELOPMENT CONCEPT

This instrument was developed based on the findings from a CCPD (Customer Centered Product Definition) process. Together with our partners, Dade Behring, global marketing research was conducted in 7 countries across North America, Europe and Japan and input from 596 laboratories in total was extracted. We have used this input to develop DIRs (Design Input Requirements) with the features listed below as the main development targets:

1. Reduce downtime and prompt troubleshooting
2. Efficient sample management
3. Efficient system operation
4. Efficient reagent management

From this, we set "Increased Efficiency of Laboratory Testing" as the development goal.

SPECIFICATION

Table 1 shows the main specification of CS-2000*i*/2100*i*.

Table 1 *CS-2000i/2100i specification*

Specifications	Sysmex CS-2000*i*/2100*i*
Principles	Multi- Wavelength Detection System: Transmitted Light Detection Method • Clotting Assays: 405, 660, 800 nm (Percentage Detection Method) • Chromogenic Assays: 405, 340 nm (Rate Method) • Immunoassays: 575, 800 nm (Rate Method, VLIn Method) • Aggregation Assays†
Detector	10 channels for Clotting Assays, Chromogenic Assays and Immunoassays (4 of 10 channels for Aggregation Assays) • The transmitted light (or A/D value) is detected every 0.1 seconds. • Maximum Reading Time is 1800 seconds.
Parameters	Clotting Assays: PT, aPTT, Fbg, TT, Extrinsic Factors (II, V, VII, X), Intrinsic Factors (VIII, IX, XI, XII), PS, PC Chromogenic Assays: AT-III, PLG, α2-AP, PC, FXIII, PAI Immunoassays: D-Dimer, VWF:Ag Aggregation Assays: VWF: RCo, Platelet Aggregation†
Throughput	PT: 180 tests/h PT and aPTT: 115 tests/h PT, aPTT, Fbg and ATIII: 100 tests/h
Sample Volume	PT, aPTT 50 µL; FXIII 20 µL Fbg 10 µL; PC 15 µL TT 50 µL; D-Dimer 50 µL Extrinsic Factors 5 µL; VWF:Ag 15 µL Intrinsic Factors 10 µL; VWF:RCo 10 µL ATIII, α2-AP, PLG 16 µL; PAI 16 µL
Reagent Holder	40 positions (10°C) 5 positions (room temperature)
Auto Sampler	Capacity of 50 samples (5 × 10 tube racks)
STAT	5 holders
Cuvettes	Automatically supplied from an internal hopper. Capacity: 500 discrete cuvettes
Sample Aspiration	The sample probe, with a liquid surface sensor, quantitatively aspirates plasma or serum from centrifuged whole blood samples
Quality Control	x-bar control, Levy-Jennings control Multi-rule (Westgard Rule) monitoring 1200 data points × 750 parameters stored in memory
Data Storage	10,000 samples results with reaction curves
Print Out	Graphic or Data Printer (option)
Dimensions W × D × H (mm) Weight (kg)	IPU and Main Unit: (including rack sampler) Approx. 775 × 675 × 865 (mm) Approx. 100 (kg) Pneumatic Unit: Approx. 280 × 355 × 400 (mm) Approx. 17 (kg)
Power Requirement	117 / 220 / 240V AC ± 10% (50 or 60Hz)
Power Consumption	Main Unit 800VA max., Pneumatic Unit 280VA max.
Optional Equipment	Graphic Printer, Data Printer

† under development

TECHNOLOGY

The CS-2000*i* has a changed measurement principle and enhanced measurement criteria. Though there is a lot of new technology, we will especially give an introduction to the 5 new features mentioned below.

1. Multi-Wavelength Detection System

The CS-2000*i* has adapted its detection principle from the scattered light detection method employed on the CA series to a transmitted light detection method. The configuration of the detection unit of the CS-2000*i* is as follows (***Fig. 2***). Light from the halogen lamp is dispersed in 340, 405, 575, 600 and 800 nm wavelengths by 5 filters. The spectroscopic light is carried to the detector by an optical fiber and then shines on the mixture of sample and reagent in the cuvette. The light transmitted through the mixture is detected at all wavelengths, every 0.1 seconds, by a photo-diode and converted into an electronic signal. The clotting time and the dOD/min are derived from this signal by a microprocessor. We call this system the "Multi-Wavelength Detection System", because it measures the sample at all 5 wavelengths. This system has 10 detection channels and these can all be used for Clotting assays, Chromogenic assays, Immunoassays and Aggregation assays (4 of 10 channels only) using preset parameters. Consequently, the TAT (turnaround time) is enhanced when there are many orders of Chromogenic assays and Immunoassays.

The Multi-Wavelength Detection System analyzes the data from all wavelengths and automatically selects the optimum wavelength for measuring a Clotting assay on lipemic samples and low fibrinogen samples . When the result is influenced by an interfering substance in the sample, the system selects the appropriate sub-wavelength and automatically calculates the clotting time. Clotting assays use 660 nm as the default wavelength and 800 nm as the sub-wavelength except for the fibrinogen assay (Clauss method). The fibrinogen assay uses 405 nm as its default wavelength and 660 nm as its sub-wavelength. The measurement range for fibrinogen is also extended by this wavelength switching function.

Tables 2-4 show the within-run reproducibility of each measurement parameter.

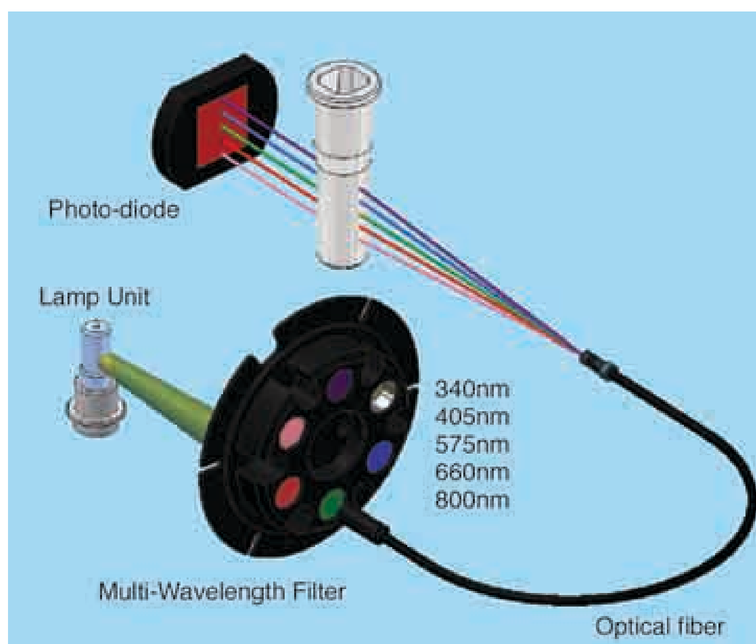


Fig. 2 *Multi-Wavelength detection system*

Table 2 *Within-run reproducibility of clotting assays*

	PT						aPTT		Fbg	
	CPN			CPP			CPN	Ci-Trol 3	CPN	CPP
	sec	%	INR	sec	%	INR	sec	sec	mg/dL	mg/dL
1	11.1	85.0	1.06	19.5	30.6	1.82	27.2	63.2	272	85
2	11.1	85.0	1.06	19.3	31.0	1.80	27.2	64.7	268	88
3	11.1	85.0	1.06	19.4	30.8	1.81	27.3	65.0	268	78
4	11.1	85.0	1.06	19.5	30.6	1.82	27.2	63.6	272	89
5	11.0	86.6	1.05	19.5	30.6	1.82	27.5	63.1	272	84
6	11.1	85.0	1.06	19.4	30.6	1.81	27.1	63.8	272	83
7	11.0	86.6	1.05	19.8	31.0	1.84	27.1	63.3	264	84
8	11.0	86.6	1.05	19.8	30.8	1.84	27.1	63.6	272	82
9	11.1	85.0	1.06	19.4	30.6	1.81	27.2	63.8	268	80
10	11.1	85.0	1.06	19.6	30.6	1.83	27.1	65.0	264	83
11	11.2	83.4	1.06	19.8	30.6	1.84	27.1	63.6	260	83
12	11.1	85.0	1.06	19.5	31.0	1.82	27.1	63.7	256	82
13	11.1	85.0	1.06	19.3	30.8	1.80	27.1	63.2	264	78
14	11.1	85.0	1.06	19.5	30.6	1.82	27.3	64.5	256	83
15	11.0	86.6	1.05	19.8	30.6	1.84	27.3	63.8	260	79
16	11.1	85.0	1.06	19.3	31.0	1.80	27.0	63.3	268	83
17	11.1	85.0	1.06	19.3	31.0	1.80	27.1	64.5	260	81
18	11.0	86.6	1.05	19.7	30.1	1.83	27.2	64.1	268	84
19	11.1	85.0	1.06	19.6	30.4	1.83	27.0	63.8	264	77
20	11.0	86.6	1.05	19.3	31.0	1.80	27.3	63.2	268	83
Mean	11.07	85.40	1.057	19.52	30.54	1.819	27.18	63.84	265.8	82.5
SD	0.06	0.88	0.005	0.18	0.41	0.015	0.12	0.60	5.3	3.1
%CV	0.5%	1.0%	0.4%	0.9%	1.3%	0.8%	0.4%	0.9%	2.0%	3.7%

PT: Dade Innovin, aPTT: Dade ACTIN FSL, Fbg: Dade Thrombin Reagent, CPN: Control Plasma N, CPP: Control Plasma P

Table 3 *Within-run reproducibility of chromogenic assays*

	ATIII		PC		PLG		APL	
	CPN	CPP	CPN	CPP	CPN	CPP	CPN	CPP
	%	%	%	%	%	%	%	%
1	93.9	30.5	100.0	32.3	104.4	35.4	105.2	34.5
2	93.3	30.7	100.0	33.5	105.3	35.4	102.4	35.9
3	92.3	31.5	108.4	28.7	103.4	34.4	102.4	34.5
4	94.3	33.6	101.2	31.1	100.4	33.4	105.2	35.9
5	93.4	33.0	97.5	31.1	102.4	35.4	105.2	35.9
6	93.3	32.2	108.4	29.9	103.4	34.4	103.8	33.1
7	94.0	33.2	102.4	29.9	104.4	35.4	105.2	35.9
8	93.7	30.0	107.2	32.3	106.3	34.4	103.8	34.5
9	92.9	28.9	104.8	32.3	105.3	35.4	108.1	33.1
10	93.4	33.6	101.2	32.3	102.4	35.4	103.8	37.3
11	95.0	31.4	102.4	34.7	104.4	34.4	105.2	35.9
12	94.8	31.1	102.4	29.9	101.4	34.4	103.8	37.3
13	94.7	30.5	100.0	27.5	101.4	34.4	105.2	35.9
14	94.1	30.5	106.0	29.9	106.3	34.4	108.1	37.3
15	94.8	31.5	102.4	31.1	106.3	35.4	105.2	37.3
16	93.4	29.6	100.0	32.3	102.4	34.4	103.8	35.9
17	93.9	30.3	102.4	29.9	102.4	35.4	105.2	38.7
18	94.7	32.2	98.7	29.9	99.4	33.4	105.2	38.7
19	92.9	33.3	102.4	32.3	105.3	34.4	105.2	35.9
20	95.5	31.7	108.4	32.3	99.4	34.4	105.2	37.3
Mean	93.92	31.47	102.81	31.16	103.53	34.70	104.86	36.04
SD	0.83	1.38	3.32	1.72	2.00	0.66	1.45	1.57
%CV	0.9%	4.4%	3.2%	5.5%	1.9%	1.9%	1.4%	4.3%

ATIII: Berichrom Antithormbin III (A), PC: Berichrom Protein C, PLG: Berichrom Plasminogen, APL: Berichrom α2-Antiplasmin, CPN: Control Plasma N, CPP: Control Plasma P

Table 4 Within-run reproducibility of immunoassays

	D Dimer		VWF:Ag	
	Control I	Control II	CPN	CPP
	μg/L	μg/L	%	%
1	560	2456	90.5	35.7
2	559	2346	92.2	35.4
3	585	2396	90.7	35.9
4	558	2511	90.5	36.4
5	557	2446	89.5	33.8
6	585	2410	86.3	33.8
7	570	2458	89.9	34.7
8	574	2335	94.3	35.4
9	570	2364	92.9	33.1
10	570	2479	94.2	33.7
11	562	2355	95.9	34.8
12	577	2417	92.7	35.5
13	575	2464	92.2	35.4
14	581	2396	88.9	34.4
15	563	2480	86.8	34.4
16	558	2495	90.3	34.7
17	567	2501	85.7	36.0
18	566	2417	90.5	38.2
19	578	2453	89.5	33.7
20	566	2398	82.4	34.3
Mean	569.0	2428.8	90.30	34.97
SD	9.0	53.4	3.23	1.18
%CV	1.6%	2.2%	3.6%	3.4%

D-Dimer: D-Dimer PLUS, vWF:Ag : vWF Ag ,
Control I & II: D-Dimer Control Plasma I & II,
CPN: Control Plasma N

2. HIL Check

HIL is the acronym for Hemolysis, Icterus and Lipemia. Measurement results obtained from some instruments, which use an optical detection method, may be affected by these substances.[3, 4] The HIL check function automatically checks for the presence of interfering substances in the sample by the unique analysis algorithm of the Multi-Wavelength Detection System (***Fig. 3***). Each substance has a specific absorbance spectrum. For example, bilirubin has its peak wavelength at 455 nm and hemoglobin has its peak wavelength at 415 to 430, 540 and 575 nm. Lipemia has a broad absorbance peak (***Fig. 4***). Absorbance measurements at 405, 575 and 660 nm are used to classify interferences into a negative or positive judgement before ordered sample measurement begins. If the absorbance is greater than any of the criteria, the symbol (*) is attached on the left side of the numeric result value when any one of the errors occurs. Red blood cells contain phospholipids, and contain coagulation activity similar to that of platelet factor 3. If released by hemolysis, these phospholipids could shorten the aPTT of hemolyzed samples[5, 6]. Therefore, it is very important to check for pre-analytical variables such as hemolysis, icterus and lipemia before measurement of a coagulation test.

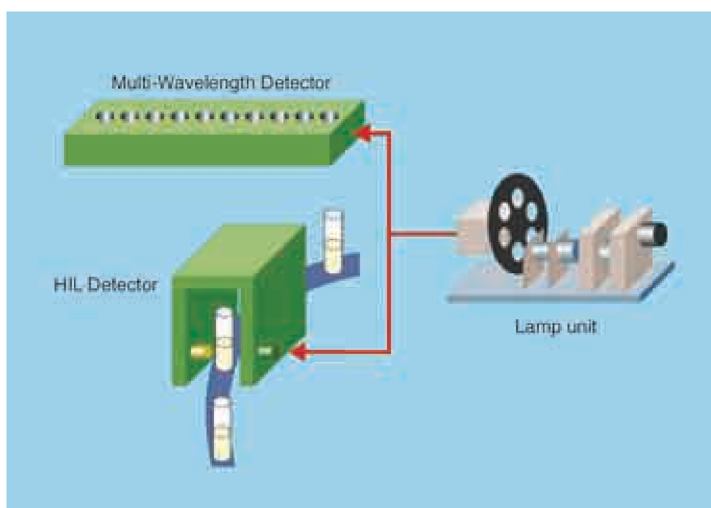
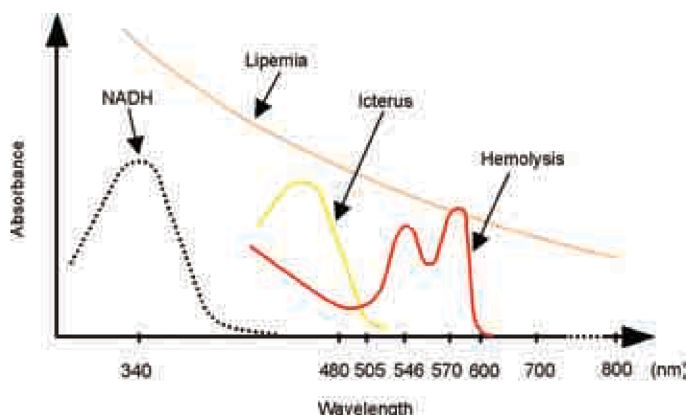


Fig. 3 *HIL check outline*



	405 nm	575 nm	660 nm
Hemolysis	+	+	-
Icterus	+	-	-
Lipemia	+	+	+

Fig. 4 *Relationship between absorbance and interfering substances*

3. Cuvette Mixing System for Aggregation assays

The VWF:RCo (VWF Ristocetin cofactor) and the Platelet Aggregation assay† need stirring for the mixture of sample and reagent in the cuvette during the reaction. The CS-2000*i* has a rotating magnet under 4 of the 10 detection channels so that the mixture can be stirred when using a special cuvette that has an internal stir bar (***Fig. 5***).

This mixing system makes it possible to measure aggregation assays on a general coagulation instrument.

Table 5 shows the reproducibility of VWF:RCo.

† under development

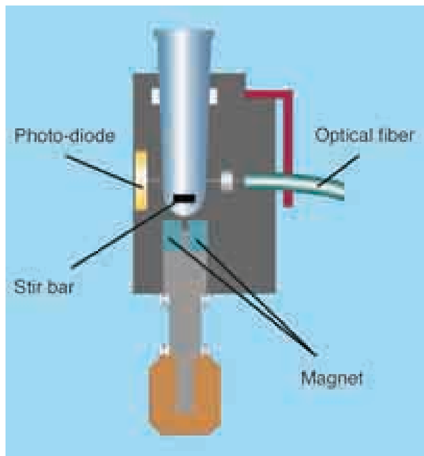


Fig. 5 *Cuvette mixing system*

Table 5 *Within-run reproducibility of VWF:RCo*

	VWF:RCo	
	CPN	CPP
	%	%
1	84.7	20.6
2	82.4	24.1
3	76.2	19.9
4	71.9	22.8
5	78.5	21.3
6	82.2	21.2
7	86.4	24.0
8	90.9	24.6
9	72.7	23.7
10	85.8	23.4
11	82.7	22.1
12	82.6	20.9
13	78.5	20.8
14	86.7	20.5
15	74.3	23.0
16	95.3	20.2
17	75.4	20.5
18	83.5	20.1
19	70.6	21.9
20	80.9	20.3
Mean	81.11	21.79
SD	6.44	1.54
%CV	7.9%	7.1%

VWF:RCo: BC von Willebrand Reagent, CPN: Control Plasma N, CPP: Control Plasma P

4. Ultraviolet Filter (340nm)

The Multi-Wavelength Filter has an ultraviolet region (340nm) that makes it possible to measure Coagulation Factor XIII (synthetic substrate method). The principle of Berichrom FXIII is based on the decrease in NADH activity which is detected by monitoring its absorbance at 340 nm. Routine coagulation screening tests do not detect Factor XIII deficiency since the TT, PT and aPTT results are all normal, provided that the remainder of the coagulation system is intact. Therefore, it is useful to perform this assay to determine what led to a hemorrhagic tendency in such a situation[7, 8]. ***Table 6*** shows the reproducibility of Factor XIII.

Table 6 Within-run reproducibility of factor XIII

	FXIII	
	CPN	CPP
	%	%
1	97.5	34.5
2	104.3	33.5
3	104.7	33.8
4	103.8	33.8
5	102.9	34.8
6	98.4	32.8
7	102.9	33.1
8	105.2	33.8
9	102.0	33.5
10	102.5	33.8
11	106.1	33.8
12	103.8	33.8
13	103.4	33.8
14	100.6	33.5
15	100.2	35.5
16	104.7	34.5
17	101.6	35.2
18	102.9	32.8
19	100.6	33.5
20	106.6	32.1
Mean	102.73	33.80
SD	2.39	0.81
%CV	2.3%	2.4%

FXIII: Berichrom FXIII, CPN: Control Plasma N, CPP: Control Plasma P

5. Advanced User Interface

The CS-2000*i* has a separate Information Processing Unit (IPU), which processes the data generated by the Main Unit. It is operated using a 17" touch panel display, keyboard and mouse using a Windows XP operating system. The software of this system was designed to optimize the Main Unit with a convenient and high functionality. Routine measurement and normal use can operate via the touch panel and detailed setting can be performed using the mouse and the keyboard which are attached to the IPU. Moreover, the menu has a user-friendly layout with a completely new design (***Fig. 6 and 7***).

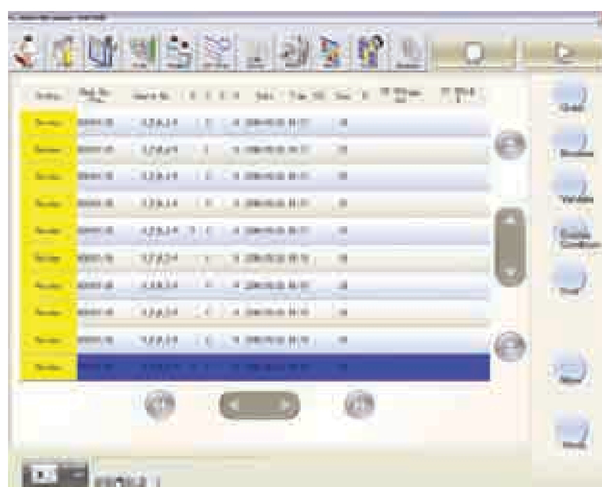


Fig. 6 *Joblist screen*

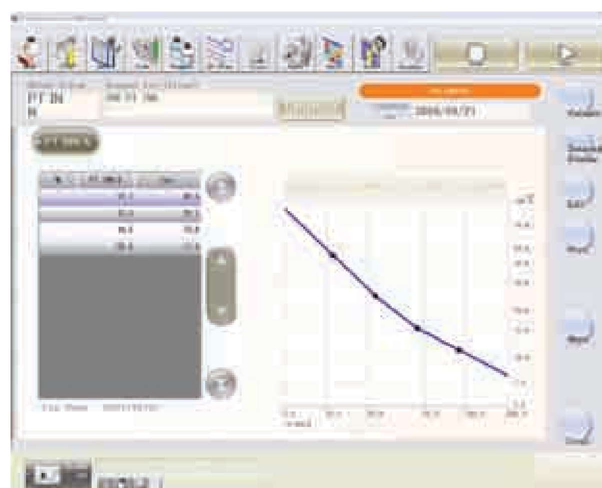


Fig. 7 *Calibration curve screen*

6. Enhancement of Reagent Management

The CS-2000*i* employs a double reagent table which allows additional reagents to be set or replenished without interruption to measurement. The reagent table has 5 outer reagent racks and 5 inner reagent racks (***Fig. 8***). The outer reagent racks can hold 6 reagent vials and the inner reagent racks can hold 2 reagent vials. A total of 40 reagents, controls and calibrators can be set on this table, in any position. There are also 5 diluent positions (room temperature). A cooling system maintains the reagent table at approximately 10°C. Reagent positions (rack number and position) and reagent information (reagent name, lot number and vial type etc.) can be input by an automatic barcode reading function (***Fig. 9***). Each reagent rack has 1 position in which the reagent can be stirred. The system automatically manages reagent volume and can handle up to 3 vials of the same reagent.

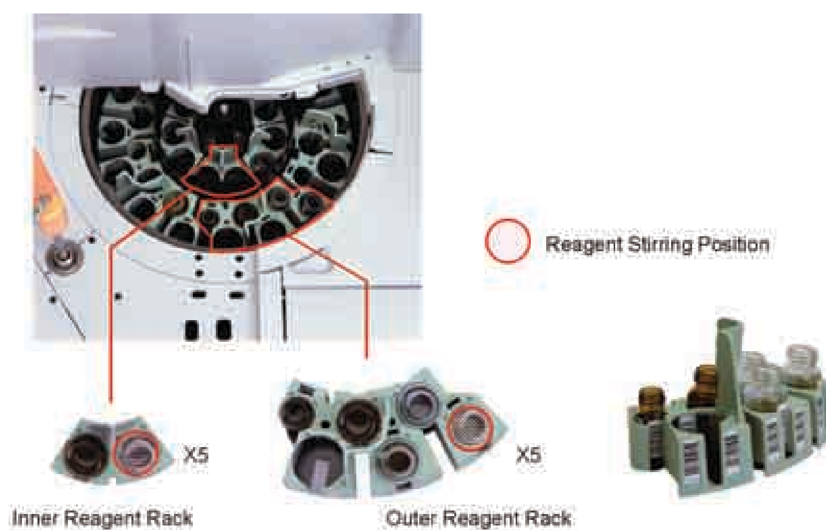


Fig. 8 *Reagent rack*

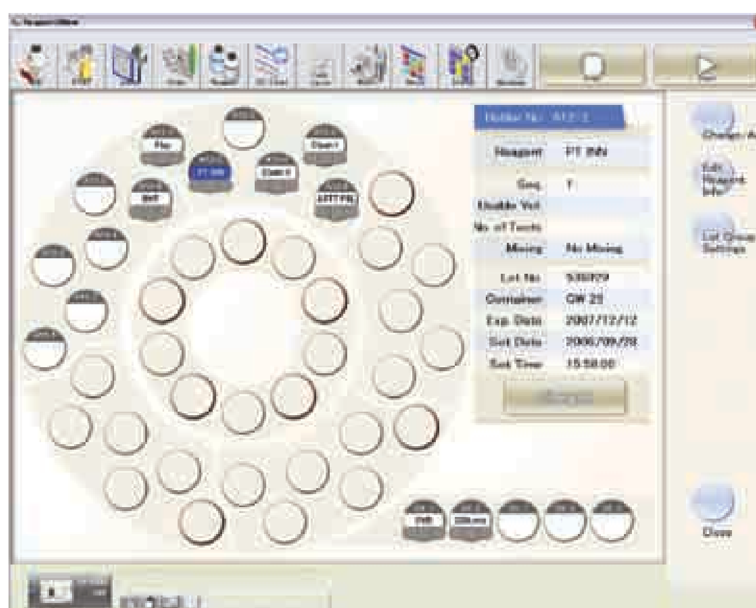


Fig. 9 *Reagent screen*

CONCLUSION

In this article we have introduced the CS-2000*i*, especially the new functions and state-of-the-art technology. With the development of this system, we have achieved a next generation platform which provides various assays from screening tests to tests for the prevention of relapse. The Factor XIII assay and the vWF:RCo assay can be used as new parameters and many new functions are built into this instrument. Moreover, a new additional function including Platelet Aggregation Assay is under development as part of upgraded software in the future.
Because our ultimate target is to achieve a complete analyzer in the Hemostasis field, we will continuously concentrate our efforts to accomplish it.

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